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ORIGINAL ARTICLE

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Metabolic Associated Fatty Liver Disease in Type 2 Diabetes Mellitus and Correlation with Risk Factors

Ashok Kumar, Jay Patel**, Shivani Bansal***, Aditya Chaudhary*****

Abstract

***Background:* "Metabolic Associated Fatty Liver Disease (MAFLD) previously Non-Alcoholic Fatty Liver Disease (NAFLD)" is an emerging and prevalent co-morbidity among Indian patients with type 2 diabetes mellitus (T2DM). However, data regarding the diagnostic utility of transient elastography (Liver Stiffness Measurement) in this population remain limited.**

***Objective:* This cross-sectional observational study aimed to determine the prevalence and severity of MAFLD in T2DM patients using Liver Stiffness Measurement by transient elastography and evaluate its association with metabolic parameters.**

***Methods:* A total of 135 adult T2DM patients underwent comprehensive clinical, anthropometric, and biochemical assessments. Hepatic evaluation was done using transient elastography (FibroScan) to quantify liver stiffness and steatosis. Metabolic dysfunction-associated steatohepatitis (MASH) was defined by the presence of elevated alanine aminotransferase (ALT) levels or evidence of hepatic fibrosis.**

***Results:* The prevalence of MAFLD was 67.4%, with a female predominance (62.2%), although no significant correlation with age or gender was observed. MAFLD was significantly associated with higher body mass index (BMI) ($p = 0.0365$) and presence of metabolic syndrome (74.5% vs. 25.5%, $p = 0.0001$). Patients with MAFLD exhibited elevated random plasma glucose, HbA1c, triglyceride levels, and lymphocyte counts compared to non-MAFLD counterparts. The Fatty Liver Index was significantly elevated in MAFLD patients, whereas liver function tests and fibrosis scores did not differ significantly between groups.**

***Conclusion:* This study demonstrates a high prevalence of MAFLD among T2DM patients, closely linked to metabolic syndrome, elevated triglycerides, and disrupted glucose metabolism. Non-invasive tools such as the Fatty Liver Index and liver stiffness measurement effectively identify individuals at risk.**

***Key words:* Non-Alcoholic Fatty Liver Disease (NAFLD), Metabolic Associated Fatty Liver Disease (MAFLD), Type 2 Diabetes Mellitus (T2DM), Fatty Liver Index (FLI), Liver Stiffness Measurement (LSM). Controlled Attenuation Parameter (CAP).**

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia due to insulin resistance and/or relative insulin deficiency. With approximately 463 million adults affected globally and a projected increase to 578 million by 2030, T2DM is a growing public health concern[1]. Among its numerous complications, metabolic asociated fatty liver disease (MAFLD) has emerged as a highly prevalent hepatic manifestation, affecting up to 55.5% of individuals with T2DM[2]. The condition previously referred to as non-alcoholic fatty liver disease (NAFLD) has also been described as metabolic dysfunction – associated fatty liver disease (MAFLD), reflecting the same spectrum of disease with greater emphasis on underlying metabolic dysfunction[3].

MAFLD encompasses a spectrum ranging from simple steatosis to metabolic dysfunction associated steatohepatitis (MASH), which can progress to advanced liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). MAFLD in patients with T2DM is often asymptomatic, yet it is significantly associated with increased morbidity and mortality. Liver fibrosis, in particular, is recognised as a key determinant of long-term outcomes in MAFLD patients. Liver fibrosis correlates with complications such as diabetic nephropathy, cardiovascular disease, neuropathy, and even certain malignancies[4,5].

Early identification and risk stratification of liver fibrosis in diabetic individuals is therefore critical for timely intervention and prevention of disease progression. Transient elastography, commonly known by the commercial name FibroScan®, is a non-invasive imaging technique that assesses liver stiffness as a surrogate for fibrosis. It has become a preferred tool for evaluating liver fibrosis in patients with MAFLD due to its ease of use, rapid results, and good diagnostic accuracy particularly for moderate to advanced fibrosis stages[6,7]. However, factors such as obesity, inflammation, and hepatic steatosis can

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influence measurement accuracy, and its effectiveness in detecting early fibrosis remains limited.

Despite the increasing burden of MAFLD among T2DM patients in India, data on the application and diagnostic utility of Liver Stiffness Measurement (LSM) in this population remain scanty. Given the high prevalence of metabolic risk factors such as obesity, dyslipidaemia, and hypertension, there is a pressing need for regional studies that assess the burden of MAFLD and explore its correlation with these risk factors in diabetic patients. This study aims to evaluate the prevalence and severity of MAFLD among individuals with type 2 diabetes mellitus using Liver Stiffness Measurement and to investigate the correlation between liver stiffness and metabolic risk factors such as glycaemic control, lipid profile, BMI, and duration of diabetes. This will help in identifying high-risk individuals who may benefit from early intervention, thus improving long-term outcomes in this vulnerable population.

Recent studies have highlighted the burden of MAFLD among diabetics. Wong *et al* (2023) reported a 70% prevalence of MAFLD in T2DM using MRI-based techniques[8], while Yilmaz *et al* (2022) demonstrated that MAFLD significantly increases cardiovascular risk independent of glycaemic status[9]. However, previous studies often lacked uniform diagnostic criteria or adequate stratification based on fibrosis severity. Most prior Indian studies have used ultrasound, whereas this study uses Liver Stiffness Measurement and Fatty Liver Index, giving a more accurate stratification.

This lacuna underscores the need for regional studies assessing MAFLD burden in diabetic cohorts, which formed the rationale for our study.

Material and Methods

This cross-sectional observational study was conducted over a period of one year following approval from the Institutional Ethics Committee (IEC). A convenient sample of 135 participants was enrolled after obtaining informed consent. Adults aged 18 years and above with T2DM were included. Exclusion criteria comprised individuals with significant alcohol intake (≥30 g/day in men and ≥20 g/day in women), pregnant women, those using steatogenic drugs such as corticosteroids, and patients with known chronic liver diseases including hepatitis B, hepatitis C, autoimmune hepatitis, haemochromatosis, Wilson's disease, primary biliary cirrhosis, or drug-induced hepatitis. All enrolled participants underwent detailed clinical evaluation, including medical history, physical examination, and anthropometric measurements such as body mass index (BMI) and waist circumference. Fasting venous blood samples were drawn, and measurements of aspartate transaminase (AST), alanine transaminase (ALT), serum bilirubin, lipid profile (consisting of low-density lipoprotein (LDL), high-density lipoprotein (HDL), serum triglycerides, and total cholesterol), and fasting blood sugar were conducted. Screening for hepatitis B surface antigen and anti-HCV antibodies was done to exclude viral hepatitis.

Obesity was defined as a BMI ≥25 kg/m^2 as per Asian Criteria and central obesity as waist circumference ≥90 cm in males and ≥80 cm in females, as per WHO standards. Hypertension was considered present if the patient was on antihypertensive treatment or had systolic blood pressure ≥140 mmHg or diastolic pressure ≥90 mmHg. Dyslipidaemia was defined either by prior diagnosis, use of lipid-lowering therapy, or the presence of abnormal lipid parameters total cholesterol >200 mg/dL, triglycerides >150 mg/dL, HDL-C <40 mg/dL, or LDL-C >130 mg/dL. The diagnosis of metabolic syndrome was based on IDF (International Diabetes Federation) criteria, requiring central obesity along with two or more of the following: elevated triglycerides, low HDL-C, raised blood pressure, or elevated fasting plasma glucose. ALT and AST were considered elevated at values >33 IU/L in males and >25 IU/L in females. as per AASLD practice guidelines[10]."

All patients underwent transient elastography (TE) using the FibroScan 530 Compact (Echosens, Paris, France), performed by a single experienced operator. Liver stiffness measurements (LSM) and controlled attenuation parameter (CAP) values were recorded. At least 10 valid LSMs were obtained per patient, with a required success rate >60% and interquartile range/median <30% to ensure measurement reliability. Based on established thresholds, significant fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4) were defined by LSM values of ≥7.0 kPa, ≥8.7 kPa, and ≥11.5 kPa, respectively. CAP values >233 dB/m indicated hepatic steatosis, with mild (234 - 269 dB/m), moderate (270 - 300 dB/m), and severe (>301 dB/m) steatosis (EASL clinical practice guidelines)[11] further categorised. MASH was defined as disease progression in MASLD patients who had elevated ALT levels (more than 6 months) or significant fibrosis[12]. The Fibrosis-4 (FIB-4) index was calculated using the formula: FIB-4 = (Age × AST)/(Platelet count × √ALT). The primary outcomes assessed were the proportion of diabetic patients with various grades of MAFLD and the correlation of liver stiffness with cardio-metabolic risk factors and the FIB-4 score. Statistical analysis was conducted using the SPSS version 26. Descriptive statistics were used to summarise the baseline characteristics of the study population. Associations between liver stiffness and clinical or biochemical variables including age, sex, BMI, duration of diabetes, dyslipidaemia, liver function tests, and FIB-4 index were analysed using univariate and multivariate regression models.

"APRI score was calculated as: "{AST (IU/L)/upper normal limit of AST (IU/L)}/platelet count (10^9/L)" "APRI was calculated as a validated non-invasive marker of fibrosis. An APRI >0.7 indicated significant fibrosis, ≥1.0 suggested progression to F3, and ≥2.0 indicated cirrhosis, based on a 2024 meta-analysis[13]". Fatty Liver Index (FLI) was calculated as a validated non-invasive marker of fibrosis and steatosis, which varies between 0 and 100. A score of FLI ≥60 was defined as having fatty liver, whereas FLI score <60 was inconclusive or non-fatty liver[14]. FIB-4 score <1.3 - rules-out advanced fibrosis, 1.3 - 2.67 ⇒ indeterminate zone, ≥2.67 ⇒ suggests advanced fibrosis[11].

Sample size calculation

Sample size estimation was performed using the OpenEpi, Version 3.0, open-source calculator (SSPropor). For a finite population size of 1,000,000 (N), with a hypothesized outcome frequency of 50% ± 8% (p), absolute precision of 8% (d), and a design effect (DEFF) of 1, the sample size was calculated using the formula: n = [DEE*Np(1-p)]/[(d2/Z21-≥ /2*(N-1)+p*(1-p)]. Considering the loss of data of 10%; adjusted sample size was 151 - 10% of (151) = 136. rounded off to 135.

Results

Among the 135 patients with T2DM, the prevalence of Metabolic Associated Fatty Liver Disease (MAFLD) was 67.4% (n = 91). The study cohort had female (62.2%) predominance as compared to males (37.8%), with a female-to-male ratio of 1.64:1. Participants were stratified into MAFLD (n = 91) and non-MAFLD (n = 44) groups. No statistically significant associations were identified between MAFLD and gender (p = 0.8144) as well as with age group (p = 0.3306). But the association of MAFLD was significant with BMI; indicating higher incidence of MAFLD with overweight and obese category (p = 0.0365) (Table I). Patients with MAFLD showed significantly higher liver stiffness values compared to non-MAFLD individuals (p <0.001) (Table II), Post-hoc analysis showed significant differences in LSM values between normal versus advanced fibrosis, normal versus cirrhosis, and significant fibrosis versus cirrhosis groups (p <0.05). The prevalence of metabolic syndrome was significantly higher in the MAFLD group (74.5%; n = 82) compared to the non-MAFLD group (25.5%; n = 28, p = 0.0001) (Table III).

Anthropometric and haemodynamic parameters reported no significant association between MAFLD and non-MAFLD groups (p >0.05). Among glycaemic parameters, MAFLD group had high random blood sugar (224.35 ± 69.47 mg/dL versus 181.64 ± 94.03 mg/dL, p = 0.0035) and HbA1c levels (9.58 ± 2.25 mmol/mol versus 7.78 ± 1.86 mmol/mol, p <0.0001). Regarding lipid profiles, triglyceride levels were significantly elevated in the MAFLD group (201.13 ± 92.28 mg/dL versus 169.48 ± 74.11 mg/dL, p = 0.0492), whereas no significant association was reported among total lipid, HDL, and LDL levels. Haematological parameters showed no significant association between MAFLD and non-MAFLD, except lymphocyte counts which were significantly higher in the MAFLD group (31.05 ± 6.95 versus 28.20 ± 8.45, p = 0.0396). Liver function test parameters did not reveal significant differences between the groups, including total bilirubin, direct bilirubin, SGOT, SGPT, ALP, total protein, serum albumin, and serum globulin levels. ALP levels were slightly higher in the MAFLD group (165.21 ± 56.85 IU/L versus 144.68 ± 59.99 IU/L, p = 0.055), though this did not reach statistical significance (Table IV).

Table I: Comparison of baseline characteristics of T2DM patients with respect to MAFLD.

Variables	MAFLD (N = 91)		Non-MAFLD (N = 44)		p-value
	N	%	N	%	
Gender					
Male	35	68.6	16	31.4	0.8144
Female	56	66.7	28	33.3	
Age Group					
35 - 49 years	44	65.7	23	34.3	0.3306
50 - 59 years	29	76.3	9	23.7	
≥60 years	18	60.0	12	40.0	
BMI					
18.5 - 24.9 (Kg/m^2)	32	56.1	25	43.9	**0.0365**
25.0 - 29.9 (Kg/m^2)	36	80.0	9	20.0	
≥30.0 (Kg/m^2)	23	69.7	10	30.3	

Table II: Liver stiffness measurement in T2DM patients with respect to MAFLD.

Liver stiffness measurement	MAFLD (N = 91)		Non-MAFLD (N = 44)		p-value
	N	%	N	%	
Normal (kPa)	23	42.6	31	57.4	**p <0.001**
Significant liver fibrosis (kPa)	18	58.1	13	41.9	
Advanced liver fibrosis (kPa)	29	100.0	0	0.0	
Cirrhosis (kPa)	21	100.0	0	0.0	
Comparison					**p-value**
Normal *versus* Significant fibrosis					(p >0.05)
Normal *versus* Advanced fibrosis					**<0.05**
Normal *versus* Cirrhosis					**<0.05**
Significant fibrosis *versus* Advanced fibrosis					**<0.05**
Significant fibrosis *versus* Cirrhosis					**<0.05**
Advanced fibrosis *versus* Cirrhosis					ns (p >0.05)

Table III: Association of metabolic syndrome in T2DM patients with respect to MAFLD.

Metabolic Syndrome	MAFLD (N = 91)		Non-MAFLD (N = 44)		p-value
	N	%	N	%	
Present	82	74.5	28	25.5	**0.0001**
Absent	9	36.0	16	64.0	

Table IV: Comparison of laboratory parameters in T2DM patients with respect to MAFLD.

	MAFLD (N = 91)	Non-MAFLD (N = 44)	p-value
Anthropometric parameters			
Waist Circumference (cm)	95.51 ± 12.55	92.65 ± 12.59	0.2172
Hip Circumference (cm)	100.11 ± 13.68	97.59 ± 15.83	0.3426
Blood pressure measurement			
Systolic blood pressure (mmHg)	133.03 ± 16.37	128.86 ± 14.58	0.1533
Diastolic blood pressure (mmHg)	81.11 ± 11.02	78.55 ± 9.70	0.1911
Glycaemic parameters			
Random Blood Sugar (mg/dL)	224.35 ± 69.47	181.64 ± 94.03	**0.0035**
HbA1c (mmol/mol)	9.58 ± 2.25	7.78 ± 1.86	**<0.0001**
Haematological parameters			
Haemoglobin (g/dL)	12.86 ± 2.11	13.18 ± 1.58	0.3742
Platelets (10^9/μL)	2.33 ± 0.88	2.24 ± 0.96	0.5897
RBC (Cells/μL)	4.98 ± 3.82	4.63 ± 0.55	0.5471
PCV (%)	39.74 ± 10.36	39.28 ± 4.16	0.7774
MCV (fl)	80.50 ± 11.18	82.25 ± 10.39	0.3848
TLC (cells/μL)	7306.02 ± 2121.80	7527.05 ± 2026.36	0.5659
Neutrophils (cells/μL)	62.10 ± 7.92	62.06 ± 12.78	0.9822
Lymphocytes (cells/μL)	31.05 ± 6.95	28.20 ± 8.45	**0.0396**
Lipid Profile			
Total lipid (mg/dL)	226.48 ± 101.03	194.68 ± 100.44	0.0882
HDL (mg/dL)	41.31 ± 11.26	40.75 ± 10.38	0.7817
LDL (mg/dL)	131.24 ± 43.68	124.86 ± 71.38	0.5226
Triglycerides (mg/dL)	201.13 ± 92.28	169.48 ± 74.11	**0.0492**
Liver function test			
Total bilirubin (mg/dL)	0.66 ± 0.12	0.8 ± 0.77	0.0917
Direct bilirubin (mg/dL)	0.24 ± 0.07	0.25 ± 0.16	0.6138
SGOT (IU/L)	31.42 ± 17.18	29.36 ± 20.21	0.5390
SGPT (IU/L)	34.63 ± 20.37	29.43 ± 17.18	0.1466
ALP (IU/L)	165.21 ± 56.85	144.68 ± 59.99	0.055
Total Protein (g/dL)	7.64 ± 0.63	7.68 ± 0.67	0.7354
Serum albumin (g/dL)	4.5 ± 0.56	4.44 ±0.54	0.5560
Serum Globulin (g/dL)	3.14 ±0.4	3.22 ± 0.42	0.2858

The Fib-4 score, the APRI score showed no significant difference between the MAFLD and non-MAFLD groups (p >0.05). However, the Fatty Liver Index (FLI) was significantly higher in the MAFLD group (62.8 ± 23.7) compared to the non-MAFLD group (48.8 ± 25.5, p = 0.0021) (Table V).

Table V: Fib 4 score, APRI score and fatty liver index in T2DM patients with respect to MAFLD.

Variables	MAFLD (N = 91)	Non-MAFLD (N = 44)	p-value
Fib 4 score	1.52 ± 1.37	1.40 ± 0.93	0.6005
APRI Score	0.65 ± 0.63	0.59 ± 0.48	0.5779
Fatty liver index (FLI)	62.8 ± 23.7	48.8 ± 25.5	**0.0021**

Discussion

Metabolic Associated Fatty Liver Disease (MAFLD) previously Non-alcoholic fatty liver disease is increasingly recognised as a major health concern, particularly among individuals with T2DM. This study highlights the intricate relationship between MAFLD and cardiometabolic risk factors, emphasizing the importance of early identification and management in diabetic patients. The incidence of MAFLD in the present study was found to be 67.4%. While Kosmalski *et al* reported a higher MAFLD incidence of 71%[15]. Studies by Choudhary *et al*, Agarwal *et al*, and Kalra *et al*, reported a lower incidence of MAFLD, at 55.7%, 57.2%, and 56.5%, respectively[16-18]. These variations in prevalence may be attributed to differences in study populations (e.g., sample size, demographics), diagnostic criteria (e.g., biopsy vs. imaging), and regional metabolic profiles (e.g., dietary habits, genetic predispositions). Nonetheless, the consistently high prevalence across these studies underscores the need for proactive screening for MAFLD in patients with T2DM.

Metabolic syndrome is a well-recognised risk factor for MAFLD, driven by shared pathophysiological mechanisms such as insulin resistance, obesity, and dyslipidaemia. In the present study, metabolic syndrome was significantly more prevalent in the MAFLD group (74.5%) compared to the non-MAFLD group (25.5%; p = 0.0002), reinforcing the strong association between these conditions. This finding is consistent with existing literature, which suggests that metabolic syndrome not only increases the risk of MAFLD but also contributes to disease progression, leading to fibrosis and potential liver-related complications. Insulin resistance, a hallmark of metabolic syndrome, promotes hepatic fat accumulation by increasing de novo lipogenesis and impairing lipid clearance, thereby exacerbating MAFLD severity. Additionally, obesity and dyslipidaemia further contribute to liver steatosis and inflammation, creating a pro-fibrotic environment. Our results are consistent with Agarwal *et*

al, who also reported the higher prevalence of metabolic syndrome in the MAFLD subgroup compared to those without MAFLD (61.9% vs. 13.2%, p <0.001). Despite no statistically significant differences in other anthropometric parameters (p >0.05), the MAFLD group exhibited a significantly higher mean BMI (27.3 ± 5.1 kg/m^2) compared to the non-MAFLD group (25.96 ± 5.24 kg/m^2; p = 0.0365), reinforcing obesity as a key contributing factor in MAFLD development. Our findings align with those of Choudhary *et al*, and Kosmalski *et al*, who also reported significant differences in anthropometric parameters between individuals with and without MAFLD[15,16].

Dyslipidaemia is a well-established metabolic abnormality in MAFLD, characterised by elevated triglycerides, increased LDL cholesterol, and reduced HDL cholesterol. These lipid disturbances contribute to hepatic fat accumulation, insulin resistance, and inflammation, all of which play a critical role in MAFLD pathogenesis. In our study, total lipid levels were elevated in the MAFLD group (226.48 ± 101.03 mg/dL) compared to the non-MAFLD group (194.68 ± 100.44 mg/dL; (p = 0.0882). While this suggests a trend toward lipid dysregulation in MAFLD patients, the lack of statistical significance may be attributed to inter-individual metabolic variability, dietary factors, or sample size limitations. Notably, triglyceride levels were significantly higher in the MAFLD group (201.13 ± 92.28 mg/dL versus 169.48 ± 74.11 mg/dL, p = 0.0492). This finding reinforces the strong association between hypertriglyceridaemia and MAFLD, as elevated triglycerides contribute to hepatic lipid accumulation, oxidative stress, and the progression of liver disease. Increased triglyceride levels are often a marker of insulin resistance, a key driver of MAFLD development. Additionally, LDL cholesterol levels were slightly elevated in the MAFLD group, but the difference was not statistically significant. While LDL is known to contribute to cardiovascular risk and liver fat deposition, its impact on MAFLD progression were less pronounced compared to triglycerides. Other metabolic factors, such as insulin resistance and inflammation, may play a more dominant role in the lipid dysregulation observed in MAFLD. Liver function tests (SGOT, SGPT, ALP) showed elevated levels in MAFLD patients; however, these differences did not reach statistical significance, suggesting that many cases in our cohort may represent early-stage MAFLD without substantial liver damage.

The FIB-4 and APRI scores are widely used non-invasive clinical tools for assessing liver fibrosis, particularly in MAFLD patients, as they help estimate fibrosis severity without the need for liver biopsy. These indices are calculated using routine biochemical and clinical parameters, making them practical for use in clinical settings. In our study, the mean FIB-4 and APRI scores were slightly higher in the MAFLD group compared to the non-MAFLD group; however, the differences did not reach statistical significance. While this suggests a possible trend toward increased fibrosis risk in MAFLD patients, the lack of statistical significance may be attributed to sample size limitations, inter-individual variability, or the early-stage nature of fibrosis in some patients. Liver Stiffness Measurement (LSM) and Fatty Liver Index (FLI) are valuable non-invasive tools for assessing liver fibrosis and hepatic steatosis, respectively. LSM, typically measured using elastography techniques, evaluates fibrosis severity by detecting liver stiffness, which increases as fibrosis progresses, making it particularly useful for identifying high-risk MAFLD patients. FLI, a metabolic score derived from clinical and biochemical parameters such as BMI, triglycerides, gamma-glutamyl transferase (GGT), and waist circumference, serves as an effective screening tool for hepatic steatosis, especially in high-risk populations like individuals with T2DM. Both markers offer a cost-effective, non-invasive approach to MAFLD assessment, reducing the need for liver biopsy and facilitating early diagnosis and management. Our study found a significant association between LSM and fibrosis severity in MAFLD patients, reinforcing its role as a reliable fibrosis assessment tool. This finding aligns with Esteban *et al,* who reported that T2DM patients with MAFLD had higher median liver stiffness (5.6 kPa [4.5 - 7.3]) compared to non-MAFLD individuals (4.8 kPa [4.2 - 5.8], p = 0.004), suggesting an increased risk of fibrosis progression in MAFLD patients, emphasizing the need for early detection and monitoring[19]. Similarly, FLI was significantly higher in the MAFLD group, with 77.8% of MAFLD patients having an FLI ≥60 compared to 60.5% in the non-MAFLD group (p = 0.0365), and the mean FLI was also significantly elevated in MAFLD individuals (62.8 ± 23.7 versus 48.8 ± 25.5, p = 0.0021).

Conclusion

This study confirms the high prevalence of MAFLD in T2DM patients and its strong association with metabolic syndrome, hypertriglyceridaemia, and impaired glucose metabolism. Non-invasive markers like the Fatty Liver Index and liver stiffness measurement proved useful in identifying at-risk individuals. Further research with larger, more diverse cohorts and longitudinal designs is needed to confirm these findings and explore the long-term implications of FLI in MAFLD progression and management.

Ethics statement and Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. Informed consent was obtained from the patients regarding the use of their clinical data. All the patient specific data was kept in strict confidence.

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ORIGINAL ARTICLE

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Effect of Haemodialysis on Pulmonary Functions in Patients of End-Stage Renal Disease

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Abstract

***Introduction:** Chronic kidney disease (CKD) is an irreversible and progressive disorder marked by the gradual loss of kidney function, ultimately leading to end-stage renal disease (ESRD)[1]. CKD affects virtually all organ systems, with the respiratory system being one of the most impacted[3]. ESRD patients frequently experience a range of pulmonary complications such as pulmonary oedema, pleural effusion, acute respiratory distress syndrome, pulmonary fibrosis, calcification, pulmonary hypertension, haemosiderosis, pleural fibrosis, and sleep apnoea syndrome[4]. These respiratory issues significantly contribute to the overall morbidity.*

***Aim:** To determine effects of haemodialysis on pulmonary functions in patients with end-stage renal disease on haemodialysis.*

***Methods:** This hospital-based cross-sectional observational study examined 88 ESRD patients on maintenance haemodialysis at SN Medical College, Agra, from January 2023 to June 2024. All participants undergoing maintenance haemodialysis for >3 months were eligible for participation in study. Pulmonary function tests were conducted one hour before and after dialysis to assess the impact of haemodialysis on respiratory function.*

***Result:** The study included 88 ESRD patients on maintenance haemodialysis, with a mean age of 48.60 ± 10.98 years and a male predominance (52.30%). Post-haemodialysis, significant improvements were observed in pulmonary functions: FVC increased from 24.78 ± 7.69% to 58.95 ± 11.70%, and FEV1 from 36.12 ± 9.39% to 52.07 ± 10.70%. Our results suggest that performing haemodialysis in patients with end-stage renal disease (ESRD) improves pulmonary functions after dialysis sessions.*

***Conclusion:** Haemodialysis significantly enhances pulmonary function in ESRD patients, improving FVC, FEV1, and the FEV1/FVC ratio, highlighting its role in mitigating respiratory impairments.*

Introduction

Chronic kidney disease (CKD) is an irreversible and progressive disorder marked by the gradual loss of kidney function, ultimately leading to end-stage renal disease (ESRD)[1]. Patients with ESRD require renal replacement therapy through dialysis – either haemodialysis or peritoneal dialysis or kidney transplantation to survive[2]. CKD affects virtually all organ systems, especially in its advanced stages, with the respiratory system being one of the most impacted[3]. ESRD patients frequently experience a range of pulmonary complications such as pulmonary oedema, pleural effusion, acute respiratory distress syndrome, pulmonary fibrosis, calcification, pulmonary hypertension, haemosiderosis, pleural fibrosis, and sleep apnoea syndrome[4]. These respiratory issues significantly contribute to overall morbidity and reduced quality-of-life.

Haemodialysis improves pulmonary function by removing excess body fluid, reducing water content in the lungs, and decreasing pulmonary capillary permeability. This helps alleviate pulmonary oedema and pleural effusion, enhancing lung compliance and reducing airway resistance, thereby improving overall respiratory function in ESRD patients. This study investigates the short-term effects of haemodialysis on pulmonary function, using pulmonary function tests (PFTs) to assess the respiratory benefits in patients undergoing maintenance haemodialysis. The assessment of the role of haemodialysis in improving pulmonary function is pivotal and continues to be a field of research.

Material and Methods

The study was a hospital-based cross-sectional, observational study conducted at the Department of

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Medicine, SN Medical College, Agra, from January 2023 to June 2024. It involved 88 patients with end-stage renal disease who had been on maintenance haemodialysis for more than three months. Participants aged 18 - 75 years, of both sexes, who provided written informed consent and were clinically stable were included. Exclusion criteria included a history of smoking, chronic lung disease, infections, acute renal injury, heart failure, myopathies, arrhythmias, tuberculosis, or cirrhosis. Patients who were debilitated and unable to co-operate with spirometric maneuvers were also excluded. The study received ethics clearance from the Department of Medicine's Ethics Committee, and patients were free to withdraw at any time.

Conventional Haemodialysis (HD) was performed using Fresenius Medical Care 4008-S machine, with four-hour sessions, a dialysate infusion rate of 500 mL/min, and blood flow rates between 300 and 350 ml/min. A bicarbonate buffer and a biocompatible membrane were used.

Detailed patient history, clinical examinations, and demographic data (age, sex, BMI, pre- and post-HD weight, smoking status, and presence of diabetes, hypertenison) were collected .GFR was measured using the Cockcroft and Gault formula. Fasting peripheral blood samples were obtained before midweek HD sessions for standard biochemical analyses. These analyses included CBC, serum bilirubin, albumin, ALT/AST, serum creatinine, urea, electrolytes, total protein, ferritin, calcium, phosphorus, intact parathormone (PTH), and haemoglobin. Pulmonary function tests, using a Medicaid Spirometer, were performed one hour before and after dialysis to measure FEV1, FVC, PEFR, and the FEV1/FVC ratio, categorizing lung functions into normal, restrictive, or obstructive pathologies. Additional data included ECG, abdominal ultrasonography, and chest X-ray PA view.

Data were organised in Excel and analysed with SPSS version 25.0 using descriptive and inferential statistics, including t-tests, ANOVA, and chi-square tests, with a significance level of $p < 0.05$. Results were presented in graphs and tables.

Results

In this study of 88 patients, majority were aged 41 - 50 years (36.3%), followed by 51 - 60 years (30.7%). The mean age was 48.60 ± 10.98 years. Most patients were male (52.3%), from lower socio-economic status (58.0%), and had hypertension (90.9%). 59.1% were of normal weight, 31.8% were overweight, and 9.1% underweight.

Most patients had been on haemodialysis for 1 to 5 years (51.13%).

Table I: Baseline characteristics of study participants.

Age Group (Years)	Frequency (n = 88)	Percentage	Mean±SD (Minimum - Maximum)
18 - 30	5	5.7%	48.60 ± 10.98 (20 - 70 years)
31 - 40	11	12.5%	
41 - 50	32	36.3%	
51 - 60	27	30.7%	
>60	13	14.8%	
Gender			
Male	46	52.3%	
Female	42	47.7%	
Socio-economic Status			
Lower	51	58.0%	
Middle	37	42.0%	
Hypertension			
Yes	80	90.9%	
No	8	9.1	
BMI (kg/m^2)	**Frequency (n = 88)**	**Percentage**	
Underweight (18.5)	8	9.1%	
Normal weight (18.5 - 22.9)	52	59.1%	
Overweight/obese (>22.9)	28	31.8%	
Duration of Haemodialysis			
3 Months - 6 Months	9	10.22%	
>6 Months - 1 Years	27	30.68%	
1 Year - 5 Years	45	51.13%	
>5 Years	7	7.95%	

Table II: Baseline anthropometric parameters of study participants.

Anthropometric Parameters	Mean±SD	Minimum	Maximum
Weight (in kg)	60.41 ± 7.88	45.6	88.0
Height (in cm)	163.7 ± 6.72	140.1	181.2
BMI (Kg/m^2)	22.60 ± 3.30	15.8	31.7

Table III shows mean of various pre-haemodialysis parameters.

Table III: Pre-haemodialysis Laboratory parameters.

Pre-Haemodialysis	Mean±SD	Minimum	Maximum
Estimated GFR (mL/min/1.73 m^2)	8.34 ± 1.77	4.4	11.7
Fasting Blood Glucose (mg/dL)	110.75 ± 28.64	74	251
HB (g/dL)	9.08 ± 1.16	6.5	12.2

TLC Count (cells/µL)	7129.44 ± 2241.44	3088	13241
Platelet Count (lakhs/µL)	1.86 ± 0.89	1.0	5.1
Albumin (g/dL)	4.32 ± 0.73	3.3	6.6
Bilirubin (mg/dL)	0.53 ± 0.09	.4	.7
ALT (U/L)	41.15 ± 19.93	11.3	96.5
AST (U/L)	58.96 ± 11.98	30.7	85.1
Calcium (mg/dL)	9.10 ± 0.33	8.4	9.8
Phosphorus (mg/dL)	5.15 ± 0.86	3.2	6.6
Sodium (mmol/L)	138.14 ± 0.58	136.8	140.2
PTH (pg/mL)	568.33 ± 174.50	194.2	1014.3

Statistically significant pre-to-post-haemodialysis changes were observed in levels of serum urea and serum creatinine (Table IV). Urea decreased from 140.48 ± 19.69 mg/dL to 64.84 ± 12.89 mg/dL (p = 0.046), and creatinine decreased from 9.17 ± 1.13 mg/dL to 5.66 ± 1.12 mg/dL (p <0.001).

The mean bicarbonate level increased from 20.42 ± 1.01 mmol/L before haemodialysis to 27.61 ± 5.71 mmol/L after haemodialysis, though this change was not statistically significant (p = 0.207).

Table IV: Comparing effects of haemodialysis on kidney functions in patients of end-stage renal disease before and after haemodialysis.

Kidney Functions	Pre-Haemodialysis (Mean±SD)	Post-Haemodialysis (Mean±SD)	p-value
Urea (mg/dL)	140.48 ± 19.69	64.84 ± 12.89	**0.046**
Creatinine (mg/dL)	9.17 ± 1.13	5.66 ± 1.12	**0.000**
Bicarbonates (mmol/L)	20.42 ± 1.01	27.61 ± 5.71	0.207

Before haemodialysis, the mean forced vital capacity (FVC) was 24.78 ± 7.69%, which significantly improved to 58.95 ± 11.70% after treatment (mean difference: - 34.00%, t = - 19.40, p <0.001). Forced expiratory volume in one second (FEV1) also increased from 36.12 ± 9.39% to 52.07 ± 10.70% (mean difference: - 16.47%, t = - 12.13, p <0.001). The FEV1/FVC ratio improved from 69.22 ± 9.78 to 82.0 ± 7.00 (mean difference: - 12.76, t = - 8.72, p <0.001). Additionally, peak expiratory flow rate (PEFR) rose from 45.10 ± 12.24 L/min to 52.35 ± 10.24 L/min (mean difference: - 7.47 L/min, t = - 10.22, p <0.001). All changes were statistically significant, indicating improved pulmonary function post-haemodialysis.

Table V: Comparing effects of haemodialysis on pulmonary functions in patients of end-stage renal disease before and after haemodialysis

Pulmonary Functions	Pre-Haemodialysis	Post-Haemodialysis	Mean Difference	t value	p-value
FVC (%)	24.78 ± 7.69	58.95 ± 11.70	- 34.00 ± 16.43	- 19.40	**<0.001**
FEV1 (%)	36.12 ± 9.39	52.07 ± 10.70	- 16.47 ± 12.73	- 12.13	**<0.001**
FEV1/FVC	69.22 ± 9.78	82.0 ± 7.00	- 12.76 ± 13.71	- 8.72	**<0.001**
PEFR (L/min)	45.10 ± 12.24	52.35 ± 10.24	- 7.47 ± 6.86	- 10.22	**<0.001**

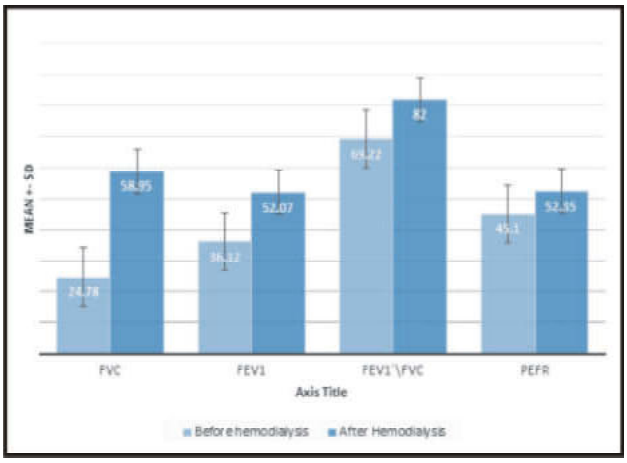

Fig. 1: *Mean pulmonary functions before and after haemodialysis.*

Pre-haemodialysis, no significant correlations were found between pulmonary function parameters across age groups. Post-haemodialysis. The FEV1/FVC ratio showed a significant improvement across age groups, indicating better pulmonary function after haemodialysis (p <0.05). Other parameters also showed improvement, but the differences were not statistically significant.

Table VI: Comparing effects of haemodialysis on pulmonary functions in patients of end-stage renal disease before and after haemodialysis with age.

Age (years)		N	Pulmonary Functions			
			FEV1 Mean±SD	FVC Mean±SD	FEV1/FVC Mean±SD	PEER Mean±SD
Pre-	≤30	5	41.06 ± 2.64	29.34 ± 2.20	72.22 ± 12.08	48.02 ± 5.91
Haemodialysis	31 - 40	11	39.93 ± 10.86	27.91 ± 11.70	70.64 ± 5.70	47.50 ± 14.25
	41 - 50	32	35.74 ± 9.59	24.09 ± 7.22	69.0 ± 11.90	44.70 ± 13.42
	51 - 60	27	34.89 ± 10.73	23.90 ± 7.63	69.0 ± 9.75	44.50 ± 11.40
	>60	13	34.49 ± 4.65	23.88 ± 5.59	67.88 ± 6.15	44.14 ± 12.16
	Total	88	36.12 ± 9.39	24.78 ± 7.69	69.22 ± 9.78	45.10 ± 12.24
p-value			0.399	0.364	0.918	0.930
Post-	≤30	5	59.94 ± 6.94	68.26 ± 3.72	88.30 ± 7.68	59.78 ± 5.04
Haemodialysis	31 - 40	11	55.41 ± 7.63	64.24 ± 14.96	85.85 ± 6.40	57.77 ± 11.18

	41 - 50	32	52.78 ± 11.42	59.56 ± 11.94	84.12 ± 4.86	52.39 ± 12.40
	51 - 60	27	50.64 ± 12.01	56.42 ± 9.57	79.70 ± 6.58	49.86 ± 6.88
	>60	13	47.45 ± 7.11	54.68 ± 11.74	75.88 ± 7.22	49.98 ± 8.78
	Total	88	52.07 ± 10.70	58.95 ± 11.70	82.0 ± 7.00	52.35 ± 10.24
p-value			0.144	0.071	**<0.001**	0.087

Table VII: Correlation of pulmonary function Pre-haemodialysis and Post-haemodialysis.

Pre-haemodialysis		Post-haemodialysis			
		FVC	FEV1	FEV1/FVC	PEFR
FVC	Pearson's Correlation Co-efficient	-0.036	-0.142	-0.017	0.140
	p-value	0.736	0.188	0.874	0.193
FEV1	Pearson's Correlation Co-efficient	0.035	0.395**	0.004	**0.045**
	p-value	0.747	0.000	0.973	0.678
FEV1 / FVC	Pearson's Correlation Co-efficient	0.159	0.061	0.075	**0.011**
	p-value	0.138	0.575	0.489	0.918
PEFR	Pearson's Correlation Co-efficient	0.208	-0.247*	0.024	0.864**
	p-value	0.052	**0.020**	0.827	0.000

**Correlation is significant at the 0.05 level (2-tailed).*
***Correlation is significant at the 0.01 level (2-tailed).*

Discussion

End-stage renal disease (ESRD) progresses from chronic kidney disease (CKD) and necessitates renal replacement therapy, such as haemodialysis (HD) or peritoneal dialysis (PD), to sustain life[5]. Haemodialysis, which involves extracorporeal blood filtration, is essential for managing ESRD while patients await a kidney transplant. CKD patients often face respiratory issues, and dialysis can sometimes improve pulmonary functions.

Our study assessed the impact of haemodialysis on pulmonary function in ESRD patients, finding that the most affected age group was 41 - 50 years, with a mean age of 48.60 years The majority of participants were male (52.3%), coming from lower socio-economic backgrounds (58.0%), and had hypertension (90.9%). which was comparable to other studies like Yilmaz *et al*[6] who found the mean age of the study population to be 49.51 years and 51.8% were male in their study and Momeni *et al*[7] who reported the mean age as 42.40 years with 30 out of 50 patients being male. Most patients had a normal BMI, with some classified as overweight or underweight. Majority of patients were receiving haemodialysis for 1 - 5 years (51.13%). Mane *et al*[8] reported that out of 103 participants, 46 (44.66%) had been receiving haemodialysis for the preceding one to three years, whereas 41 (39.81%) had been receiving it for the preceding six to twelve months. Sharma *et al*[9] found that only 10% of the patients had been receiving haemodialysis for less than six months, whereas 45 patients (90%) were receiving it for 6 months-3 years.

We observed significant improvements in biochemical parameters post-haemodialysis, including notable decreases in urea and creatinine levels and an increase in bicarbonate levels, though the latter was not statistically significant.

Mane *et al*[10] reported that prior to haemodialysis, the mean urea was 140.48 mg/dL; this improved to 64.84 mg/dL. Before haemodialysis, the mean creatinine was 9.17 mg/dL; it was later improved to 5.66 mg/dL. In contrast, Steinhorst *et al*[11] noted a notable increase in renal function following 40 haemodialysis sessions.

Spirometric measures also showed significant post-dialysis improvements in FEV1(36.12% *versus* 52.07%), FVC (24.78% *versus* 58.95%), FEV1/FVC (69.22 *versus* 82.00) and PEFR (45.10 L/min *versus* 52.35 L/min) when compared from Pre-haemodialysis to Post-haemodialysis. Momeni *et al*[12] reported an increase in FEV1 and a significant decrease in FEV1/FVC after haemodialysis. Similarly, Hasan *et al*[13] observed that after haemodialysis, patients FEV1\FVC showed statistically significant improvements. Sharma *et al*[14] also showed similar findings in their study.

Our findings indicate a general decline in pulmonary function with increasing age, with younger CKD patients showing more pronounced improvements in pulmonary function post-haemodialysis, although the differences were not statistically significant ($p > 0.05$), except for the FEV1/FVC ratio, which showed a highly significant improvement ($p < 0.05$). Notably, FEV1 had a strong positive correlation with itself post-haemodialysis, but no significant correlations were found between FEV1 and other parameters. Before haemodialysis, PEFR exhibited a significant negative correlation with FEV1 and a significant positive correlation with itself (PEFR). After haemodialysis, PEFR continued to show a significant positive correlation with itself but no significant correlations with other parameters (FVC, FEV1/FVC).

Our results suggest that haemodialysis can positively impact pulmonary function in ESRD patients, supporting some studies while differing from others. The observed improvements in respiratory parameters may be attributed to reduced fluid overload and alleviated respiratory symptoms associated with renal failure. The discrepancies in findings across studies highlight the need for further research to comprehensively understand the effects of haemodialysis on respiratory health. Overall, haemodialysis appears beneficial in enhancing pulmonary function, offering potential relief from respiratory issues related to kidney failure.

Conclusion

Our study found that haemodialysis significantly improves both biochemical and spirometric parameters in ESRD patients. While pulmonary function declines with age, haemodialysis appears to benefit younger patients more, though not statistically significant. Overall, haemodialysis enhances pulmonary function, particularly for FVC, FEV1, FEV1/FVC ratio, and PEFR.

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ORIGINAL ARTICLE

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Clinical Profile of Patients with Refractory Hypothyroidism

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Abstract

***Introduction:** Hypothyroidism is one of the most prevalent endocrine illnesses. Some patients fail to achieve adequate suppression of Thyroid Stimulating Hormone (TSH) despite receiving Levothyroxine (LT4) in doses equal to or higher than 1.9 µg/Kg. This condition is known as refractory hypothyroidism (RH). To understand RH better, we conducted a cross-sectional study, analysing the clinical and laboratory profiles of such patients.*

***Methods:** RH patients on LT4 ≥1.9 µg/Kg bodyweight and TSH >5.5 µIU/mL were included in the study. Pregnant and lactating women were excluded. The participants were interviewed about timing of LT4 ingestion, use of any concomitant drugs, symptoms of overt hypothyroidism and symptoms of any GI diseases. Four item Morisky Medication Adherence Scale (MMAS-4) was used to assess the adherence to medication. Investigations included blood tests, DEXA scan, and a GI evaluation in case of GI symptoms.*

***Results:** The study included 60 patients, who were predominantly female (96.7%). Weight gain (90%) and fatigue (88.3%) were the most commonly reported symptoms of overt hypothyroidism. Poor adherence to therapy was observed in 68.33% participants based on MMAS-4, and 61.7% were on concomitant proton pump inhibitor (PPI). Upper GI endoscopy was performed on 26 participants, with 13.3% testing positive for Helicobacter pylori (H. pylori) infection. No cases of malabsorptive gastrointestinal diseases were identified.*

***Conclusion:** In cases of RH, non-pharmacological causes should be assessed first. Our findings indicate that poor adherence to therapy and concurrent use of PPI are the most frequent contributors to RH. Additionally, H. pylori infection was identified in a subset of patients, highlighting its potential role. Gastrointestinal disorders should also be thoroughly investigated, as they lead to RH.*

***Key words:** Refractory hypothyroidism, Thyroid stimulating Hormone, Levothyroxine.*

Introduction

Hypothyroidism is a common clinical condition that is caused by a deficiency of the thyroxine hormone. Hypothyroidism can be classified as primary (due to thyroid hormone deficiency), secondary [due to Thyroid stimulating hormone (TSH) deficiency], tertiary [due to Thyrotropin-releasing hormone (TRH) deficiency], and peripheral (extra-thyroidal). Levothyroxine (LT4) is the treatment of choice. Patients with clinical features of hypothyroidism, and with biochemical confirmation of overt hypothyroidism, are started on 1.5 - 1.8 µg LT4 per Kg of bodyweight[1]. Treatment targets include normalisation of TSH concentration and resolution of symptoms. However, some patients do not achieve adequate suppression of TSH despite receiving LT4 doses equal to or higher than 1.9 µg/kg. This condition is known as refractory hypothyroidism (RH).

Non-compliance to treatment, timing of LT4 ingestion relative to meals, concomitant use of other drugs such as proton-pump inhibitors (PPI), and pregnancy are the most common non-pathological cause of RH. Gastrointestinal (GI) diseases such as *Helicobacter pylori* (*H. pylori*) infection, inflammatory bowel disease (IBD), celiac disease, lactose intolerance, gastroparesis, etc., and poor conversion of tetraiodothyronine (T4) to triiodothyronine (T3) due to less effective deiodinase D2 enzyme, are the main pathological reasons behind RH[2]. We decided to carry out a cross-sectional study of RH patients presenting to a tertiary care hospital and describe the clinical and laboratory parameters of such individuals.

Methodology

This was a single centre, cross-sectional, observational study, carried out at a tertiary care teaching hospital in Western Maharashtra from April 2022 to April 2024. Adults who were on LT4 dose ≥1.9 µg per Kg bodyweight with serum TSH concentrations >5.5 µIU/mL were included. Pregnant and lactating women were excluded.

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The proportion of RH was taken as 10% among all patients with overt hypothyroidism who are on LT4 therapy[3]. Finite correction factor of 100 was applied (based on number of patients of RH likely to visit endocrine and medical OPD during the study period), and a sample size of 60 was calculated, for 95% confidence interval (CI).

The study participants were interviewed about timing of LT4 ingestion, use of any concomitant drugs, symptoms of overt hypothyroidism and symptoms of any GI diseases. Four item Morisky Medication Adherence Scale (MMAS-4) was used to assess the adherence to medication in the study participants[4]. A score of 0 or 1 was taken as poor adherence.

All study participants underwent the following investigations: complete blood count, liver function test, lipid profile, blood sugar fating, blood sugar post-prandial, and DEXA scan for whole body fat percentage. Patients with symptoms suggestive of GI diseases were subjected to an upper GI endoscopy along with Rapid Urease Test (RUT) and D2 biopsy if indicated. Written informed consent was taken from each participant. Ethical approval was obtained from institutional ethics committee.

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analysed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA). Data had been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests were used for a difference in mean involving independent samples or unpaired samples.

Results

In our study, total 60 patients were enrolled, out of which 58 (96.7%) were female and 2 (3.3%) were male. The clinical and biochemical characteristics of the study population is shown in Table I.

54 out of 60 participants reported the symptom of weight gain and 53 out of 60 participants reported the symptom of fatigue. Fig. 1 shows the various symptoms of overt hypothyroidism reported by the study participants.

Table I: Clinical and biochemical characteristics of the study population.

Parameter	Mean	Standard Deviation
Age (years)	40.7	± 12.2
Height (cm)	156	± 5.28
Weight (Kg)	74.62	± 7.19
BMI[$] (Kg/m^2)	30.91	± 3.20
TSH[#] (µIU/mL)	9.38	± 3.16
Thyroxine Dose (µg)	161.03	± 24.05
Thyroxine Dose (µg/ Kg bodyweight)	2.15	± 0.29
Duration of Treatment (years)	8.23	± 3.42
Haemoglobin (g/dL)	11.77	± 1.62
Total Bilirubin (mg/dL)	0.62	± 0.25
AST[€] (U/L)	34.18	± 8.68
ALT[¥] (U/L)	39.61	± 7.91
Fasting Blood Sugar (mg/dL)	123.7	± 30.34
Post-prandial Blood Sugar (mg/dL)	175.37	± 53.71
Total Cholesterol (mg/dL)	179.25	± 44.41
Triglycerides (mg/dL)	144.08	± 28.07
LDL[¶] (mg/dL)	92.85	± 34.90
HDL[£] (mg/dL)	52	± 7.45
Total Body Fat Percentage (%)	37.82	± 3.02

[$]BMI: Body Mass Index, [#]TSH: Thyroid Stimulating Hormone, [€]AST: Aspartate Aminotransferase [¥]ALT: Alanine Aminotransferase [¶]LDL: Low Density Lipoprotein [£]HDL: High Density Lipoprotein.

68.33% (n = 41) participants were found to have poor adherence to therapy based on MMAS-4. 61.7% (n = 37) participants were on concomitant PPI therapy. 5% (n = 3) patients gave history of ingesting food within 60 minutes of taking LT4.

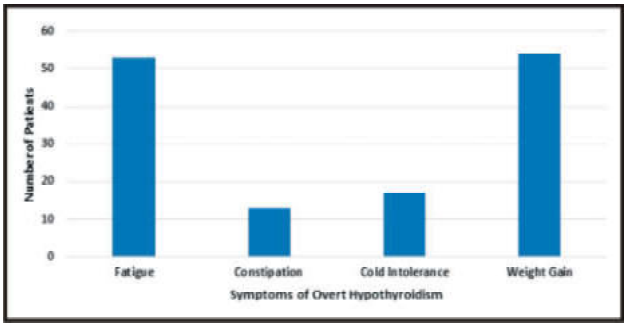

Fig. 1: *Symptoms of overt hypothyroidism in the study population.*

26 out of 60 study participants underwent upper GI endoscopy. 13.3% (n = 8) were found to have *H. pylori* infection by Rapid Urease Test (RUT). No patients were found to have any malabsorptive GI diseases.

Discussion

This cross-sectional observational study was carried out at a tertiary care teaching hospital in Western Maharashtra. The mean age of the study population was 40.7 ± 12.2 years and 96.7% of study participants were female. The commonest symptom of overt hypothyroidism reported by the participants, were weight gain (90%) and fatigue (88.3%). Symptoms of hypothyroidism are often non-

specific and show large variations. These may include fatigue, lethargy, cold intolerance, weight gain, constipation, and dry skin[5]. In a population based case-control study commonly reported symptoms by hypothyroid patients included tiredness (81%), and dry skin (63%)[6].

Mean LT4 dose among the study population was 161.03 ± 24.05 µg or 2.15 ± 0.29 µg/Kg bodyweight. A retrospective cohort study of 5749 hypothyroid patients showed a mean daily thyroxine dose of 1.14 µg/Kg bodyweight[7]. In patients with RH, TSH continues to be high despite a relatively higher dose of LT4. Monteiro *et al* evaluated ten female patients for RH and found that the baseline LT4 dosage ranged from 2.5 to 5.3 µg/Kg/day[8].

The mean BMI of the study population was 30.91 ± 3.20 Kg/m^2 and the mean total body fat percentage was 37.82 ± 3.02%. Hypothyroidism decreases the basal metabolic rate and causes decreased thermogenesis. It has also been shown to correlate with a higher BMI and a higher prevalence of obesity[9]. On the other hand obese individuals are also found to have high TSH and low free T4 levels. The underlying cause of these alterations in thyroid functions are not known; however, some scientists suggest an increased deiodinase activity leading to a high conversion rate of T4 to T3. This could be a defence mechanism in obese individuals for counteracting the accumulation of fat by increasing energy expenditure[10].

Poor adherence to LT4 therapy was very high among the study population (68.33%). Poor adherence is influenced by a complex interplay of factors, and despite extensive research into nearly 200 variables, including patient demographics, disease characteristics, and treatment regimens, no single factor reliably explains non-compliance. Communication breakdowns, especially in elderly patients with memory issues, unresolved concerns about side-effects or disbelief in the diagnosis are the common culprits[11]. Patients increasingly seek autonomy in decision-making, and healthcare providers must shift from persuasion to partnership, supporting informed choices rather than enforcing prescriptions. A cross sectional study of 337 patients on LT4 therapy in Lebanon, showed that 54.9% had low adherence to medication[12]. Using the 8-item Morisky Medication Adherence Scale (MMAS-8), Al Kindi *et al*, showed that among 400 hypothyroid patients; 157 (39.2%), 139 (34.8%), and 104 (26.0%) had low, medium, and high drug adherence, respectively[13].

Drugs like iron, calcium, statins and PPI can decrease the effectiveness of LT4 therapy and cause an increase in the patients' TSH concentration[14]. As patients are advised to take both LT4 and PPI before breakfast, they invariably end up taking both these medications concomitantly. A systematic review showed that concomitant use of LT4 and PPI causes a significant increase in TSH concentration[15]. In our study, we found that 61.7% participants were on concomitant PPI therapy along with LT4.

13.3% of the study participants were found to have *H. pylori* infection by RUT. Bugdaci *et al*, reported that in patients with hypothyroidism, chronic *H. pylori* gastritis may be responsible for an inadequate response to treatment[16]. However, routine testing for *H. pylori* is not recommended in patients with RH, until unless they are symptomatic.

Our study is a single centre study with a small sample size. This is a major limitation of the study. We did not conduct a Levothyroxine absorption test as there is no gold standard protocol for the same.

Conclusion

To conclude, we found that RH patients have very high BMI, with commonest presenting symptoms being weight gain and fatigue. Poor adherence and concomitant use of PPI were the most prevalent cause for ineffective therapy among these patients. A subset of patients was also found to have *H. pylori* infection. The physician should review the medications and compliance history in patients presenting with RH. Once non-pharmacological causes have been ruled, a history of GI diseases should be taken and patient should be evaluated for *H. pylori* infection, IBD, Celiac disease and other digestive tract disorders.

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ORIGINAL ARTICLE

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Correlation of Neutrophil- to-Lymphocyte Ratio with Functional Ability in COPD Patients

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Abstract

***Introduction:** Chronic Obstructive Pulmonary Disease (COPD) remains a leading cause of illness and death worldwide, especially in low- and middle-income countries like India. It is marked by chronic respiratory symptoms and progressive airflow obstruction. In recent years, systemic inflammation has gained recognition as a central factor in COPD progression. Among inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a potential indicator of disease severity and prognosis. This study aimed to evaluate the relationship between NLR and clinical, radiological, and functional parameters in patients with stable COPD.*

***Methods:** A cross-sectional study was conducted at LLRM Medical College and SVBP Hospital, Meerut, during 2023 – 2024. Sixty-one stable COPD patients aged 35 years or older were enrolled based on post-bronchodilator $FEV_1/FVC < 70\%$ and absence of exacerbation in the prior two months. All patients underwent clinical assessment, spirometry, six-minute walk test (6MWT), chest imaging, and laboratory tests including complete blood count and CRP. NLR was calculated and correlated with clinical indices, GOLD stage, and BODE index.*

***Results:** The mean age was 64.2 years, and 72% were male. The average NLR was 4.36. Most patients were in GOLD 3 category. NLR showed a negative correlation with FEV_1, FEV_1/FVC, 6MWT distance, and SpO, and a positive correlation with CRP and BODE index. NLR levels increased consistently with GOLD stage ($p < 0.001$).*

***Conclusion:** NLR appears to be a simple, cost-effective marker that correlates well with COPD severity and functional decline. It may aid in risk stratification and clinical decision-making.*

***Key words:** Chronic obstructive pulmonary disease, neutrophil-to-lymphocyte ratio.*

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable condition marked by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities, often caused by exposure to harmful particles or gases. It is a major global health issue and one of the leading causes of death worldwide. According to the WHO[1], approximately 65 million people suffer from moderate to severe COPD, with most deaths occurring in low- and middle-income countries, particularly in India and China, which together account for 66% of global COPD mortality[2].

India bears a significant COPD burden, with 55.3 million cases reported in 2016[3]. COPD prevalence increases with age and varies by region – ranging from 4.36% in Bangalore to 10% in Delhi. Key risk factors include smoking, biomass fuel use, air pollution, occupational hazards, aging, socio-economic status, and past tuberculosis. COPD also imposes a heavy economic and health-related quality of life burden and is the leading cause of disability among chronic respiratory diseases.

Systemic inflammation plays a central role in COPD pathogenesis and progression. Elevated levels of inflammatory markers such as c-reactive protein (CRP), interleukins, TNF-α, and leukocytes (neutrophilia and leukopenia) are frequently observed. Higher Neutrophil-to-Lymphocyte-Ratio (NLR) levels correlate with disease severity, reduced exercise tolerance, increased dyspnoea, and greater risk of hospitalisation and mortality.

Material and Methods

This cross-sectional study was conducted between 2023 and 2024 in the Department of Medicine at LLRM Medical College and SVBP Hospital, Meerut, Uttar Pradesh. It included patients aged 35 years and above diagnosed with Chronic Obstructive Pulmonary Disease (COPD) who were attending the Medicine and Chest outpatient departments.

All participants were evaluated through a detailed clinical history, including the duration of disease and personal habits such as smoking and alcohol use. A structured proforma was used to document history, physical findings, and investigation results. Each subject underwent a complete

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clinical examination and laboratory workup to ensure eligibility based on inclusion and exclusion criteria.

The inclusion criteria encompassed patients with COPD, defined by a forced expiratory volume in one second (FEV1) ratio forced vital capacity (FVC) less than 70% of the predicted value, and who had no exacerbation in the preceding two months. Individuals with conditions that could interfere with study outcomes – such as infections, recent myocardial infarction, heart failure, malignancies, end-stage renal or liver disease, rheumatoid arthritis, or orthopedic limitations – were excluded.

All enrolled patients underwent a series of diagnostic tests, including routine hematological and biochemical panels, chest X-ray (PA view), ECG, spirometry, and six-minute walk distance (6MWD) test. Additional parameters assessed included body mass index (BMI), BODE index, C-reactive protein (CRP) levels, and total leukocyte count (TLC), with a focus on the neutrophil-to-lymphocyte ratio.

The minimum sample size was calculated based on a 2012 study in the *Journal of Thoracic Disease*, using a COPD prevalence of 4.1%, with a 5% absolute precision and 95% confidence interval. Applying the standard statistical formula, the required sample size was estimated to be 61 participants.

Results

The present study primarily included individuals in the older age groups, with the majority (42.62%) between 60 and 69 years. Around 31.15% were below 60 years, while 22.95% belonged to the 70-79-year age range. Only 3.28% of the participants were over 80. The average age was 64.23 years, suggesting that COPD remains a condition largely affecting the elderly.

There was a clear male predominance, with 72.13% of the study population being male, and only 27.87% female. This gender imbalance may reflect known risk factor patterns such as higher smoking prevalence and occupational exposures among men.

Blood profile analysis showed a mean polymorphonuclear cell percentage of 69.45%, while lymphocytes averaged 18.17%. The neutrophil-to-lymphocyte ratio (NLR), had a mean value of 4.36 ± 1.82, indicating underlying chronic inflammation.

Pulmonary function testing revealed a mean pre-bronchodilator FEV_1 of 42.91%, and a mean FEV_1/FVC ratio of 56.02%, consistent with obstructive ventilatory patterns. GOLD staging of airflow limitation categorised the majority (57.38%) under GOLD 3, indicative of severe obstruction. Moderate (GOLD 2) and very severe (GOLD 4) cases accounted for 29.51% and 13.11% respectively.

Table I: Distribution of study participants as per GOLD classification for diagnosing COPD.

FEV1	Group	Frequency	Per cent
	Gold 2 (50 to 79%)	18	29.51%
	Gold 3 (30 to 49%)	35	57.38%
	Gold 4 (<30%)	8	13.11%
	Total	61	100%

Table II: Table describing the subjects in study population in terms of spirometry parameters.

Spirometric parameters	Parameter	Value
FEV1 (Pre) (%)	Mean (SD)	42.91 ± 10.27
	Median (IQR)	44.15 (37.0 - 51.0)
	Min - Max	17.0 - 61.0
FEV1	GOLD 2 (50 to 79%)	18 (29.51%)
	GOLD 3 (30 to 49%)	35 (57.38%)
	GOLD 4 (<30%)	8 (13.11%)
FEV1 (Post-BDR)	Mean (SD)	47.01 (10.43)
	Median (IQR)	48.15 (42.05 - 54.77)
	Min - Max	25.0 - 62.0
FEV1/FVC	Mean (SD)	56.02 (10.7)
	Median (IQR)	57.71 (52.07 - 64.09)
	Min - Max	31.55 - 70.27

This table shows:

- The mean pre-bronchodilator FEV was 42.91 ± 10.27%.
- The majority of patients were classified under GOLD 3 (57.38%, n = 35). 29.51% (n = 18) subjects were classified as GOLD 2, and the remaining 13.11% (n = 8) as GOLD 4.
- Post-bronchodilator FEV showed an improvement, with a mean of 47.01 ± 10.43%.
- The mean FEV/FVC ratio was 56.02 ± 10.7%.

Functional capacity, as evaluated by the six-minute walk test (6MWT), showed an average walking distance of 223.26 meters. The composite BODE index, which integrates body mass, airflow obstruction, dyspnoea, and exercise capacity, had a mean value of 4.48, suggesting moderate disease severity.

Table III: Table describing the subjects in study population in terms of respiratory parameters.

Other respiratory parameters	Parameter		Value
	6 Minute Walk Test (meters)	Mean (SD)	223.26 (40.31)
		Median (IQR)	223.75 (202.15 - 248.05)
		Min - Max	117.0 - 333.0

	BODE	Mean (SD)	4.48 (1.95)
		Median (IQR)	4.0 (3.0 - 6.0)
		Min - Max	2.0 - 9.0
	Chest X-ray	Normal	18 (29.51%)
		Hyperinflated Lung fields with Flattening of diaphragm	43 (70.49%)

This table shows:

- The mean distance covered in the 6-minute walk test by our subjects was 223.26 ± 40.31 meters, reflecting the functional exercise capacity of the study population.
- The BODE index had a mean value of 4.48 ± 1.95.
- Chest X-ray findings revealed that 70.49% (n = 43) of the subjects had hyperinflated lung fields with flattening of the diaphragm, while 29.51% (n = 18) had normal radiographic findings.

Radiographic findings supported these clinical patterns, with 70.49% of subjects showing signs of hyperinflation and diaphragm flattening on chest X-rays – hallmarks of emphysematous change.

Importantly, NLR showed significant inverse correlations with several parameters: oxygen saturation (r = -0.9), eosinophil percentage (r = -0.54), FEV both pre- and post-bronchodilator (r = -0.94, -1.0), FEV/FVC (r = -1.0), and 6MWT (r = -0.89). Conversely, it was positively correlated with BODE index (r = 0.89) and CRP levels (r = 0.7), confirming its utility as a surrogate marker for disease severity.

Table IV: Table showing the correlation between neutrophil-to-lymphocyte ratio and various respiratory parameters.

Parameter	Correlation Co-efficient	p value
NLR versus Spo2 (%)	-0.9	**<0.001**
NLR versus Eosinophils (%)	-0.54	**<0.001**
NLR versus FEV1 (Pre) (%)	-0.94	**<0.001**
NLR versus FEV1 (Post BDR)	-1.0	**<0.001**
NLR versus FEV1/FVC	-1.0	**<0.001**
NLR versus 6 Minute Walk Test (meters)	-0.89	**<0.001**
NLR versus BODE	0.89	**<0.001**

This table shows:

- A statistically significant negative correlation was observed between neutrophil-to-lymphocyte ratio and SpO, (%) (r = -0.9, p <0.001), eosinophil percentage (r = -0.54, p <0.001), FEV (Pre-BDR, in %) (r = -0.94, p <0.001), FEV (Post-BDR, in %) (r = -1.0, p <0.001), FEV/FVC (r = -1.0, p <0.001), and the 6-minute walk test (meters) (r = -0.89, p <0.001).
- Neutrophil-to-lymphocyte ratio showed a statistically significant positive correlation with the BODE index (r = 0.89, p <0.001).
- Thus, with increasing Neutrophil-to-lymphocyte ratio, there was a decline in the values of SpO2, FEV1 (Pre-BDR), FEV1 (Post-BDR), FVC (%), FEV1/FVC as well as 6-minute walk test (m), and vice versa. Conversely, higher values of neutrophil-to-lymphocyte ratio were correlated with higher values of BODE index and vice versa.

A progressive increase in mean NLR was observed across GOLD stages: 2.37 in GOLD 2, 4.69 in GOLD 3, and 7.4 in GOLD 4 (p <0.001), suggesting a strong association between systemic inflammation and worsening lung function.

Table V: Table showing the association of FEV1 with neutrophil-to-lymphocyte ratio.

Parameter		FEV1			p value
		GOLD 2 (50 to 79%) (n = 18)	GOLD 3 (30 to 49%) (n = 35)	GOLD 4 (<30%) (n = 8)	
Neutrophil-to-Lymphocyte Ratio	Mean (SD)	2.37(0.51)	4.69(1.15)	7.4(0.38)	**<0.001**[b]
	Median (IQR)	2.3 (2.0 - 2.62)	4.64 (3.74 - 5.61)	7.4 (7.13 - 7.67)	
	Min - Max	1.71 - 3.74	2.8 - 6.73	6.87 - 7.95	

b: One way ANOVA

The mean neutrophil-to-lymphocyte ratio was 2.37 ± 0.51 in GOLD stage 2, 4.69 ± 1.15 in GOLD stage 3, and 7.4 ± 0.38 in GOLD stage 4. There was a statistically significant association between the variables (p <0.001), indicating that increasing neutrophil-to-lymphocyte ratio was associated with worsening respiratory function in COPD.

Discussion

This cross-sectional study focused on patients with chronic obstructive pulmonary disease (COPD), with the majority (42.62%) falling in the 60 - 69 years age group. The mean age of the participants was 64.23 ± 7.28 years, consistent with the observation that COPD predominantly affects older individuals. This finding mirrors previous reports, such as the large-scale study by Liu *et al*[4], where the prevalence of COPD increased from 2.7% in the 18 - 44 age group to 13.2% in those aged 75 and above. Similarly, Gupta *et al*[5]. reported a mean patient age of 64.5 years, aligning closely with the current study's demographic.

Gender distribution showed a marked male predominance,

with 72.13% of participants being men. This trend aligns with findings from the Global Burden of Disease[6] Study, where male prevalence rates exceeded female rates (17.6% versus 14.7%, as noted by Koul *et al*[7]). On the contrary, studies by Christopher *et al*[8]. and Parasuramalu *et al*[9] found higher female prevalence (56.9% and 51.5%, respectively), likely due to regional differences in risk exposure. In India, men are more likely to smoke and work in pollutant-heavy industries, while women face indoor air pollution due to biomass fuel use – factors that may influence gender distribution across regions.

The mean pre-bronchodilator FEV_1 was 42.91 ± 10.27%, while the post-bronchodilator FEV_1 was 47.01 ± 10.43%. According to GOLD classification, 57.38% of patients were categorised under stage 3 (severe COPD), 29.51% under stage 2 (moderate), and 13.11% under stage 4 (very severe). The FEV/FVC ratio averaged 56.02 ± 10.7%, reinforcing the presence of obstructive airway disease. These values align with the study by Sangroula *et al*[10], which reported similar stage distribution, with most patients in stages 2 - 4.

Exercise capacity was measured using the six-minute walk test (6MWT). The average distance covered was 223.26 ± 40.31 meters, indicating reduced physical endurance, which is typical for patients with advanced disease. In contrast, other[11] studies have reported higher mean distances: 533 meters (Zeng *et al*[12]), 411 meters (Fujitomo *et al*[13]), 360 meters (Kerti *et al*[14]), and 345.76 ± 109.12 meters (Shah *et al*[15]). The differences likely stem from variation in disease severity, baseline fitness, and comorbidities across study populations.

The mean BODE index – an integrated score reflecting BMI, airflow obstruction, dyspnoea, and exercise capacity – was 4.48 ± 1.95. This suggests moderate-to-severe disease. Other studies, such as those by Li *et al*[16] (mean BODE = 3.0 ± 2.1) and Kaur *et al*[17] (mean BODE = 5.66 ± 2.64), have shown varying results based on participant profiles and disease stages.

Radiological findings supported the clinical assessment, with 70.49% showing hyperinflation and flattened diaphragms, consistent with emphysematous changes, while 29.51% had normal chest X-rays, likely representing earlier disease.

An important aspect of this study was the correlation of systemic inflammation, as reflected by neutrophil-to-lymphocyte ratio (NLR), with disease severity. NLR was significantly negatively correlated with FEV_1 both pre- ($r = -0.94$, $p < 0.001$) and post-bronchodilator ($r = -1.0$, $p < 0.001$), 6MWT ($r = -0.89$, $p < 0.001$), and SpO_2, ($r = -0.9$, $p < 0.001$). It also showed a negative correlation with eosinophils ($r = -0.54$, $p < 0.001$), suggesting a neutrophilic inflammatory pattern common in severe COPD.

Conversely, NLR was positively correlated with BODE index ($r = 0.89$, $p < 0.001$) and CRP levels ($r = 0.7$, $p < 0.001$), reaffirming its role as a systemic inflammatory marker. These findings are consistent with studies by Lee *et al*, ($r = 0.458$ for BODE, $p = 0.003$) and Cai *et al*[18], ($r = 0.5319$ for CRP, $p < 0.001$).

Furthermore, NLR increased progressively with GOLD stages: 2.37 ± 0.51 in GOLD stage 2, 4.69 ± 1.15 in GOLD stage 3, and 7.4 ± 0.38 in GOLD stage 4 ($p < 0.001$), indicating a strong link between inflammation and disease progression.

In conclusion, this study highlights the utility of NLR as a simple, accessible biomarker reflecting COPD severity, comparable to more established tools like the BODE index and CRP.

This study has highlighted that there is a significant association between NLR and worsening lung function, reduced exercise capacity, and higher BODE index in COPD patients. Importantly, it has provided evidence regarding the importance of NLR as a biomarker which can be used to assess the severity of disease in COPD.

Neutrophil-to-lymphocyte ratio can be used in low resource settings to:

- Predict exacerbations in COPD patients
- Escalate therapy according to trends in the levels
- Prognosticate COPD patients
- Grade severity of COPD patients.

However, further large-scale studies are required to validate these findings.

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REVIEW ARTICLE

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Understanding COPD and Its Effective Treatment Strategies

DG Jain, VD Jain***

Introduction

Chronic obstructive pulmonary disease (COPD) is common and is mostly due to smoking. From the clinical perspective, it is a combination of chronic bronchitis and emphysema. Productive cough for 3 or more months for at least 2 consecutive years is labelled as chronic bronchitis. In emphysema there is abnormal enlargement of the air spaces distal to the terminal bronchioles along with destruction of their walls. Though COPD cannot be cured, effective treatment strategies can alleviate symptoms, improve the quality-of-life, and also reduce the mortality risk. COPD prevalence in India (2021) is 7.4%.

Definition

- COPD is a disease state characterised by 'non fully reversible' or 'fixed' airflow obstruction. Airflow limitation is the hallmark of COPD. This has been highlighted in the GOLD classification which focuses on the decrease in FEV_1.
- There is minimal or no reversibility with bronchodilators.
- There is progressive airflow limitation with an abnormal inflammatory response of the lung to noxious substances (pollutants) and gases.
- There is minimal variability in day-to-day symptoms.
- For all practical purposes, the vicious triad of COPD consists of asthma, chronic bronchitis, and emphysema. Therefore, any patient presenting in the OPD/clinic with dyspnoea, chronic cough, or sputum production and/or a history of exposure to the various risk factors should be considered as having COPD.

Aetiology and Risk Factors

- More than 90% cases are smokers with history of >20 packs per year
- COPD is increasing in frequency globally, more so in many developing countries, due to the high incidence of outdoor and indoor air pollution: smoking, environmental and occupational pollution from dust, particulate matter, chemicals, and use of biomass fuel for cooking and heating
- Longstanding asthma
- Recurrent infections of the respiratory tract
- Genetic inheritance: Alpha1-antritrypsin deficiency (AATD) – causing emphysema
- Low socio-economic status
- Older age group and female gender have increased susceptibility

Pathophysiology

- Mucous gland hyperplasia – particularly in the larger airways, with mucus hypersecretion leading to chronic productive cough. Mucosal damage from smoke also causes:
  - Squamous metaplasia – Normal ciliated columnar epithelium is replaced by squamous epithelium.
  - Loss of ciliary function – Causing impairment of the normal functioning of the mucociliary escalator, thus causing chronic productive cough.
- Chronic inflammation and fibrosis of small airways – CD8 lymphocyte, macrophage, and neutrophil infiltration occurs with release of pro-inflammatory cytokines. Moreover, airway inflammation is perpetuated by recurrent infections.
- Emphysema – is caused by alveolar wall destruction which leads to irreversible enlargement of the air spaces distal to the terminal bronchiole, i.e., the acinus, causing loss of elastic recoil and thus hyperinflated lungs.
- Thickened pulmonary arteriolar wall and remodelling – occurs as a result of hypoxia. This causes increased pulmonary vascular resistance, pulmonary hypertension, and impaired gas exchange.
- Most common bacterial pathogens seen in COPD

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exacerbations are: *Streptococcus pneumoniae, Haemophilus influenzae, Moxarella catarrhalis*. In case of any patient not showing expected improvement within 3 - 7 days of appropriate empirical antibiotic therapy, it is advisable to get a sputum culture and sensitivity test done.

Clinical features

- Dyspnoea
- Productive cough
- Decreased exercise tolerance
- Wheeze

Signs of COPD

Significant airflow obstruction could be present before the patient becomes aware of it.

- Raised respiratory rate (RR).
- Barrel chest (Hyperexpanded).
- Expiratory time is prolonged to >5 sec., along with pursed lip breathing.
- Accessory muscles of respiration are in use.
- Quiet breath sounds – especially in the lung apices, with or without wheeze.
- Quiet heart sounds – due to overlying hyperinflated lung.
- Basal crepitations may be heard.
- Features of Cor Pulmonale and CO_2 retention:
  - Raised JVP
  - Ankle oedema
  - Warm peripheries
  - Bounding pulse
  - Plethoric conjunctivae
  - Polycythaemia
  - Flapping tremor – if CO_2 is acutely raised.

Investigations

- Pulmonary function test (PFT) with reversibility; or instant assessment with a Mini Peak Flow Meter – The quickest, easiest, and cheapest test to perform in the clinic in all patients above 5 years of age.
  - Obstructive spirometry and flow volume loops.
  - FEV_1 is reduced to <80% predicted. FEV_1 can assess the progression of COPD, but not the degree of dyspnoea.
  - $FEV_1/FVC < 0.7$
  - Minimal reversibility with bronchodilator (<10 - 15%) and steroids.
  - Total lung volume, FRC, and residual volume are increased because of emphysema, air trapping, and loss of elastic recoil.
  - Reduced TLCO and kCO due to decrease in surface area available for gas diffuse as a result of emphysema.
- Chest X-ray (PA View)
  - To rule-out any other lung conditions – cancer, bronchiectasis.
  - 'Black lung sign' – lung fields are hyperinflated with attenuation of peripheral vasculature and more than 7 posterior ribs are visible.
  - Ribs appear more horizontal.
  - Bullae may be seen, usually in the apices. Due to absence of lung markings, large bullae could be mistaken for a pneumothorax. An HRCT chest will clear any doubts.
- Blood tests
  - CBC – to rule-out anaemia.
  - Alpha-1-antitrypsin (AAT) levels – to rule-out a genetic cause.
  - CRP – could be raised in COPD, but falls after treatment with steroids.

Diagnosis

- Clinical clues – H/o smoking, progressive dyspnoea, and irreversible airflow obstruction on spirometry.
- D/D – Asthma – Responsive to both bronchodilators and steroids (Table I).
- Breathlessness – Persistent and progressive in COPD, but variable in asthma.
- Chronic productive cough – Common in COPD, but uncommon in asthma.
- Diurnal/day-to-day variability of symptoms (night-time waking with SOB/wheeze) is more in asthma.

Severity of COPD

- Mild (Stage I): FEV_1 (forced expiratory volume in 1 second) is >80% of predicted and FEV_1/FVC (forced

Table I: Differentiating characteristics of COPD and Asthma

Characteristics	Chronic Obstructive Pulmonary Disease	Asthma
Age	• >35 years	• <20 years
Symptom pattern	• Chronic cough and sputum precedes onset of dyspnoea, regardless of triggers	• Episodes related to triggers such as exercise, emotions including laughter, dust or exposure to allergens
	• Good and bad days but daily symptoms and exertional dyspnoea always present	• Symptoms worsen during night or early morning
Lung function	• Persistent airflow limitation	• Variable airflow limitation
Time course	• Symptoms gradually worsen over time	• Seasonal variation in symptoms present
	• Limited relief can be provided by rapid-acting bronchodilator treatment	• Demonstrates immediate response to bronchodilator or to inhaled corticosteroid over weeks

vital capacity) <0.7. These patients may or may not be symptomatic (cough or sputum).

- Moderate (Stage II): FEV_1 is 50 - 80% of predicted and FEV_1/FVC <0.7. FRC is increased and TLCO is decreased. These patients could be symptomatic (cough, sputum, SOB).
- Severe (Stage III): FEV_1 is 30 - 50% of predicted and FEV_1/FVC <0.7. TLCO is reduced. Hypoxia is present with signs of cor pulmonale. Patient is symptomatic and may need hospitalisation.
- Very Severe (Stage IV): FEV_1 is <30% of predicted and FEV_1/FVC <0.7.

Pharmacological Management

For COPD patients who are clinically stable, the main aim is to relieve symptoms and prevent or reduce exacerbations. Treatment in COPD should be increased gradually and stepwise. All exacerbations of COPD will need extra medication and support.

Routinely used drugs in bronchial asthma and COPD

- Bronchodilators
  - Sympathomimetics –
    - Salbutamol (SABA)
    - Levosalbutamol (SABA)
    - Terbutaline (SABA)
    - Salmeterol (LABA)
    - Formoterol (LABA)
    - Arformoterol (LABA)
    - Indacaterol (LABA)
  - Methylxanthines –
    - Theophylline
    - Aminophylline
    - Choline theophyllinate
    - Hydroxyethyl theophylline
    - Doxophylline
    - Roflumilast (PDE_4 inhibitor)
  - Anticholinergics –
    - Ipratropium bromide (Bronchodilator)
    - Tiotropium bromide (LAMA)
    - Glycopyrrolate (LAMA)
    - Leukotriene antagonists
  - Montelukast
  - Zafirlukast
    - Mast cell stabilizers
  - Sodium cromoglycate
  - Ketotifen
- Corticosteroids
  - Inhalational (ICS) –
    - Beclomethasone dipropionate
    - Budesonide
    - Fluticasone propionate
    - Flunisolide
    - Ciclesonide
  - Systemic (Oral/Intravenous) –
    - Hydrocortisone
    - Prednisolone
    - Other glucocorticoids
- Anti-IgE antibody
  - Omalizumab

For all practical purposes, drugs are divided into 'Controllers' and 'Relievers':

1. CONTROLLERS (Preventers/Prophylactic drugs)
    - Inhaled Glucocorticoids:
        - Beclomethasone, Budesonide, Fluticasone
    - Long-acting inhaled β-2 agonists (LABA):
        - Salmeterol, Formoterol
    - Theophylline: Sustained-release formulation
    - Leukotriene Modifiers:
        - Montelukast, Zafirlukast, Pranlukast, Zyleutin
    - Cromones:
        - Sodium Cromoglycate, Nedocromil sodium
    - Long-acting oral β-2 agonists:
        - Salbutamol, Terbutaline
    - Oral/Systemic Glucocorticosteroids
2. RELIEVERS (which relieve bronchoconstriction)
    - Rapid/short-acting inhaled β-2 agonist (SABA) drugs: Salbutamol, Terbutaline, Fenoterol
    - Inhaled anticholinergics:
        - Ipratropium bromide, Oxitropium
    - Short-acting oral β-2 agonists:
        - Salbutamol, Terbutaline
    - Short-acting methylxanthines:
        - Theophylline, Aminophylline
    - Systemic glucocorticosteroids
    - Others:
        - Epinephrine
        - Adrenaline

Bronchodilators

- Simple PFT may not show significant reversibility of FEV_1 with bronchodilator. However, in the long-term, bronchodilators do provide therapeutic benefit as evidenced by decreasing the dyspnoea and thereby reducing the hyperinflation of the chest.
- First, give a short-acting β-2 agonist (SABA) for symptom relief.
- If no relief, give a short-acting β-2 agonist with with a short-acting anti-cholinergic.
- If patient is still symptomatic, give a regular long-acting bronchodilator with/without an anti-cholinergic.
- Oral methylxanthines – Theophylline – can be continued as maintenance therapy along with inhaled bronchodilators and inhaled steroids – to be continued only if symptoms improve. May have an anti-inflammatory effect but watch for toxicity in the elderly.
- When used with a spacer device, inhaled therapy provides sufficient bronchodilator doses in most patients. Patient's inhaler technique should be checked once by the attending physician.
- Nebulisation – is to be used in patients who are incapable of using inhalers. Only those who show clinical benefit from nebuliser therapy may continue with its long-term use at home with a combination of salbutamol and ipratropium. Also, nebulisation is known to have a placebo effect too!

Inhaled corticosteroids (ICS)

- All patients with FEV_1 <60% predicted with h/o >2 exacerbations every year treated with antibiotics and/or oral steroids, should be prescribed inhaled corticosteroids (ICS). Ideally used in combination with a bronchodilator, inhaled steroids do reduce the severity and frequency of exacerbation in severe COPD, but have not helped in slowing the decline in lung function.
- Patients should be made aware and warned about steroid side-effects.

Inhaled combinations of bronchodilators and steroids to manage COPD

These are available as metered dose inhalers:-

1. Single-inhaler dual therapy (SIDT) combination containing –
    - ICS (inhaled corticosteroid) + LABA (long-acting β-2 agonist), or LABA + LAMA (long-acting muscarinic receptor antagonist). The combination of ICS + LABA contains Formoterol fumarate 6 mcg + Budesonide 100/200/400 mcg. The combination of LABA + LAMA contains Formoterol fumarate 12 mcg + Glycopyrronium bromide 25 mcg. Glycopyrronium bromide – also known as Glucopyrrolate – blocks the muscarinic acetylcholine receptors in the bronchial smooth muscles with its action lasting up to 24 hours, thereby providing sustained bronchodilatation. These combination inhalers are indicated for maintenance treatment of airflow obstruction in COPD – including chronic bronchitis and emphysema.

2. Single-inhaler triple therapy (SITT) combination – for patients who remain uncontrolled, leading to moderate-to-severe exacerbations. The SITT is a newer development and has shown benefits in effectively preventing exacerbations due to improved efficacy, reduced inhaler use, and enhanced compliance. This combination inhaler contains –

    - LABA + LAMA + ICS – Indicated for maintenance treatment to prevent and relieve symptoms associated with COPD. The three drugs being used are Fluticasone furoate 100 mcg + Umeclidinium 62.5 mcg + Vilanterol 25 mcg. The mechanism of action of these 3 drugs is as follows:

        - Vilanterol (LABA) – Causes smooth muscle relaxation in the airways by binding to β-2 adrenergic receptors, leading to bronchodilatation and increased airflow. It also boosts the anti-inflammatory properties of corticosteroids.
        - Fluticasone furoate (ICS) – Inhibits the inflammatory cell response and cytokine production leading to a reduction in airway inflammation, thus helping prevent exacerbations associated with chronic inflammation. Also, corticosteroids elevate the expression of β-2 receptors and protect them from downregulation when exposed to LABAs.
        - Umeclidinium (LAMA) – Prevents smooth muscle constriction in the airways by blocking acetylcholine receptors. Apart from preventing bronchoconstriction, this action also widens the airways.

Even then, acute exacerbations of COPD (AECOPD) usually require hospitalisation.

Oral steroids

- Needed in cases of severe COPD exacerbation. In such cases, since it is usually difficult to discontinue oral steroids, try to taper down the dose to the lowest possible.
- Danger of osteopenia and osteoporosis should be avoided by suitable prophylaxis with calcium and vitamin D supplementation.

Oxygen – short-term therapy via cylinder or long-term via oxygen concentrator for:

- Patients in respiratory failure (PaO_2 <7.3 kPa or PaO_2 of 7.3 - 8 kPa) with features of secondary polycythaemia, pulmonary hypertension, or peripheral oedema – need to be given oxygen for at least 15 hours daily (including sleep time).
- Low flow oxygen (2 - 4 lit./min) via nasal prongs is generally quite adequate.

Vaccination

- Seasonal influenza vaccine – administered annually.
- Both types of pneumococcal vaccines – once in 5 years: PPSV23 (pneumonia polysaccharide vaccine) and PCV13 (pneumonia conjugate vaccine).

Antibiotics – No role of prophylaxis.

Mucolytics

- Helpful in patients with chronic productive cough and have shown reductions in COPD exacerbations.
- Reduce sputum viscosity and facilitate expectoration.
- Give for 4-weeks and continue if there is improvement.

Asthma-COPD Overlap Syndrome (ACOS)

Patients showing persistent airflow limitation plus one or more features of asthma (wheezing, bronchial hyperresponsiveness, or sputum eosinophilia) are labelled as ACO. Though uncommon, it worsens symptoms, exacerbations and quality-of-life (QoL), and increases the use of rescue drugs.

Eosinophilic ACO responds better to ICS + LABA than LABA alone, reducing hospitalisation and improving mortality outcomes. GINA (2023) advocates ICS + LABA as first-line therapy for most ACO patients.

Summary of treatment

- Any patient in acute exacerbation (i.e., too breathless to talk + respiratory rate >24/min + SpO_2 <90%) should be referred for emergency management to a hospital.
- Primary treatment: Quit Smoking. After stabilizing the acute condition with appropriate measures, refer the patient to a Tobacco De-addiction Centre.
- If there is shortness of breath (SOB) only on strenuous physical exertion without any previous h/o hospitalisation, prescribe MDI Salbutamol (ASTHALIN) – 2 puffs SOS/QID.
- If there is shortness of breath (SOB) even at rest or on mild activity without any previous h/o hospitalisation, prescribe:

- Short-acting β-Agonist (SABA) – MDI Salbutamol (ASTHALIN) – 2 puffs SOS/QID.
- Long-acting β-Agonist (LABA) Salmeterol + LAMA (Tiotropium bromide).

- If there is history of any previous hospitalisation, start the following MDIs:
  - Salbutamol – 2 puffs SOS/QID
  - LABA + LAMA + ICS (Fluticasone or Budesonide)
- In a case of exacerbation, add an antibiotic, preferably Azithromycin 500 mg OD x 5 days.
- For cough with expectoration – Syp. Bromhexine 10 mL TDS.
- For dry cough – Syp. Noscapine.
- May add bronchodilator Tab. Doxofylline 400 mg BDS or Tab. Acebrophylline 100/200 mg BDS.
- If there is no relief or improvement, refer to the Medicine Emergency of the nearest hospital.

Non-pharmacological management

For patients who are clinically stable:

1. Cessation of smoking
2. Education
3. Diet
4. Pulmonary rehabilitation
5. Psychological and social support

- Cessation of smoking
  - Decreases the smoking-related decline in lung function.
  - Nicotine replacement therapy may be tried to aid smoking cessation.
- Education
  - Improves the will to quit smoking and manage one's illness.
- Pulmonary rehabilitation – Is initiated on an OPD basis to reduce recurrent hospital admissions, improve exercise tolerance and quality-of-life. Patients with COPD tend to have reduced muscle mass in the lower limbs as compared with healthy same-age controls. Reduction in muscle mass is, by itself, reflective of the severe nature of the COPD and its systemic effects.
  - To improve muscle mass, a graded exercise programme is initiated.
  - Patient is guided and educated about lifestyle modifications and breathing techniques are taught.
- Diet
  - To minimise respiratory effort, obese patients are advised and guided to lose weight.
  - Nutritional supplementation – Very breathless patients could be in a catabolic state due to a low calorific intake. This may cause the BMI to fall, which thereby causes a deterioration in the pulmonary functions, reduction in diaphragm mass, fall in exercise capacity, leading to increased mortality risk. Improving muscle mass and body weight should be a top priority – achieved by a well-balanced diet and nutritional supplementation.
- Psychological and social support
  - Patients with COPD are seen to show remarkable improvement with practical support and a psychologically encouraging and cheerful environment in the home and day care centre.
  - Care givers should make special efforts to keep the patients free from any form of mental stress, anxiety, and depression.

An Approach to COPD in the clinic

- Establish diagnosis and assess severity – PFT, CXR.
- Rule-out other causes for symptoms – anaemia, pulmonary embolism, ILD, pneumothorax, large emphysematous bullae, arrhythmia, heart failure, thyroid dysfunction, mental depression.
- Counsel the patient to quit smoking.
- Review the ongoing treatment of COPD – optimise the doses of bronchodilators and/or inhaled corticosteroids.
- Assess for the need to nebulise – with SABA/LABA/ICS.
- Check SpO_2 and go for ABG if SpO_2 <92% – assess whether LTOT (long-term oxygen therapy) is needed.
- Check vaccination status.
- Decide if the patient needs pulmonary rehabilitation.

Steroid trial to help distinguish asthma from COPD

- Needed only if the diagnosis is unclear.
- Method: Measure FEV_1 and slow VC (vital capacity) before and after:–

- Either a high dose ICS for 6 - 8 weeks,
- Or a 2-week course of oral prednisolone – 30 mg/day.

>15% increase in FEV_1 implies steroid reversibility – therefore patient is likely to be an asthmatic.

>15% increase in slow VC points to markedly reduced air-trapping – s/o significant asthma.

Bronchodilator reversibility test to help distinguish asthma from COPD

- Firstly, check the FEV_1. Then administer a SABA (short-acting β-2 agonist) inhaled via a spacer or via a nebulizer. After 15 - 20 minutes of this inhalation, check the FEV_1 again.
- Now subtract the pre-test value from the post-test value and then divide the difference by the pre-test value, and express as a percentage increase from baseline. >15% increase or >200 mL is indicative of bronchodilator reversibility.
- Before going for bronchodilator reversibility testing, avoid short-acting bronchodilator in the preceding 6 hours, a long-acting bronchodilator in the preceding 12 hours, or a long-acting anticholinergic or a sustained release theophylline in the preceding 24 hours.

COPD exacerbations

- Diagnosis is practically clinical.
- Result in mild symptoms in those with relatively preserved lung function.
- Can result in marked morbidity in patients with limited respiratory reserve.
- A large number of patients fail to regain their pre-morbid lung function and/or quality-of-life after an exacerbation.
- Patients who suffer frequent exacerbations, show a more rapid FEV_1 decline than those who have fewer exacerbations.
- Frequency of exacerbations increases with the severity of COPD.
- Exacerbations are more frequent in winter – likely because viruses have a better survival in the cold and people crowd together indoors.

Summary of management of acute exacerbation of COPD

- First assess severity of exacerbation:–
  - Measure RR, SpO_2, FEV_1, BP, pulse for tachycardia.
  - Check for peripheral perfusion, level of consciousness, mental state.
- Exclude a pneumothorax – clinically and/or radiologically.
- In a hypoxic patient, administer controlled oxygen (24 - 35%) via a Venturi facemask – aim should be SaO_2 88 - 92%; also, salbutamol nebulisation.
- Establish an IV line.
- Check ABG.
- Get an ECG done.
- Send requisition for CXR.
- Blood tests: CBC (for WCC), CRP, RBS, KFT (for potassium), etc.
- Optimise volume status.
- If possible, take a short history: to know the patient's normal functional status, e.g., exercise tolerance and need for assistance in day-to-day activities. Check previous hospital notes (for severity of disease; and to find out if previously decisions were taken regarding ventilation or resuscitation.
- Bronchodilator nebulisation – Salbutamol 2.5 - 5 mg + Ipratropium 500 mcg on arrival and 4 - 6 hourly thereafter. Run the nebuliser with air, not oxygen.
- Oxygen therapy to be continued – try to maintain saturations between 80% and 90%.
- ABG to be repeated after 60 minutes to ensure improvement if patient is hypoxic or acidotic. Repeat ABG if there is clinical deterioration.
- Antibiotics may be considered if sputum is purulent, patient has fever, and there are changes in the chest x-ray.
- Systemic steroids – Prednisolone 30 mg/day for 1 - 2 weeks – may be added in cases of exacerbations who are hospitalised or more breathless.
- IV aminophylline may be considered if patient is not showing improvement with nebulisations.
- Consider intensive care – a consultant-led decision with the patient and family – intensive mechanical ventilation. Document all this in the medical notes in the patient's case file. Also consider resuscitation status.
- Consider NIV (non-invasive ventilation) – pH <7.3, hypoxia, hypercapnia, patient conscious.
- Consider doxapram – an intravenous respiratory

stimulant – if NIV is not available or is not tolerated.

- Consider non-invasive ventilation (NIV) – supports patients who are in exacerbation, conscious, and having respiratory acidosis (pH <7.35), hypoxia, and hypercapnia.
- Intubation in ICU if no response to medication – Consider invasive mechanical ventilation.
- DVT prophylaxis.
- Early mobilization – to prevent muscle wasting.
- Nutritional support.

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REVIEW ARTICLE

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Therapeutic Drug Monitoring (TDM) in Clinical Practice

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Abstract

Therapeutic drug monitoring (TDM) is an ever-evolving process that consists of two components: measurement of drug levels, and interpretation of the values obtained by clinicians. It has mainly been used for optimizing treatment, assessing efficacy of drugs, ensuring patient safety, screening for drug-drug interactions, monitoring compliance, etc. In order to unmask the true potential of TDM, clinicians need to have adequate knowledge of the correct matrix, correct time of sample collection, and the correct analytical method to be used. As beneficial as TDM is, it is important to understand that it should be done only for a handful of drugs that fulfill previously established criteria. The practice of TDM has advanced greatly with the introduction of pharmacogenomics, pharmacogenetics, and artificial intelligence, progressing towards the development of personalised medicine.

Key words: Therapeutic drug monitoring, TDM, patient safety, drug efficacy, drug concentration.

Introduction

Therapeutic drug monitoring (TDM) may be defined as a process that involves drug concentration measurement in biological fluids and interpretation of the obtained values by physicians. This multidisciplinary process requires the application of knowledge of pharmaceutic, pharmacokinetic and pharmacodynamic principles that facilitates safety and efficacy assessment of the drug in question, which in turn helps in personalizing drug treatment regimens for patients[1].

Albader *et al*[2] define TDM as "the measurement of serum drug and/or anti-drug antibody (ADA) concentrations."

Almukainzi defines TDM as, "detecting concentrations of a drug in a biological fluid at a single or several periods following a drug intake for adjusting and customizing drug dosage and administration"[3].

Zijp *et al* define TDM as "the quantitative measurement of drug concentrations to assess adequate exposure, resistance, or side-effects to medication"[4].

Kang *et al* define TDM as "the clinical laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures"[1].

Since the introduction of TDM during the 1960s and 70s, the primary focus behind the concept has been to improve patient outcome by decreasing adverse drug reaction (ADR) rates and toxicity incidences; however, the scope of TDM has been broadened and now includes compliance monitoring, individualisation of therapy, efficacy assessment, drug-drug interactions monitoring, assessing response to new treatment, monitoring abuse and investigating unusual treatment responses and adverse reactions[1,3].

Although the process of TDM is based on the assumption that drug levels correlate with pharmacodynamic effects of a drug[5], it is worth remembering that measurement of drug levels is one of the two components of TDM. It is the combination of drug concentration measurement and clinical interpretation of the obtained values that make TDM an invaluable tool, that can be used to personalise drug treatment[6].

Evolution of TDM

Even though the profession of medicine has, since long, known how minute differences in dosing can lead to undesired outcomes (toxicity, therapeutic failure due to subtherapeutic dosage), it was not until 1932 that drug monitoring was introduced[7]. In the following decades, significant events occurred that lead to the introduction of the concept of TDM[7]: 1.) Scientists started questioning the "one-size-fits-all" approach, as applied to drug administration, 2.) Serum level measurement for drugs like Penicillin and Streptomycin was made possible for the first time, in 1948, 3.) A study by Finney DJ, that talked about the importance of drug monitoring, was published in 1965[8]. All these events led to discussions on drug pharmacokinetics, drug-drug interactions, and the importance of monitoring drug levels, which ultimately brought the concept of TDM into existence. The period between 1970 and 1990 was of particular significance in the history of therapeutic drug monitoring, as multiple

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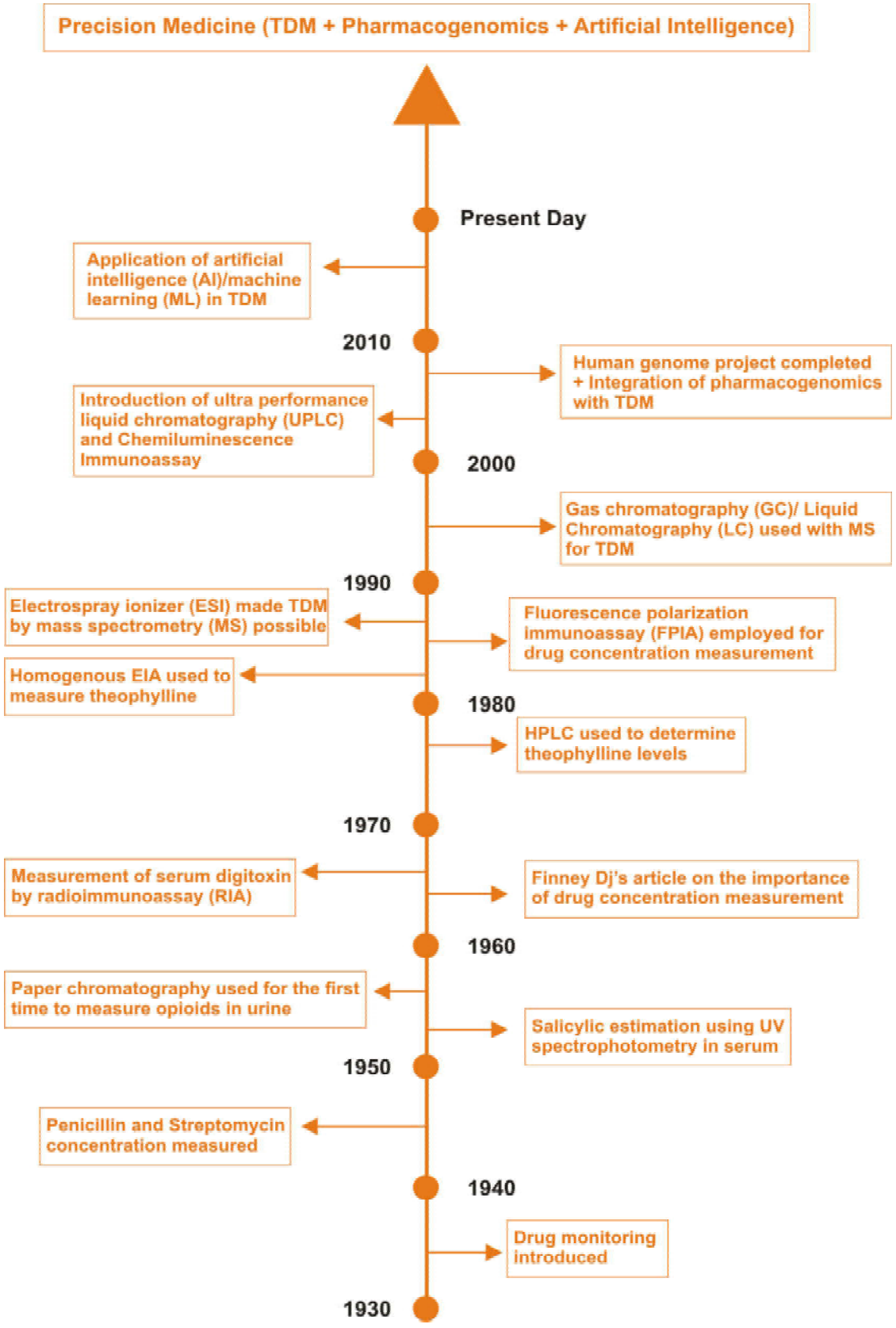

Fig. 1: *Evolution of TDM.*

analytical techniques, such as gas chromatography, high performance liquid chromatography (HPLC), and different types of immunoassays[9] were introduced for the purpose of measuring serum drug concentrations. 1990s onwards, there was introduction of better chromatographic techniques, combination of chromatographic techniques with mass spectrometry (MS), and invention of non-invasive modalities (such as wearable biosensors), for the purpose of measuring drug levels, that led to an increase in the TDM practices. Advancement of pharmacogenomics and pharmacogenetics, brought about by completion of the human genome project in early 2000s, has given rise to the fields of pharmacogenomics and pharmacogenetics, which when combined with TDM can lead to a significant improvement of patient outcomes and improve our understanding of various therapeutic responses[1].

Criteria to be fulfilled by drugs for TDM

While all drugs used may require monitoring, classical TDM is done for drugs that follow the following criteria[1,7,10,11]:

1. Presence of inter-individual variability

   This is seen mainly due to various pharmacokinetic factors. Drugs showing significant inter-individual variability include phenytoin, amitriptyline, chlorpromazine, warfarin, tacrolimus, etc[12,13].

2. The drug has a narrow therapeutic index

   Blix *et al* define Narrow Therapeutic Index (NTI) drugs as the ones "with small differences between their therapeutic and toxic doses, implying that small changes in dosage or interactions with other drugs could cause adverse effects[14]."

   Classic examples of NTI drugs include lithium, aminoglycosides, digoxin, rifampicin, theophylline, warfarin, phenytoin, phenobarbital, etc[14].

3. Existence of correlation between plasma concentration of the drug and clinical response/toxicity

   This criterion is fulfilled by majority of drugs and is essential for drugs undergoing TDM. A classic example of drugs that fall into this category are aminoglycosides (e.g., gentamicin). Drugs belonging to this group mediate clinical efficacy by employing concentration dependent killing, which essentially translates to these drugs having better antimicrobial activity at peak concentrations[15].

4. Interpretation of therapeutic and toxic effect of the drug not possible clinically or with the aid of a biomarker

   Drugs used in psychiatry (e.g., lithium, anti-psychotics, tricyclic antidepressants, etc), immunosuppressants (e.g., tacrolimus, cyclosporine, etc.) and digoxin are some of the drugs that do not have established biomarkers and necessarily require maintenance of concentration within set limits[16].

5. Consistent administration of the drug for a duration long enough to justify treatment modification

   Except in life-threatening conditions, the patient should have been taking the drug for long enough to reach steady-state concentration (i.e., for a duration long enough to cover at least five half-lives), before doing TDM.

TDM is not done if a drug's effects can be observed clinically, like in case of anti-hypertensives, anti-diabetics, etc., or if the drug has measurable biomarkers that can serve as clinical outcome surrogates (e.g., Prothrombin time (PT) - International Normalised Ratio (INR) for warfarin)[17]. Additionally, it is not recommended for drugs that do not have a well-established concentration-clinical effect relationship. Drugs having a delayed onset of action (e.g., selective serotonin reuptake inhibitors (SSRIs), prodrugs (e.g., clopidogrel) and those taken via non-systemic routes for local action (e.g., steroids taken via inhalational route) do not have an established concentration-effect relationship, which makes the utilisation of TDM for these drugs non-beneficial[18].

In the context of inflammatory bowel disease (IBD), TDM has often been described to be of two types: Proactive and Reactive. While proactive TDM includes measurement of drug concentration at pre-determined intervals irrespective of the disease status, reactive TDM involves drug level monitoring in presence of active disease/flare-ups. Table I summarises the differences between proactive and reactive TDM.

Biological samples(/matrices) used in TDM

Usage of blood-based matrices (whole blood, plasma or serum) has been the gold standard practice due to an established relationship between therapeutic efficacy of drugs and their concentration in blood/serum, but due to the invasive nature of collection, usage of other matrices such as hair, urine, sweat, saliva and also the relatively less invasive finger prick sampling technique, has been on the rise.

Table II lists the different matrices, drugs they have been employed for, and their advantages and disadvantages.

Table I: Differences between Proactive and Reactive TDM

	Proactive TDM	Reactive TDM
Time of measurement of concentration[19]	At pre-determined intervals	Levels are measured because of presence of active disease or during flare-ups
Presence of active disease[19]	No	Yes
	Done in asymptomatic patients/patients in remission[20]	Done in patients with symptoms or findings suggestive of active disease
Goal[21]	To ensure that therapeutic drug levels are being maintained	To check if disease persistence/flare-up is due to ADAs or subtherapeutic concentration or in spite of having optimal concentration
	To decrease the incidence of anti-drug antibodies (ADAs), and subsequent loss of response	
Reduction of development of ADAs and drug failure	More	Less
Cost effective[22]	More	Less

Table II: Matrices used for TDM.

S. No.	Type of matrix	Drugs	Advantage(s)	Disadvantage(s)
1.	Whole blood	Immunosuppressants (Tacrolimus[23], Sirolimus[24], Everolimus[24], Cyclosporine[24]) Anti-psychotics (Quetiapine[25])	Allows for measurement of drugs that get sequestered inside blood cells[24]	1. Hematocrit and plasma protein level variations can affect results[26] 2. Anticoagulants used might interfere with the results[27]
2.	Plasma	Direct oral anticoagulants (Apixaban, Rivaroxaban)[28], Immunosuppressants (Mycophenolic acid[24])	1. Relatively larger volume can be obtained, as compared to serum, from a blood sample[29] 2. Less time consuming (clotting of blood not required)[29] 3. Sample can be used for whole blood analysis as well[29]	1. Anti-coagulants might interfere with the results by affecting protein binding (heparin causes lipolysis which causes an increase in the concentration of non-esterified fatty acids that displace drugs bound to plasma proteins) and disturbing the stability of the matrix[29] 2.Preservatives added to anticoagulants may affect results[29]
3.	Serum	Direct oral anticoagulants (Apixaban, Rivaroxaban)[28] Anti-psychotics (Quetiapine[25])	Since anti-coagulants are not used, there is less interference with results	Clotting of blood is time consuming[29]
4.	Liquid finger prick blood (LFB)/Dried Blood Spot (DBS) sampling	Immunosuppressants (Tacrolimus[30], Cyclosporine[31]), tyrosine kinase inhibitors[32], adalimumab[33]	1. Less invasive as compared to other blood-based matrices 2. Longer shelf life of sample	1. Less precise and accurate[33] 2. Dependence on spot homogeneity in DBS[33]
5.	Sweat	Beta lactams(flucloxacillin, imipenem, and cefepime)[34], Levodopa[35]	Non-invasive[36]	1. Contamination of samples is very common[35] 2. Concentration of drugs might vary depending on rate of sweating[35] 3. Dilution with respect to plasma is variable across different drugs[37]
6.	Urine	Polymyxin B[38], Angiotensin receptor blockers (ARBs)[39], opioids[40]	1. Non-invasive[40] 2. More economical[40] 3. Fast results[40]	1. Dilution (due to diuretics) may interfere with results[40] 2. High false positive rates[40]
7.	Saliva[41]	Immunosuppressants (Cyclosporine[42], Mycophenolic acid[43], Prednisolone[44]) Anti-microbials (Gentamicin[45]) Anti-epileptics (Levetiracetam[46], Carbamazepine, Phenytoin and Phenobarbital[47])	1. Non-invasive 2. Frequent sampling possible 3. Self-sampling possible 4. More economical	1. Levels affected by flow rate of saliva[48] 2. Salivary pH may alter levels[48] 3. Blood contamination affects results
8.	Hair	Anti-tubercular drugs[49], anti-retroviral drugs[50,51], antihypertensive drugs[52]	1. Long duration of growth allows study of compliance[52] 2. Easy availability[52] 3. Easy to store samples[52]	1. Pigmentation variability affects drug incorporation[53] 2. Drug diffusion from sweat might interfere with results[54] 3. External contamination might alter findings[54]
9.	Cerebrospinal fluid (CSF)	Anti-retroviral drugs[55], Venlafaxine[56], Vancomycin[57]	Good indicator of brain tissue exposure to drug(s)[55]	1. Ageing is associated with an increased permeation of drugs into CSF[55] 2. Neuroinflammation disrupts BBB and allows for more drug to enter CSF[55] 3. Invasive[55]
10.	Vitreous fluid	Anti-epileptics (carbamazepine, phenytoin, phenobarbital)[58], Opioids[59]	1. Does not undergo postmortem redistribution (PMR) like blood[58,59]	1. Invasive and limited to usage in investigations done postmortem 2. Vitreous levels do not correspond to serum levels in most cases

			2. Easy to collect[58]	
11.	Synovial fluid	Opioids[60], Cocaine[60], Vancomycin[61], Meropenem[61], Non-steroidal anti-inflammatory drugs (NSAIDs)[62]	1. Good representatives of local concentration	1. Invasive 2. Limited volume available 3. Joint disorder might affect drug levels[62]
12.	Bone	Anticonvulsants (Carbamazepine[63]), Anesthetics, Antidepressants (Duloxetine, Venlafaxine, Amitriptyline)[64], Antihypertensives (Atenolol, Bisoprolol)[65], Antipsychotics (Quetiapine[66]), Benzodiazepines, NSAIDs, opioids	Useful for postmortem studies	1. Invasive 2. Not beneficial for drugs used for a short time period

Timing of sample collection for TDM

In most cases, drug concentration measurement is done after steady-state concentration has been attained, i.e., when the rate of administration of a drug equilibrates with its rate of elimination. This state is typically achieved after 5 half-lives, but may be achieved earlier, if a loading dose has been administered. However, in patients with metabolism or excretion impairments, measurements may be done prior to reaching steady state concentration, to avoid toxicity development especially if the patient is receiving drugs with long half-lives[5].

Table III lists the suitable time of blood collection based on the indication.

Table III: Blood sample collection for TDM.

S. No.	Indication	Time of blood collection
1.	Suspected toxicity	Immediately[5]
2.	Poor therapeutic control in life-threatening conditions	Immediately[5]
3.	Levels of antibiotics that employ concentration dependent killing (aminoglycosides)	1 - 2 hours after oral administration (to obtain peak values, i.e., maximum concentration of drug attained post-administration)[5] and once trough levels, i.e., minimum concentration post-administration (usually attained just before the next dose) have been achieved[67]
4.	Routine plasma concentration (aminoglycosides)	Immediately prior to administering next dose (to obtain trough levels)[5]
5.	Antibiotics by intravenous route	30 minutes post-infusion[5]

Sample collection, storage and processing

After determining the best time for sample collection, for measuring drug levels in serum, venipuncture is performed and the blood obtained is collected in plain gel-free vacutainers and allowed to clot.

Gel containing vacutainers were commonly used previously, as the gel enabled faster separation of serum from other blood components[68]. But in many cases, it was observed that usage of such vacutainers, during storage, yielded a false low drug concentration due to absorption of drugs on the gel[69,70]. Steuer *at al* also noted that this finding was more pronounced in cases of lipophilic and highly plasma protein bound drugs[68,71].

Once the serum is separated, the sample is centrifuged, following which the serum is pipetted and put in polypropylene tubes for storage. The temperature at which samples are stored varies from drug to drug, but most commonly, for short-term storage, samples are kept at –20°C, and for long-term storage at –80°C[72].

Assay methods employed for performing TDM

Considering that TDM is used for many time-sensitive indications, such as dose adjustment and toxicity diagnosis, an ideal assay method is one that can generate results fast, thereby allowing physicians to make therapeutic modifications in a timely manner, that can affect outcomes[73].

Analytical methods commonly used for performing drug assays can be divided into three broad categories: Spectrophotometry, Chromatography and Immunoassays.

i. Spectrophotometry: It a technique based on the central principle that molecules and atoms, when exposed to light of different wavelengths, absorb a portion of it. This method relies on measuring the amount of light absorbed by a compound, which is considered to be proportional to the concentration of the said compound in a solution, as explained by Beer Lambert's law.

ii. Chromatography: This method, currently the gold standard technique, may be defined as a separation technique that relies on the principle that different constituents of a solution react differently with the stationary and mobile phases, based on their physical and chemical characteristics, which allows for their identification, separation, and quantification[74]. Three types of chromatographic techniques that are currently being used for measuring serum concentration of drugs are thin layer chromatography (TLC), gas liquid chromatography (GLC), and high performance liquid

chromatography (HPLC). While TLC is a simple method that yields fast results, is cost effective, and may be used for on-site TDM,[75] GLC and HPLC are the more commonly used techniques that are usually combined with mass spectrometry (MS) or ultraviolet (UV) to yield more advanced and reliable results.

iii. Immunoassays: rely on antigen-antibody reactions to quantify an analyte[76]. Different types of immunoassays, such as, radio immunoassay, enzyme immunoassay and fluorescent immunoassay, are being used in therapeutic drug monitoring.

Table IV summarises the advantages and disadvantages of some commonly used techniques used for measuring serum concentration of drugs.

Table IV: Advantages and disadvantages of commonly used analytical methods

Method	Advantage(S)	Disadvantage(S)
Spectrophotometry[77]	• Simple to use • Cost effective • Small amount of sample required	• Excipients and sample matrix variations may interfere with the results • Non-selective
High-Performance Liquid Chromatography (HPLC)[78]	• Sensitive • Specific • Small sample amount required • Minimal sample processing	• High cost • Specialised staff and training required
Gas-Liquid Chromatography (GLC)[79]	• Cheaper reagents, making it cost effective	• Sample processing and analysis are time consuming
Radio Immuno Assay (RIA)[76,80]	• Precise • Sensitive	• Harmful effects of radiation • Higher cost of waste disposal • Cross-reactivity
Enzyme Immuno Assay (EIA)[81]	• Specific • Cost effective	• Cross reaction with other drugs and compounds • False negative result due to established thresholds
Fluorescence polarisation Immunoassay (FPIA)[76,82]	• Simple • Precise • Easy to perform	• Interference by matrix components • Less sensitive than other immunoassays

After a method is selected, it requires validation before being employed for drug concentration measurements. Factors such as accuracy, precision, detection limits, reproducibility, and robustness are some of the parameters considered while performing validation[1,83].

Guidelines for TDM

The need for conducting TDM for various indications has prompted multiple agencies and regulatory bodies to develop guidelines and consensus panel recommendations. These agencies include:

1. *Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (*AGNP)

   AGNP is a Germany-based "interdisciplinary association" that primarily conducts research on neuro- and psychopharmacology[84].

   The AGNP-TDM working group released its consensus guidelines on therapeutic drug monitoring of psychiatric drugs in 2004, which was later updated in 2011[85] and 2017[86] to include drugs used in neurology as well.

2. International League Against Epilepsy (ILAE)

   ILAE is an organization that primarily aims to "ensure that health professionals, patients and their care providers, governments, and the public world-wide have the educational and research resources that are essential in understanding, diagnosing, and treating persons with epilepsy"[87].

   ILAE does not support routine TDM of antiepileptics.

3. International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

   IATDMCT is an international organisation that mainly works to "to promote the related disciplines of therapeutic drug monitoring and clinical toxicology worldwide"[88].

   The organisation has multiple committees that focus on different groups of drugs, such as biologics, anti-infective drugs, immunosuppressants, etc., and releases consensus guidelines and panel recommendations for or against conducting TDM of drugs.

4. World Anti-doping Association (WADA)

   WADA is an organisation that works to "develop, harmonise and coordinate anti-doping rules and policies across all sports and countries"[89]. The organisation has developed a list of drugs that all participants are screened for, prior to and during tournaments, to determine their eligibility for participation.

5. Regional and national bodies

6. Independent studies

Table V: Drugs and their TDM recommendation status

Group	Drugs	Comments	TDM recommendation status	Recommended matrix
Drugs used in psychiatry (as per AGNP-TDM guidelines, 2017 update[86])	Mood stabilisers • Lithium, Carbamazepine • Valproate and Lamotrigine	**Lithium:** Low therapeutic index. TDM done to ensure patient safety. **Carbamazepine:** TDM done for safety issues **Valproate:** high incidence of drug-drug interactions, TDM recommended every 3 - 6 months/if there are changes in doses **Oxcarbazepine:** required for optimisation at extremes of age, pregnancy, renal insufficiency, suspected non-compliance, etc[90]	Strongly recommended Recommended	Blood-based matrices
	Typical antipsychotics • Haloperidol, Fluphenazine,Thioridazine • Chlorpromazine	High rate of serious ADRs	 Strongly recommended Recommended	-do-
	Atypical antipsychotics • Clozapine, Olanzapine • Aripiprazole, Quetiapine, Risperidone	**Clozapine:** Side-effects and inter-individual variability, significant drug-drug interactions **Olanzapine:** significant drug-drug interactions **Aripiprazole:** levels above a certain level are associated with better clinical efficacy	Strongly recommended Recommended	-do-
	Tricyclic antidepressants • **Amitriptyline, Imipramine, Clomipramine** • **Desipramine**	TDM done for safety concerns (serious cardiac ADRs)	 Strongly recommended Recommended	-do-
	Serotonin Norepinephrine Reuptake Inhibitors: Duloxetine, Venlafaxine	TDM required for dose adjustments	Recommended	-do-
	Selective serotonin Reuptake Inhibitors: • Citalopram • Escitalopram, Fluvoxamine, Vortioxetine	**Citalopram:** maintaining levels is associated with lesser rates of hospitalisation Others: to check for compliance	Strongly recommended Recommended	-do-
Drugs used in neurology/ neurological conditions (as per AGNP-TDM guidelines, 2017 update[86])	**Anti-convulsants** • **Carbamazepine, Phenobarbital, Phenytoin, Valproic acid** • **Lamotrigine, Oxcarbazepine, Zonisamide, Tiagabine, Stiripentol, Rufinamide**	**Carbamazepine:** The metabolite also contributed to ADR development **Phenytoin:** follows "dose-dependent pharmacokinetics"[91] **Lamotrigine:** Half-life variable in presence of other anti-epileptics	Strongly recommended Recommended	Blood-based matrices
	Anti-dementia drugs • Donepezil	These is a positive association of clinical improvement with drug level	Recommended	-do-
Drugs used in cardiology/ cardiovascular conditions (as per Japanese Circulation Society (JCS) TDM guidelines[92])	**Vancomycin** in infective endocarditis	To reduce ADR development rates and to adjust dose in case of non-responders	Strongly recommended[92]	Blood-based matrices
	Aminoglycosides for Infective endocarditis	To reduce ADR development rates	Recommended[92]	-do-
	Digoxin	To decrease the incidence of digoxin intoxication and to bring down ADR development rates	Recommended[92]	-do-
	Amiodarone	Usually done to screen for compliance, and to check the safety and efficacy when dose or form is changed	Recommended[92]	-do-
	Bepridil (class 4 anti-arrhythmic)	For safety reasons (higher doses are associated with QT prolongation) and to screen for compliance	Recommended[92]	-do-
Drugs used in pulmonology/ respiratory conditions	**Theophylline**	Narrow therapeutic index, significant drug-drug interactions[93]	Recommended[93,94]	Plasma
	Caffeine	Recommended under certain conditions: [94]	Might be recommended[94]	-do-

		1. Clinical effect not evident 2. Toxicity is suspected		
Immuno-suppressants	**Tacrolimus**[23]	High inter-individual variability[24]	Recommended[95] by IATDMCT	Whole blood
	Cyclosporine[24]	High inter-individual variability[24] +		-do-
	Sirolimus[24]	drug-drug interactions[24]		-do-
	Everolimus[96]	High inter-individual variations and a narrow therapeutic index[96]	Recommended[96] by IATDMCT	-do-
Drugs used in chemotherapy (anti-cancer drugs)	**Methotrexate**	Significant inter- and intra-individual variations, several drug-drug interactions, and unpredictable renal clearance[97]	Recommended	Plasma
	Busulfan	Associated serious adverse drug reactions, drug-drug interactions, and inter-individual variation with high doses[97]	Recommended	-do-
	5 Fluorouracil	Serious adverse drug reactions, significant	Recommended[98]	-do-
		intra- and inter-individual variability[97]	(Study "endorsed" by IATDMCT)	
	Imatinib	Significant inter- and intra-individual variability[99]	Recommended[99] by IATDMCT	-do-
	Paclitaxel	Inter-individual variations[100]	Recommended[100] by IATDMCT	-do-
Drugs used in chemotherapy (anti-microbial agents)	**Aminoglycosides**	Reduced ADR rates and a shorter length of hospital stay	Recommended in critically ill patients[101] by a panel consisting of members nominated by International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), European Society of Intensive Care Medicine (ESICM), International Society of Antimicrobial Chemotherapy (ISAC), and Pharmacokinetic/Pharmacodynamic (PK/PD) and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	Blood-based matrices
	Beta-lactams	To achieve desired levels and decreasing ADR rates		-do-
	Linezolid	Significant inter- and intra-patient variability		-do-
	Teicoplanin	High inter-individual variability		-do-
	Vancomycin	Volume of distribution and clearance of Vancomycin are altered in critically ill patients		-do-
	Voriconazole	Drug shows significant intra- and inter-individual variability in terms of pharmacokinetics	Recommended[102]	Serum
	Itraconazole	Unpredictable bioavailability and presence of significant drug-drug interactions	Recommended[102]	-do-
	Posaconazole		Mandatory under certain conditions such as: [102] • GI pathology affecting absorption • Compliance issue • Doubt of invasive fungal infection	-do-
	5-FC (5-flucytosine)		Mandatory to avoid toxicity development[102]	-do-

Implications of TDM

1. Efficacy assessment and treatment optimisation

Lim *et al* and Rane *et al* observed that utilizing TDM for determining drug doses in patients on anti-epileptic drugs provided a reduction in frequency of seizure episodes and ADR development rates[103,104]. Similarly, Vande *et al*, demonstrated that for biological agents, such as TNF-alpha inhibitors, TDM-guided dosage regimen was associated with fewer flares during the course of treatment[105], and a study conducted by Syverson *et al* concluded that proactive TDM in patients receiving Infliximab provided better disease control as compared to non-TDM guided treatment, in

inflammatory bowel disease patients[106].

Braal *et al* performed a cost-effective analysis of employing TDM-guided tamoxifen therapy in early breast cancer cases and concluded that the TDM intervention was associated with a higher number of life years and quality adjusted life years (QALYs), and relatively lesser healthcare expenses[107].

2. Ensuring patient safety

Since the introduction of TDM in the 1960s, one of the common indications for its use has been prevention of adverse drug reactions and toxicity development. For instance, in their studies, Steetman *et al*, and Darko *et al* utilised TDM to determine doses that helped reduce the incidence of nephrotoxicity development in patients taking aminoglycosides and vancomycin respectively[108,109].

A retrospective study conducted by Charfi *et al* revealed that TDM of digoxin played an important role in prevention of toxicity development especially in older adults[110].

3. Compliance monitoring

Utilizing TDM especially in cases where inadequate response to treatment is being observed, can help us understand if the reason underlying therapeutic failure is related to compliance before other causes are considered.

Gerona *et al* used Isoniazid concentrations in hair to assess adherence to ATT in people living with HIV[111].

Avataneo *et al* utilised TDM to monitor adherence in cases of resistant hypertension and screen for factors that contributed to poor compliance in such patients. This study revealed that a total of 42 per cent of enrolled patients were not adhering to the prescribed treatment, which was perceived as "drug resistance" due to inadequate response[112].

Similarly, Kylleso *et al* performed a study in treatment resistant schizophrenia cases and discovered a significant percentage of people who were diagnosed with this condition had undetectable levels of previously used antipsychotics, which strongly pointed towards a lack of compliance on patients' part[113].

4. To monitor drug-drug interactions

A review study conducted by Spina *et al*, on drug-drug interactions associated with second generation antipsychotics (Clozapine, Risperidone, Quetiapine, etc), recommended utilizing TDM when a cytochrome P450 inducer or inhibitor was to be given concomitantly, especially for drugs with a narrow therapeutic index (risperidone, sertindole)[114].

Gagno *et al* uncovered a case of drug-drug interaction when a patient who was on Imatinib for a gastrointestinal stromal tumour, presented with tumour growth and TDM revealed subtherapeutic levels of the drug due to concomitant consumption of carbamazepine, a CYP3A4 and P-gp inducer[115].

Gex-Fabry *et al* emphasized on the importance of including TDM database for monitoring drug-drug interactions during post-marketing surveillance[116].

5. To reduce healthcare costs

A systematic review article by Marquez-Megias *et al* demonstrated that "TDM strategy" of dosing anti-tumour necrosis factor (TNF) drugs in inflammatory bowel disease (IBD) patients was more cost saving as compared to an "empiric strategy"[117.]

And a meta-analysis by Ricciuto *et al* similarly concluded that reactive TDM provided a better "cost benefit" as compared to empiric treatment in IBD patients receiving Infliximab[118].

6. In forensic studies and toxicology

In the current scenario, with many matrices available for performing TDM, it has become possible to screen for drugs and other substances post-mortem. Bone has been used as a TDM matrix in post-mortem studies to screen for anticonvulsants, antidepressants, opioids, etc[63,64]. Similarly, vitreous fluid has been used in forensic studies to screen for cocaine and opioid misuse.

TDM can also aid in suspected cases of homicide and suicide resulting from administration/intake of drugs in lethal doses. For instance, in 2007, a 24-year-old woman was murdered by administration of a toxic dose

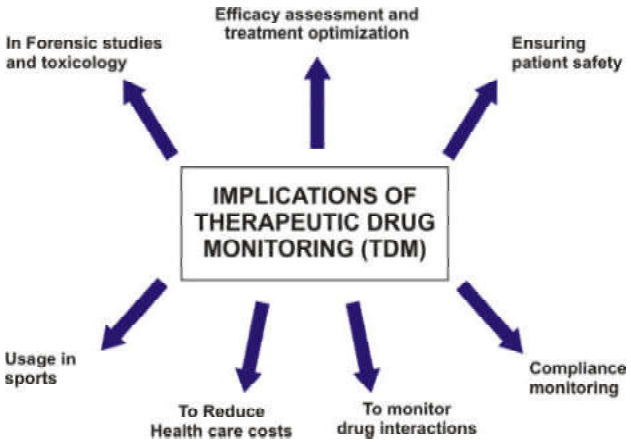

Fig. 2: *Implications of therapeutic drug monitoring.*

of propofol. Blood propofol concentration measurement was pivotal in solving this case[119].

Similarly, three members of a family were given toxic doses of colchicine which initially caused all the three individuals to develop non-specific symptoms, like vomiting and diarrhoea, and later turned out to be fatal for all three patients. Measurement of colchicine in the serum and urine of the third patient helped the clinicians reach the diagnosis of colchicine toxicity[120].

Homicide by Arsenic poisoning is yet another scenario that is commonly diagnosed, post-mortem, using TDM. Duncan *et al* reported a case of a patient who presented with non-specific features to a hospital. The patient succumbed to the illness before the correct diagnosis could be made. On performing routine post-mortem toxicology screening on liver, urine, blood and hair samples, a diagnosis of arsenic poisoning was made by the treating physicians[121].

7. Usage in sports

TDM is used in sports to detect doping amongst athletes. World Anti-doping Association (WADA) utilizes drug/substance concentration monitoring in different matrices to screen for potential abuse[122].

WADA tests for drugs such as anabolic steroids, beta 2 agonists, glucocorticoids, diuretics (such as acetazolamide, furosemide, bumetanide, spironolactone), vaptans (such as tolvaptan, conivaptan), desmopressin, erythropoietin receptor agonists (such as darbopoetin), TGF-β antagonists (such as Luspatercept, Sotatercept), GnRH analogues (such as goserelin, busurelin), GH analogues, GHRH analogues (such as sermorelin and tesamorelin), growth factors (such as IGF-1, FGF, PDGF, VEGF), aromatase inhibitors (such as letrozole, anastrolozole), SERMs (such as Clomifene, Fulvestrant, Raloxifene, Tamoxifen), stimulants (such as cocaine, amphetamine, mephentermine), opioids (such as morphine, tramadol, methadone), beta blockers (such as propranolol, sotalol, esmolol), etc[122]. The most commonly used matrix is urine, and abuse is determined on the basis of limits set by previous studies.

TDM and precision medicine

Precision medicine, also referred to as personalised medicine, has been introduced as the successor of evidence based medicine with both the fields opposing the concept of "one size fits all" approach to drug therapy[10]. This branch of medicine requires physicians to take genetic, environmental and lifestyle factors into account while prescribing drugs[123].

TDM which is considered to be a "snapshot" of drug exposure and the effect of genetic, environmental, nutritional factors, concomitant drug use, etc., on drug levels[124], can significantly contribute towards development of precision medicine by improving our understanding of pharmacokinetics and pharmacodynamics at individual level[125].

While pharmacogenomics and pharmacogenetics are being advocated as potential aids in the development of personalised medicine[126], concurrent usage of TDM can help achieve target concentrations more effectively. In this combined setup, pharmacogenomics can help determine the initial dose, and TDM can be used to monitor and adjust subsequent doses according to concentrations and pharmacodynamics characteristics[127].

For example, TDM and pharmacogenomics are being increasingly employed together to develop personalised medicine for Isoniazid (INH) in patients suffering from Tuberculosis[128]. A study conducted by Jing *et al*, in Chinese pulmonary tuberculosis patients, utilised analysis of N-acetyltransferase 2 (NAT2) gene polymorphisms to categorize subjects into fast, intermediate, and slow acetylators. On the basis of this information, patients were given different doses of isoniazid. Drug concentrations were then measured and assessed for each patient, which led to development of a model that helped in estimation of appropriate doses for all the three groups[129].

Underdosing of tacrolimus has been historically associated with graft rejection while overdosing increases the risk of development of ADRs. Studies have shown that in patients who express CYP3A5, tacrolimus levels are lower than non-expressors, which results in a higher proportion of graft rejection cases[130]. A study conducted by Schönfelder *et al* revealed that administration of genotype-guided tacrolimus therapy led to attainment of equivalent trough levels in transplant patients, which in turn resulted in similar incidences of graft rejection, nephrotoxicity, and development of anti-HLA antibodies amongst CYP3A5 expressors and non-expressors[131].

TDM and Artificial Intelligence (AI)

Machine learning (ML), a subset of AI may be used for designing prediction models. While this can help in bringing down the number of samples required for TDM, large training sets are required for development of such models[132]. Pioneering work in this field was done by Woillard *et al*, who developed prediction models for tacrolimus and mycophenolic acid, which provided better results than the existing Bayesian estimation approach[133]. Advantageous usage of ML in TDM was further proven by Huang *et al*, who used an ML model to accurately predict trough vancomycin

levels in children[134].

Similarly, machine learning may aid in the development of population pharmacokinetic models. These models are usually developed to understand how patient-specific factors can alter various pharmacokinetic parameters. When compared with traditional pharmacometrics models for selection of covariates, the ML models provided comparable results in a short amount of time[132].

Based on the findings of their study, Dijkman *et al* concluded that an integrated approach, utilizing both TDM and dosing algorithms, can be used to create personalised treatment, for patients on antiepileptic medication, which helps in more effective target attainment than using TDM alone[135].

TDM in India

TDM is carried out in either large tertiary care teaching hospitals or corporate hospitals. While multiple labs have set up drug concentration measurement facilities, their lack of association with physicians who might be able to clinically interpret the findings, disqualifies them from being considered as TDM centers[136].

There are certain issues specific to India that hamper the growth of TDM in the country[136]:

1. The therapeutic ranges are usually taken from studies conducted in developed countries, many of which fail to take ethnic factors unique to Indians into consideration.
2. TDM requires expensive resources and setups, which is difficult to achieve in India. Justifying these expenses in addition to the enormous healthcare burden is one of the major challenges that hamper TDM development in the country.
3. Skilled manpower is needed to set up and run TDM facilities and currently, there are no official programs that equip individuals with the desired set of skills.
4. There is lack of awareness amongst healthcare workers regarding the application and utility of performing TDM.
5. There are quality standard issues due to lack of regulations regarding mandatory standard maintenance in the country.

Conclusion

Therapeutic drug monitoring can help improve treatment outcomes and safety profile for patients. It is a complex process that requires a multidisciplinary approach comprising of clinicians, pharmacologists, as well as other healthcare workers involved in patient care. Quality TDM requires adoption of standard operating procedures which must be implemented thoroughly.

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CASE SERIES

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Sjögren's Disease: A True Multisystem Masquerader

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Abstract

We report a series of three cases of a common autoimmune disorder, Primary Sjögrens Disease. The hallmark of this disease is glandular involvement presenting as sicca symptoms in the form of dry eyes and dry mouth. But in our series all three cases did not have sicca symptoms and presented with extraglandular involvement in the form of hypokalaemic paralysis with distal renal tubular acidosis in case 1, autoimmune hepatitis and massive splenomegaly with thrombocytopenia in case 2 and Acute Transverse Myelitis with NMO spectrum disorder in case 3. A lip biopsy led to a confirmed diagnosis in all 3 cases.

All patients responded to immunosuppressive treatment. We wish to highlight the fact that Sjögren's Disease can present without typical sicca symptoms and have solely extraglandular manifestations which a clinician should be aware of, and lip biopsy which is a minor procedure should be done wherever necessary to confirm the diagnosis.

Key words: Primary Sjögren's Disease, sicca symptoms, extraglandular involvement, lip biopsy.

Introduction

Sjögren's Disease is a rheumatological disease with varied clinical manifestations. Although it is classically known to present with glandular manifestations in the form of dry eye and dry mouth in the majority of patients, but it can have many extra-glandular systemic manifestations, as has been reported extensively in literature. It can affect all systems with varying frequency with musculoskeletal and cutaneous being most common followed by renal, haematological, neurological, respiratory and gastrointestinal. However, the majority of patients presenting with extra-glandular systemic involvement have been shown to have sicca symptoms, either on history or on objective evaluation of tear production like Schirmer's test or Tear film Break Up Time (TBUT). We report 3 cases of Sjögren's disease who presented with extra-glandular manifestations affecting renal, GIT and neurological system, respectively, but did not have classical sicca symptoms on history and even on objective evaluation.

Case 1

A 20-year-old woman presented with a 4 months history of bilateral symmetrical polyarthrlagias mainly over large joints like shoulder, hips and knees along with constitutional symptoms like low grade fever, easy fatiguability and generalised weakness. She did not have a history suggestive of connective tissue disorders like oral ulcers, photosensitivity, dry eyes, dry mouth, Raynaud's phenomenon, muscle weakness, etc. However, she had a significant past history of 4 - 5 episodes of hematemesis 4 years back which was managed conservatively and a history of itchy maculopapular rashes over bilateral lower limb. On examination, she had significant pallor, and maculopapular rashes over lower limbs. Abdominal examination revealed moderate splenomegaly, 10 cm below left costal margin till the umbilicus.

On basis of history and examination our diagnostic possibilities were:

Chronic Infections like Malaria, Kala Azar, TB, Brucellosis.

Non-Infectious conditions like Portal Hypertension, and Haematological disorders including malignancies.

Autoimmune Rheumatic Diseases: Rheumatoid Arthritis, SLE, Still's Disease.

Investigations:

CBC, ESR	6.5/3900/49000, 51 mm/hr s/o Pancytopenia P/S - Normocytic and Normochromic RBCs with reduced leucocytes and platelets with no atypical cells.
Reticulocyte Count	1.9%
CRP	18 mg/L (<10 mg/L)
LFT	T Bil 1.2 mg/dL SGOT 187 U/L, SGPT 105 U/L ALP 640 U/L
KFT	Urea 44 mg/dL Cr 0.8 mg/dL
Total Protein Albumin	7.2g/dL 3.3 g/dL
U R/M U C/S	pH 5.8 Protein -ve WBC 1 - 2/hpf RBC 1 - 2/hpf No growth

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Iron Profile	Within Normal Limits
Vit B12/FA	Normal
DCT/ICT	Negative

Ultrasound of abdomen and Doppler showed splenomegaly of 20 cm. Liver echotexture was normal with no evidence of portal hypertension. No lymphadenopathy or ascites were noted.

Upper GI endoscopy was also normal with no evidence of portal hypertension.

Investigations: (Case 1)

rK 39 Antigen, Malarial Antigen, Scrub, Brucella serology	Negative
HBsAg, Anti HCV, HIVI/II	Negative
RF, Anti CCP	Negative
Total IgG levels	1608 mg/dl (<1500)
Serum protein electrophoresis	Polyclonal gamma globulin spike
ANA (IF method)	**1:80 (speckled pattern)**
Anti SMA, LKM, AMA	Negative
ENA profile	
Anti dsDNA	Negative
Anti Sm	Negative
Anti Ro (SSA)	**Positive 66 (<20)**
Anti La (SSB)	**Positive 58 (<20)**
Anti RNP	Negative
Anti Histone	Negative

In view of pancytopenia and splenomegaly, a possibility of haematological malignancy or lymphoma was considered. However, the patient refused a Bone marrow biopsy. Moreover, there was absence of peripheral and intrabdominal lymphadenopathy making lymphoma less likely.

In view of deranged LFT (SGOT/SGPT/ALP) a possibility of autoimmune hepatitis or overlap syndrome was entertained, however considering negative Anti LKM, ASMA and AMA, this possibility was less likely, so a liver biopsy was deferred.

In view of negative history of photosensitivity, oral ulcers, alopecia, etc., and negative results of RF, Anti CCP, anti dsDNA and antiSm and possibility of rheumatoid arthritis and connective tissue disease like SLE were less likely.

Considering high titres Anti Ro/La positivity Sjögren's disease was considered, so further tests were done. Schirmer's Test was negative, F stain did not reveal any abnormality, and Tear film Break Up Time (TBUT) was normal in both eyes (>10 s). Salivary flow estimation could not be done in our centre.

So, to confirm the diagnosis of Sjögren's Disease we did a lip biopsy, which showed extensive lymphoplasmacytic infiltrates around minor salivary glands and ducts with *Focus score* >1 suggestive of Sjögren's Disease.

Final Diagnosis: Sjögren's disease without sicca symptoms with extra-glandular involvement in the form of massive splenomegaly with pancytopenia with hepatitis.

Management: Patient was treated with oral steroids 1 mg/kg. Her symptoms improved after 2 weeks of follow-up; her pancytopenia improved (9.8/4500/1.2), LFT improved (T Bil1.1/SGOT 77/SGPT 55, ALP 360). Spleen size also reduced to 7 cm below left costal margin. Patient is on follow-up and planned for steroid tapering and adding a steroid sparing agent.

Case 2

A 50-year-old women presented to the emergency department with complaints of weakness in all four limbs. She was fine when she went to bed at night. However, she woke up at 2 AM and found that she was not able to move any of her limbs. She had around 2 bowls of food at night. There was no history of any antecedent illness, decreased sensations over her body, fever, slurring of speech, neck pain, headache, vomiting or joint pains. There was no past history of diabetes, hypertension or thyroid disorder and no history of similar complaints in the past.

On examination, she was conscious, oriented with intact higher mental functions. No neck stiffness or Kernig's sign was elicited. Motor examination revealed a power of 1/5 across all 4 limbs with decreased tone, absent deep tendon reflexes, mute plantar reflex and normal sensory examination.

Investigations: (Case 2)

CBC, ESR	9.9/8900/71,000, 25 mm/hr
KFT	Urea 45 mg/dL Cr 0.6 mg/dL
Na/K	139 meq/L/**1.6 meq/L**
Ca/ Mg	8.5 mg/dL/2.1 mg/dL
LFT	T Bil 0.5 mg/dL/SGOT30 U/L/SGPT31 U/L/ALP129 U/L
Blood gas analysis	**pH 7.317** **HCO3 14.2 mmol/L** **pCO2 28.7 mmHg** **Anion Gap 7.5 mmol/L**
Urine pH	**6.5**
Spot Urinary K^+	**30 meq/L (20 - 100)**
Urinary Anion Gap ($Na^+ + K^+ - Cl^- + HCO3^-$)	**Positive**

Viral Markers – HBsAg/Anti-HCV/HIV- 1/2 negative

In view of normal anion gap metabolic acidosis and

hypokalaemia with high urinary pH (>5.5), high normal spot urinary potassium in spite of hypokalaemia, and a positive anion gap we suspected distal renal tubular acidosis (RTA).

Further investigations were done to look for an underlying connective tissue disease.

ANA by IF Method	**1:80 /Speckled Pattern**
ENA Profile	
Anti dsDNA	Negative
Anti Sm	Negative
Anti Ro (SS-A)	**Positive - 58 (<20)**
Anti La (SS-B)	**Positive - 36 (<20)**
Anti RNP	Negative
Anti Histone	Negative

Since patient did not have sicca symptoms, objective tests for tear production were done which were also within normal limits.

Schirmer's Test – Normal (>10 mm in 5 minutes)

Tear Film Break Up Time (TBUT) – Normal

To further evaluate for Sjögren's disease we did ultrasound of head and neck region, a which showed multiple hypoechoic nodules in B/L parotid and submandibular glands. X-ray KUB did not show any nephrolithiasis sometimes seen in cases of RTA. A lip biopsy was carried out which showed extensive lymphoplasmacytic infiltrates around minor salivary glands and ducts with *Focus score >1* suggestive of Sjögren's disease.

Final Diagnosis: Sjögren's disease without sicca symptoms with extra-glandular involvement in the form of distal renal tubular acidosis leading to hypokalaemic periodic paralysis.

Management: The patient was managed with intravenous potassium chloride infusion. Her weakness recovered within a day. Prednisolone was given at dosage of 1 mg/kg for 4 weeks with plan to taper after 4 weeks. She was also started on, potassium citrate solution to which patient responded. She was discharged with proper dietary instructions.

Case 3

A 35-year-old woman presented with sudden onset weakness of both lower limbs with loss of touch and cold sensation till nipples, and had difficulty in perceiving bladder and bowel sensation. On examination, she had a power of 1/5 in both lower limbs and absent deep tenon reflexes with positive Babinski's response. Sensory system showed reduced pain and temperature sensation till nipples (T-4 leval).

A diagnosis of Acute Transverse Myelitis was made and patient was given pulse intravenous methylpred nisolone injection.

Investigations: (Case 3)

CBC, ESR	10.5/8900/249000, 35 mm/hr P/S -Normocytic and Normochromic smear
CRP	14 mg/L (<10 mg/L)
LFT	T Bil 1.2 mg/dL SGOT 47 U/L, SGPT 42 U/L ALP 140 U/L
KFT	Urea 32 mg/dL, Cr 0.7 mg/dL
Serum Protein, Albumin	6.5g/dL, 3.8 g/dL
HbsAg, Anti HCV, HIV	Negative
CSF Examination	Protein 65 mg/dL Sugar 76 mg/dL Total Cells 30/hpf, DLC L90 N10
CSF Gram stain, C/S	Negative
ADA / Gene xpert	Negative
PCR (HSV, CMV, EBV, JE)	Negative

CSF evaluation showed mild lymphocytic pleocytosis with mildly elevated proteins, and an Infective work-up was negative. MRI of the Spine showed evidence of long segment myelitis from D2 to D6 thoracic vertebrae. Her NMO IgG/AQP4 levels were raised. She did not have evidence of optic neuritis, and a diagnosis of NMO spectrum disorder was made (NMOSD).

Other Investigations: (Case 3)

ANA by IF Method	**1:160 /Speckled Pattern**
ENA Profile	
anti dsDNA	Negative
Anti Sm	Negative
Anti Ro (SS-A)	**Positive 42 (<20)**
Anti La (SS-B)	**Positive 34 (<20)**
Anti RNP	Negative
Anti Histone	Negative

On further evaluation, ANA was positive and ENA profile revealed Anti Ro and Anti La positivity. However, she did not complain of sicca symptoms but gave history of intermittent joint pains with morning stiffness.

Her Schirmer's test and Tear film Break up time (TBUT) were normal. A Lip biopsy was done which showed extensive chronic lymphoplasmacytic infiltrates around glands and ducts with focus score >1 consistent with Sjögren's disease. She was administered 2 doses of Rituximab 1 gram 2 weeks apart to which she responded. Her power improved to 4/5 within 1 month and sensory symptoms also improved. Repeat MRI and continuation of immunosuppression is planned.

Discussion

Sjögren's disease (SD) is an autoimmune disorder affecting mainly glandular organs like major and minor salivary glands with prototypic manifestations such as dry eye and dry mouth, also known as sicca symptoms.

The interesting point in this case series is the absence of classical sicca symptoms even on objective evaluation like Schirmer's test, Tear film Break Up Test (TBUT) and F test suggesting normal tear production. However, salivary flow estimation could not be done. We want to highlight that all our patients presented with extra-glandular manifestations only.

In most of the case series of SD in Western literature, patients presented with classical sicca symptoms and parotitis[1,2]. Although it has been reported that almost 40 - 50% of cases presenting with neurological symptoms may not present with classical sicca symptoms, especially those presenting with CNS manifestations like demyelination or encephalopathy as compared to those presenting as peripheral neuropathy; however, they generally develop sicca symptoms later or show positive result on objective evaluation like Schirmer's and Tear film Break Up Test[3].

As far as Indian population is concerned, in a retrospective analysis *et al* 332 Indian patients by Sandhy, *et al* it was seen that sicca symptoms were the presenting manifestation in only 8 - 10% cases, although by further evaluation it was present in the majority (94%) of patients[4]. The authors divided their cohort into 2 groups, one with more sicca symptoms but with milder extra-glandular manifestations mainly musculoskeletal symptoms, while the other group of patients had less of sicca symptoms but more severe systemic manifestations, and higher titres of anti-Ro and La. Our patients resemble the latter group of patients.

Various studies have shown that extra-glandular manifestations are observed in 20 - 25% cases with musculoskeletal being the most common followed by cutaneous, renal, respiratory and neurological involvement[5,6].

In our first case a young patient presented with predominantly large joint polyarthralgia, pancytopenia, hepatitis (likely autoimmune), moderate splenomegaly, past history of upper GI bleed and purpuric skin rashes which are uncommon manifestations of SD. She also did not have sicca symptoms. However, arthralgias are the most common extra-glandular manifestation of SD but other manifestations such as moderate splenomegaly with pancytopenia and hepatitis are rare. Other differential diagnoses like portal hypertension, haematological disorders, tropical infections, RA, SLE, AIH and overlap syndrome were ruled out by appropriate investigations. High titres of anti-Ro and La made us suspect SD which was later confirmed by a lip biopsy.

Another unusual manifestation in these case was the presence of massive splenomegaly and transaminitis with bleeding manifestations. Very few case reports have mentioned such findings in SD. In one case report, the patient of SD had manifestations of type 2 autoimmune hepatitis along with massive splenomegaly which responded to steroids[7].

Renal involvement in SD varies from 5 - 10% all cases. It can occur in the form of distal RTA, tubulointerstitial nephritis, glomerulonephritis or IgA nephropathy. Diabetes insipidus and nephrocalcinosis have been observed in a few cases[8].

In the second case, patient presented with hypokalaemic paralysis. Generally, hypokalaemia is associated with metabolic alkalosis, so whenever it is associated with metabolic acidosis suspect distal RTA by measuring serum anion gap which should be normal along with a positive urinary anion gap and alkaline urinary pH (>5.5) in the presence of metabolic acidosis. SD was suspected in this case after serology showed high titres of anti-Ro and anti-La and was later confirmed by doing ultrasound evaluation of salivary glands and lip biopsy. She responded to potassium replacement and steroids.

In case 3, the patient presented with features suggestive of non-compressive myelopathy, diagnosed as Longitudinally Extensive Transverse Myelitis with NMOSD (NMO IgG and Aquaporin 4 positive) and responded to steroids and Rituximab.

Neurological manifestations in are common extra-glandular presentation with a prevalence of 8.5 - 70% in various case series[3], most common of which includes peripheral neuropathy, especially sensory polyneuropathy. Although motor neuropathy, mononeuritis multiplex, sensory ganglionopathy, and cranial neuropathy can also occur. CNS involvement is less common (2 - 25%)[9]. SD presenting as transverse myelitis has been reported in literature as case reports[10,11].

Cases of LETM with NMO spectrum disorder in a known case of SD have been reported[12,13], while in our patient it was the presenting feature. Also, in 30 - 40% cases, NMO antibody may be negative[14]. So, we should rule-out SD in all cases of LETM even if NMO antibody is negative and without classical sicca symptoms.

By reporting this case series we want to focus attention of readers to the fact that SD is not an uncommon disease as previously thought. Indian patients may not present with classical sicca symptoms but with various extra-glandular organs involvement like renal, neurological, respiratory,

hepatobiliary, and cutaneous. As a physician, it is important to be aware of these organs involvement and consider workup of serology, and USG of parotids which are simple non-invasive tests. Also, lip biopsy should be done in suspected cases as it is a OPD based minor procedure, with gratifying results.

Conclusion

SD is a common autoimmune connective tissue disorder with varying clinical presentations. It is a true multisystem disease. Diagnosis is easy to make in cases presenting with classical features. However, in our cases none of the patients had typical sicca symptoms, but all were serologically positive. A high index of suspicion especially in cases with hypokalaemic periodic paralysis, peripheral neuropathy and demyelinating diseases like myelitis should be there and awareness of various extra-glandular organs involvement is very essential. The importance of porforming a lip biopsy a minor procedure to confirm the diagnosis, us emphosised.

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CASE REPORT

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Oral Clues to a Silent Systemic Disease: Acute Leukaemia

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Abstract

Oral health it is an essential aspect of overall wellness and a significant indicator of systemic health. The mouth is often described as a "window to the body" as it can reveal early signs of underlying systemic diseases. In certain instances, these oral symptoms may be the initial or even the sole indicators of disease, positioning a dentist or oral health professional as the primary line of defense in early detection. In this report, we present a case involving a 39-year-old woman who exhibited gingival swelling and ecchymoses in the palate, initially suspected to have leukaemia, which was later confirmed through haematological investigations. Therefore, oral clues are not just incidental findings but often the earliest and most overt signs of a "silent" systemic disease.

Key words: Leukaemia, dental, gingival enlargement, petechiae.

Introduction:

The oral cavity is widely recognised as a reflection of overall health, often revealing early signs of systemic diseases before other symptoms emerge. Although these oral manifestations are not always unique to a specific disease, they frequently serve as important early warning signs of underlying health issues[1]. In some instances, oral findings may be the first or sole clinical evidence of a systemic disorder, emphasizing the critical role of dental professionals in early detection. Early identification of such signs is vital, as it can help clinicians achieve accurate diagnoses and initiate treatment promptly, ultimately improving patient outcomes[2]. One such classic example is Leukaemia.

Leukaemia is a malignant haematopoietic disorder characterised by uncontrolled proliferation of abnormal white blood cells, often leading to anaemia, recurrent infections, bleeding tendencies, and oral manifestations such as gingival enlargement, petechiae, and spontaneous bleeding[3]. Among its subtypes, acute promyelocytic leukaemia (APML) is a distinct variant of acute myeloid leukaemia characterised by the accumulation of abnormal promyelocytes in bone marrow and peripheral blood. Unlike other leukaemias, the disease process involves complex molecular and haematological alterations that can influence the clinical presentation and course of the illness. The pathogenesis is strongly associated with a reciprocal translocation between chromosomes 15 and 17, leading to the PML-RARA fusion gene, which disrupts normal myeloid differentiation[4]. This alteration not only defines the disease but also provides a unique therapeutic target, making APML one of the most treatable forms of leukaemia when recognised early. However, its presentation may be atypical, and timely diagnosis is critical as patients are at high risk of life-threatening haemorrhage due to associated coagulopathy. In this report, we present an unusual case of APML first suspected and subsequently diagnosed in a dental setting. This highlights the pivotal role of oral healthcare providers in identifying early manifestations of systemic haematological malignancies, especially when patients present with atypical oral or bleeding symptoms.

Case Presentation

A 39-year-old woman reported with the chief complaint of gingival swelling persisting for one month. The swelling had a gradual onset, was progressive in nature, and had reached its present size without associated pain or discharge. Her medical history revealed an episode of typhoid fever one month earlier, for which she had discontinued the prescribed medication 15 days prior to presentation. The patient underwent oral prophylaxis 10 days before visiting department.

On examination, bilateral submandibular lymph nodes were palpable, tender, soft in consistency, and not fixed to underlying structures. Intraoral examination revealed generalised gingival enlargement involving both maxillary and mandibular arches. The enlargement extended up to one-third of the labial surface of the anterior teeth and two-thirds in the maxillary posterior region. The interdental papillae were observed to be rounded, with localised areas of erythema noted on the gingiva of the anterior teeth. Additionally, these areas were covered with a yellowish-white plaque that could not be scraped off. (Fig. 1). The periodontal examination indicated no formation of pockets,

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and no mobility of teeth was detected.

The palatal mucosa showed areas of ecchymosis at the junction of the hard and soft palate in the mid-palatal region, with diffuse borders, along with multiple pinpoint erythematous lesions that were more pronounced on the right side, approximately 1 mm away from the mid-palatal raphe, with no evidence of active blood discharge (Fig. 2).

Based on these clinical observations, a provisional diagnoses of gingival enlargement secondary to an underlying systemic condition and transient thrombocytopenic purpura, was made. The differential diagnosis included drug-induced gingival enlargement, gingival fibromatosis, and necrotizing ulcerative gingivitis.

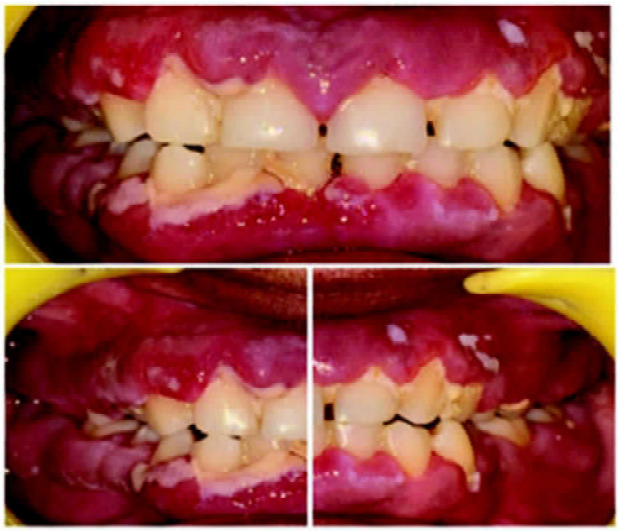

Fig. 1: *Generalised gingival enlargement.*

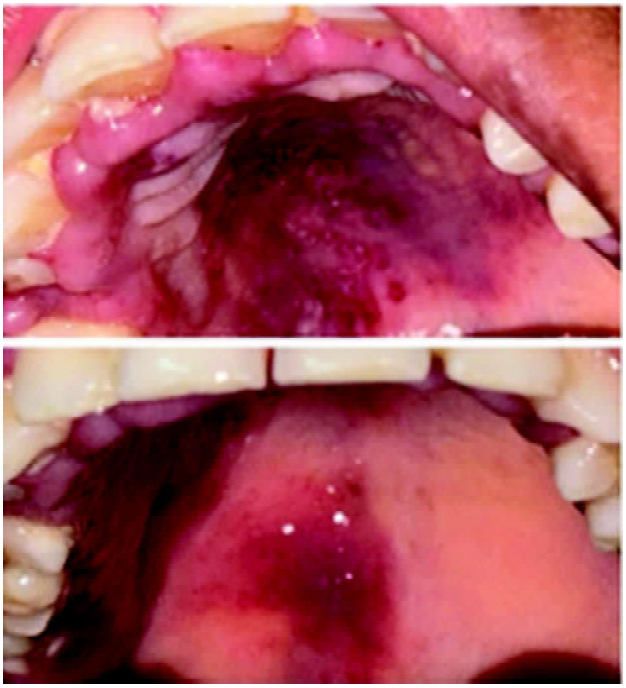

Fig. 2: *Ecchymosis on palate with multiple pin point erythematous lesions.*

The patient was advised to undergo haematological investigations, including a complete blood count (Table I), which, along with peripheral smear analysis, revealed the presence of macrocytic blast cells (Fig. 3), highly suggestive of leukaemia. The patient was then referred to a specialised oncology centre, where further diagnostic evaluation using flow cytometry, confirmed the diagnosis of acute promyelocytic leukaemia (APML). Flow erjternetric analysis revealed a blast population with CD45 din empression. Blasts showed bright CD33, moderate CD13, CD117, DR, CD99 cytofiasme MPO, TDT, and dis CD34 with abenant CD4 and CD7 cachrinian. The patient is currently undergoing chemotherapy.

Table I: Haemogram.

Haemoglobin	8.0 g/dl
White blood cells	2,32,800 cells/cumm
Platelets Blast cells	**70,000/cumm**
Promyelocytes	02%
Neutrophils	04%
Lymphocytes	22%
Monocytes	01%
Eosinophils	01%

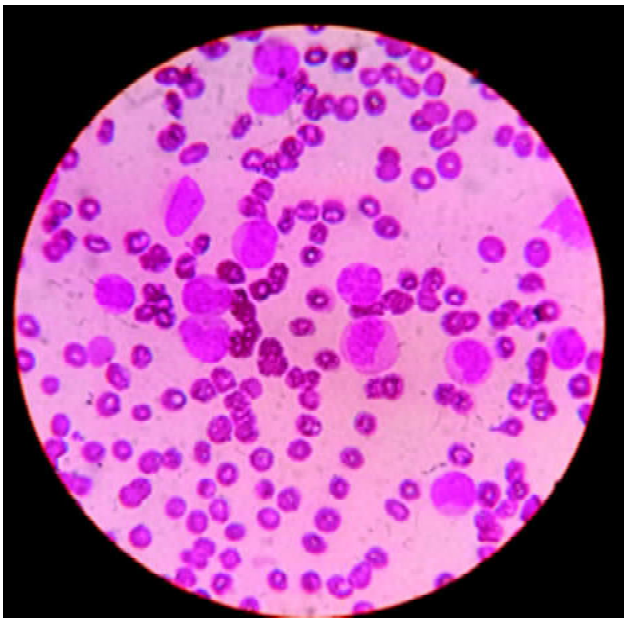

Fig. 3: *Peripheral smear showing blost cells.*

Discussion

Acute myeloid leukaemia (AML) is a rapidly progressing haematological malignancy, accounting for nearly one-fourth of adult leukaemias. Its clinical manifestations predominantly stem from haematopoietic failure, reflected as thrombocytopenia, anaemia, and leukocytosis with circulating blasts. These systemic alterations often have direct oral implications[3]. Hou *et al* reported that oral lesions are more commonly associated with acute than with chronic leukaemias[5]. Consistent with this, Adeyemo *et al* observed that within the acute subtypes, acute myeloid leukaemia (AML) occurs more frequently than acute lymphoblastic leukaemia (ALL), with oral bleeding presenting as the initial symptom in 43.2% of AML cases and gingival enlargement in 26.3% of patients[6]. These findings support the notion that oral changes may be both nonspecific and pathognomonic, serving as crucial diagnostic clues when systemic disease is not yet clinically apparent.

In the present case, generalised gingival enlargement, palatal ecchymosis, and pinpoint petechiae were the key findings that raised suspicion of an underlying haematological disorder. These features are consistent with reported oral presentations of AML, which commonly arise due to thrombocytopenia-induced bleeding tendencies, leukaemic infiltration of gingival tissues, and impaired host immune function[7]. Similarly, the ecchymoses and petechiae observed in our patient reflect platelet dysfunction and coagulopathy, hallmark complications of AML[8]. The concurrence of these manifestations in this case highlights the diagnostic value of oral findings and their potential role as sentinel signs of a life-threatening systemic malignancy.

Several case reports in the literature echo the present findings, where oral changes were the first sign of APML. Saito *et al* described gingival bleeding and pericoronitis as initial clinical manifestations[8], while Yoshida *et al* reported gingival swelling in the third-molar region as the earliest indicator[7]. Suárez-Cuenca *et al* observed that periodontal alterations can be the initial presentation of APML, stressing the importance of early recognition to prevent their rapid and potentially severe progression[9]. Collectively, these reports emphasize that oral healthcare providers must maintain vigilance when confronted with atypical gingival or mucosal lesions, particularly those accompanied by unexplained bleeding.

Conclusion

Oral changes such as gingival enlargement, ulceration, and spontaneous bleeding may represent the first clinical indicators of AML. Their early recognition is therefore crucial for timely referral and initiation of treatment. A collaborative approach between dental and medical professionals, together with patient awareness and gentle oral care practices, can help reduce diagnostic delays and treatment complications. Ultimately, prompt diagnosis and integrated management remains key to improving survival and quality-of-life in affected individuals.

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CASE REPORT

JIACM 2025; 26 (4): 217-19

Primary Bone Marrow Hodgkin's Lymphoma Presenting with Pancytopenia

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Abstract

Pancytopenia can be sired by a myriad of diseases. Hodgkin's lymphoma (HL) usually presents with lymphadenopathy. Nevertheless, few patients can present with atypical symptomatology of HL which usually poses a clinical and diagnostic challenge. Very few cases of HL with first presentation as pancytopenia without lymph node involvement are described in the literature. Here we report a case of a young adult who presented with a history of fever, malaise and weight loss for one year. He had no lymphadenopathy on physical examination. Laboratory investigations showed pancytopenia with elevated LDH. Imaging confirmed no lymphadenopathy. Bone marrow biopsy was done which showed features of HL. FDG PET-CT scan done at the time of presentation after bone marrow biopsy showed hypermetabolic skeletal involvement. Patient was started on chemotherapy and responded well to the treatment. FDG PET-CT done after 6 cycles of chemotherapy revealed complete response to therapy. Atypical forms like primary bone marrow HL present with constitutional symptoms and have a protracted clinical course. Precise and prompt recognition of Primary HL is required for successful management of this rare entity.

Key words: Hodgkin's lymphoma, pancytopenia, Reed-Sternberg cells, primary bone marrow Hodgkin's lymphoma.

Introduction

Pancytopenia is a clinico-hematological entity which is characterised by reduction of all three cell lines. It can be a feature of a wide array of diseases, ranging from benign conditions to malignant neoplasms, either primary haematologic malignancies or non-haematologic metastatic malignancies. HL involves clonal proliferation of mature B lymphocytes. Around 90% of HL are classical, whereas the remaining 10% are lymphocyte predominant[1]. HL typically presents with lymphadenopathy, most commonly involving nodes of cervical, mediastinal or axillary region. In a few patients, B symptoms like fever, weight loss and night sweats can predominate. Bone marrow infiltration is usually known to occur in advanced stages of HL which can present with symptomatic anaemia, bony pain or pancytopenia[1,2]. Primary bone marrow involvement is uncommon and primarily reported in HIV-positive patients[3]. Here we describe a case of HL that primarily involved bone marrow and was successfully treated with conventional chemotherapy.

Case report

A thirty-five-year-old man, an event manager by occupation, reported with complaints of fever, malaise and weight loss for one year. Due to this, he had multiple admissions in the past year. Each time evaluation did not reveal anything significant. Patient was discharged with symptomatic treatment each time.

On general physical examination his vitals were stable and pallor was present. He was febrile with fever upto 101° F. There was no oedema or palpable lymph nodes. Abdominal examination showed mild splenomegaly. Rest of the clinical examination was unremarkable.

Initial laboratory tests showed pancytopenia with haemoglobin 5.7 g/dL, WBC 1,500 cells/mm^3, platelet count of 81,000 cells/mm^3. Liver function showed elevated total bilirubin 3.6 mg/dL, direct bilirubin 1.8 mg/dL, AST 35 U/L, ALT 49 U/L and ALP 180 U/L. Serum albumin was 3.2 g/dL. Renal function test, serum electrolytes (Sodium 142 mEq/L, Potassium 4.8 mEq/L) were normal. Fasting lipid profile showed triglycerides 120 mg/dL and LDL 102 mg/dL. Peripheral smear showed RBCs with normocytic normochromic anaemia with few tear drop cells and pencil shaped cells, WBCs and platelets were normal in morphology and distribution but reduced in number. Corrected reticulocyte count was 1.5%. ESR and LDH were elevated. Folic acid and Vitamin B12 levels were within limits. Serum ferritin was 2,000 ng/mL with elevated transferrin saturation. Hepatitis B, hepatitis C and HIV were negative. Antibodies for EBV and CMV were negative. Mantoux test, Weil Felix test and sputum CBNAAT were negative. Pan cultures did not yield anything significant. ANA profile was negative. Chest X-ray and 2D Echocardiogram were normal.

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USG of the abdomen evinced mild splenomegaly and liver of normal size and shape. CT imaging of abdomen, chest and pelvis done revealed mild splenomegaly and no features of lymphadenopathy. Then the patient received two units of packed red blood cells.

Following this, a biopsy of the bone marrow was done. It showed Reed-Sternberg cells, epithelioid granulomas and a background composed of lymphocytes, eosinophils and histiocytes. Granulopoiesis and erythropoiesis were suppressed (Fig. 1) Immunohistochemistry for CD30 and PAX5, was positive (Fig. 2). They were negative for CD 15, CD 79a, CD 3, CD 45 and EMA. To evaluate the spread of disease throughout the whole body FDG PET CT was done which showed avid bony lesions noted in few vertebrae, bilateral scapulae, pelvic bones, bilateral femurs and humeri (Fig. 3). Liver appeared normal with no evidence of FDG avid lesion. Spleen appeared slightly enlarged in size with no evidence of FDG avid lesion. Hepatosplenic ratio was maintained. Based on the above features he was diagnosed to have Hodgkin's lymphoma. Medical oncologist consultation was sought and he was initiated on chemotherapy. He received ABVD protocol (6 cycles) as an out-patient with an excellent response. Serial monitoring done with PET CT showed interval resolution of hypermetabolic bone lesions. Following six cycles of chemotherapy, an FDG PET scan demonstrated a complete metabolic response, with no evidence of active trace uptake at any site (Fig. 4). Then he was declared as a treated case. He is currently on regular follow-up by clinical and laboratory examination every 3 months. During his most recent follow-up, conducted two years after his diagnosis, CBC showed haemoglobin 13.4 g/dL, WBC 5,990 cells/mm^3 and platelets 1.52 lakhs/mm^3.

Discussion

Hodgkin's lymphoma (HL) is typically limited to lymph nodes alone, with 2 - 16% of cases incriminating extranodal structures. Peripheral lymph node enlargement is almost always the initial presentation[1,2]. Liver, lungs, spleen, bone and bone marrow are the commonly involved extranodal sites. In HL, bone marrow involvement is uncommon between 4 - 18%, with average incidence around 10%[1]. If present, it is usually associated with extensive lymphadenopathy and advanced disease. It is reckoned a feature of generalised disease with primary arising somewhere else in the body. Bone marrow infiltration can be expected to occur more often in those who turn up with constitutional symptoms and cytopenias compared to those in whom these are absent. Typically, bone marrow involvement is designated as stage IV disease. This is because clinical stages I and II have a very meager percentage of patients with bone marrow involvement (<1%)[4,5].

HL primarily incorporating bone marrow without involvement of lymph nodes is an infrequent presentation with negligible number of reports in the literature. The reported cases are from HIV positive individuals, which is rapidly progressive. Reports from HIV negative individuals are uncommon. Amongst the cases described, patients with HIV negative Primary bone marrow Hodgkin's lymphoma (PBMHL) were more than 50 years old. Whereas HIV positive PBMHL were reported in younger patients[6]. PBMHL can pose a diagnostic difficulty as Reed-Sternberg cells may be absent in the bone marrow or tumour cells may be difficult to detect due to focal involvement of the marrow or tumour cells may be masked by expansive inflammatory cell infiltrates or fibrosis. PBMHL is usually known to be associated with a myriad of complications and poor response to conventional treatment. Mostly those with HIV negative PBMHL seldom improve with ABVD regimen[7]. Bone marrow aspiration has a limited role in prognosis of patients in early stages presenting with classical symptoms, but plays a role in patients presenting with elevated LDH, elevated ALP and cytopenias. Despite the fact that PET-CT scan plays an important role in staging HL, biopsy of bone marrow remains the gold standard test and thus helping in modulating

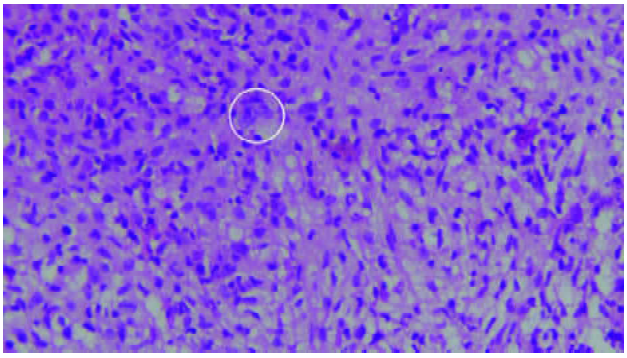

Fig. 1: *Bone marrow biopsy showing Reed-Sternberg cells (circled in white) and background composed of lymphocytes, eosinophils and histiocytes.*

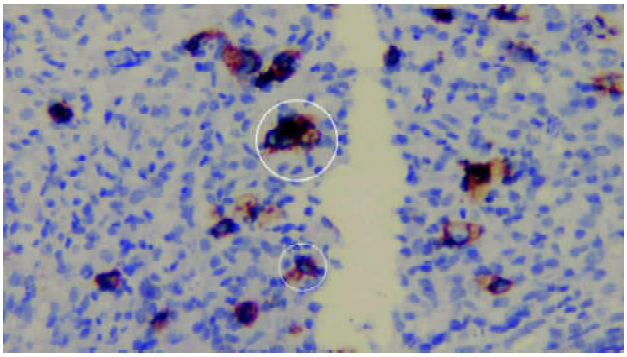

Fig. 2: *Immunohistochemistry of the bone marrow biopsy sample showing positive CD 30 staining.*

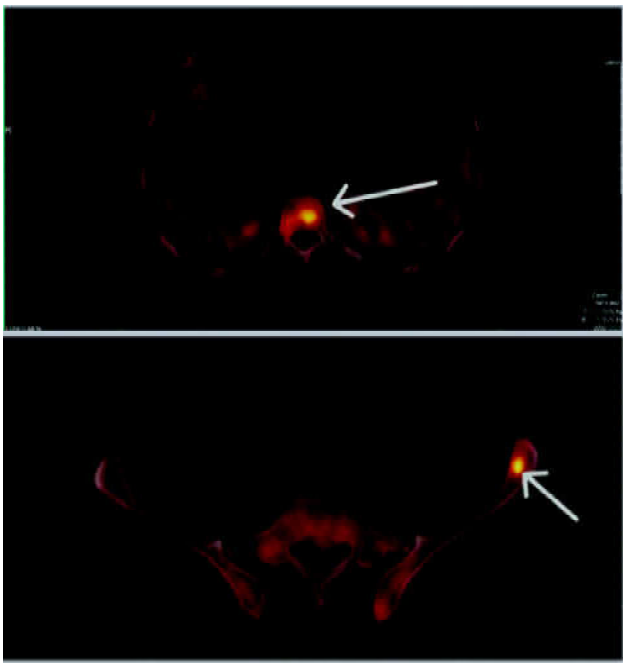

Fig. 3: *PET-CT images showing intense FDG uptake in the right ileum and thoracic vertebrae.*

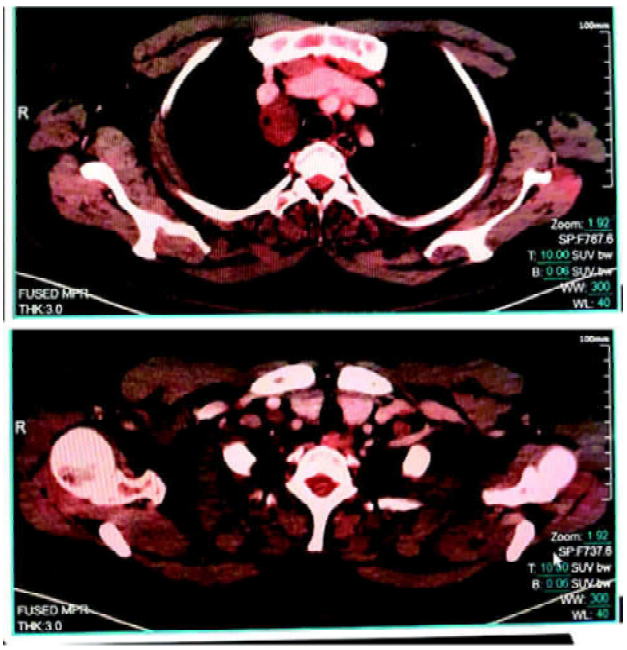

Fig. 4: *PET-CT images showing resolution of hypermetabolic bone lesions.*

treatment options and prognostic evaluation[8].

Conclusion

Primary bone marrow HL often exhibits B symptoms, cytopenias and a protracted clinical course. It poses a diagnostic dilemma and is often associated with delayed diagnosis and treatment. If a form of PBMHL is suspected, physicians should perform a bone marrow biopsy and consult a medical oncologist as soon as possible. Finally, typical Reed-Sternberg cells are not always observed in the pathological findings in patients with PBMHL. Immunophenotypic assessments should include examinations with a panel of antibodies, including HL and keep low threshold for ordering bone marrow examination in patients presenting with fever of unknown origin associated with pancytopenia.

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CASE REPORT

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Ulnar Claw Hand as Presenting Feature in Systemic Lupus Erythematosus with Sjögren's Disease

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with diverse clinical presentations, including neurological manifestations predominantly affecting the central nervous system. Peripheral nervous system involvement, although less common, significantly impacts patient morbidity and quality-of-life. This case report describes a 35-year-old woman with SLE who presented with acute peripheral neuropathy characterised by burning pain, weakness, claw hand deformity and sensory loss in the distal extremities, alongside purpuric rashes. Initial diagnostic challenges arose due to the overlapping symptoms of mixed connective tissue disease. Comprehensive evaluation, including nerve conduction studies, serological findings, elevated antinuclear antibodies, specific autoantibodies, and skin biopsy, confirmed axonal sensorimotor neuropathy secondary to vasculitis associated with SLE. The patient was treated with pulse steroids and cyclophosphamide due to the severity of her neurological symptoms. This case underscores the necessity of considering SLE in patients presenting with peripheral neuropathy, as it can occur early in the disease course and requires prompt diagnosis and management to mitigate its profound impact on quality-of-life.

Key words: Systemic lupus erythematosus (SLE), vasculitis, peripheral neuropathy.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that involves one or several organ systems over time, with damage mediated by autoantibodies and immune complexes. An estimated 37% to 90% of SLE patients have neurological symptoms, which are primarily related to the central nervous system[1,2]. In contrast, peripheral nervous system involvement in SLE is comparatively less common, occurring in about 2 - 27% of cases[3-5].

Patients with SLE who have peripheral nervous system involvement have a significantly higher risk of morbidity and a lower quality-of-life. Even though SLE has a major impact on a patient's quality-of-life, peripheral nervous system complications have not received much attention.

Sjögren's disease, characterised by the sicca complex of xerophthalmia, xerostomia, and dryness of other mucous membranes, can independently be associated with neuropathy. Patients commonly present with axonal sensorimotor neuropathy, while pure small fiber neuropathy or cranial neuropathy involving trigeminal nerve can also be seen. Sjögren's disease is also associated with sensory ganglionopathy. It is rarely associated with necrotizing vasculitis, but nonspecific perivascular inflammation may be present.

Mixed connective tissue disease (MCTD) is also associated with mild distal axonal sensorimotor neuropathy in 10% of patients.

A case of peripheral neuropathy attributed to SLE with Sjögren's disease, which initially caused a diagnostic conundrum between SLE and MCTD, is reported here.

Case

A 35-year-old woman presented with burning pain with numbness in hands and feet for 12 days, weakness of hand grip for 10 days, inability to walk for 10 days, and purpuric rash over the front of the ankle for 10 days. The patient also complained of fatigue for the past 25 days, which had progressively increased to limit her daily activities. The numbness progressed to the wrist in the upper limbs and ankle in the lower limbs. Initially, the patient had difficulty in holding slippers, and gradually, it progressed to complete loss of weight bearing on her feet with twisting of her ankle upon attempted weight-bearing. The patient; however, could walk with support, get up from a squatting position with support, and lift her legs while changing trousers. The patient simultaneously struggled to grip objects tightly, which progressed to a complete loss of ability to hold onto objects such as cups, utensils, opening taps, and buttoning or unbuttoning her shirt. The patient did not have any difficulty lifting her hand above the head.

There was no history of fever, headache, altered consciousness, vertigo, dizziness, hearing loss, blurring vision, double vision, dysphagia, dysarthria, or deviation of mouth.

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The patient also developed a rash over the bilateral ankle for the past 10 days, which was purplish, painless, and non-pruritic.

There was no history of joint pain, discoloration of fingers, tightening of the skin, photosensitivity, hair fall, oral ulcers, recurrent pregnancy loss, or any drug intake. The patient had regular menstruation with normal flow. She had three children, all born by full-term normal uneventful delivery at the hospital.

There was no history of diabetes, tuberculosis, or any other chronic disorder. There was no history of any toxin exposure or chronic drug intake. She was a vegetarian by diet, with a regular sleep pattern and had no history of chronic alcohol intake or any other addiction.

On examination, the patient was conscious and oriented to time, place, and person. Her vitals were within normal limits. On head-to-toe examination, there was visible wasting of small muscles of the hand and significant wasting in leg muscles. Local examination revealed multiple purpuric rashes over the anterolateral aspect of both ankles, with the largest measuring 7 x 2 cm (Fig.1). No other skin lesions suggestive of leprosy or thickening of nerves was present.

On neurological examination, she had claw hand deformity

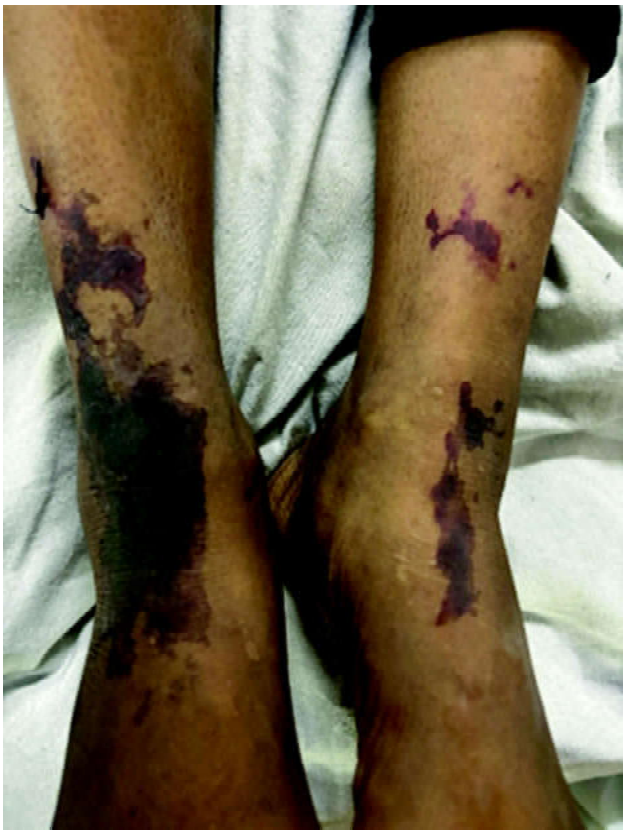

Fig 1: *Purpuric rash over the anterior aspect of both ankles.*

(Fig. 2) in both hands with atrophy of hypothenar muscles. Motor examination showed decreased power of MRC grade 1/5 at the wrist joint and ankle joint. On testing individual hand muscles, there were weak lumbricals, palmar interossei, dorsal interossei, abductor pollicis, adductor pollicis, flexor pollicis, and opponens pollicis in both hands. Deep tendon reflexes were normal except for finger flexion and ankle reflex, which were absent. On sensory examination, there was decreased sensation of all modalities in hands bilaterally up to the wrist joints and bilateral feet up to the ankle joints along the dermatomal distribution of the median and ulnar nerves. On examination of the respiratory system, there were decreased breath sounds in bilateral infrascapular regions. Other systemic examination was normal.

Laboratory examination revealed normocytic normochromic anemia, Hb 8.6 g/dL, total leukocyte count 7,700/mm^3, and platelet count 3,65,000/mm^3. ABG analysis showed pH - 7.48, pCO2 - 38 mmHg, Po2 - 98 mmHg Lactate - 1.2 mmol/L Hct of 29%, Na - 136 mmol/L, K - 3.8 mmol/L, Glucose - 87 mg/dL, HCO_3 - 28.33 mmol/L. Urine routine microscopy showed no protein. UACR levels were less than 30 mg/g. Total serum protein was 6.8g/dL (albumin - 3.5 g/dL, globulin - 3.3 g/dL). Other biochemical parameters such as serum electrolytes, serum calcium, renal function tests, and liver function tests, were normal.

Chest X-ray showed blunting of bilateral costophrenic angles suggestive of bilateral mild pleural effusion.

The cerebral spinal fluid (CSF) analysis was normal. Normal levels of CSF biochemistry were observed (protein - 40 mg/dL, Sugar - 43 mg/dL, Total cells 2/mm^3) with no cytoalbuminological dissociation. CSF Venereal Disease Research Laboratory test (CSF VDRL) was also negative. An MRI of the entire spine and brain showed no signs of acute pathology. ESR and CRP levels were significantly raised (65 mm Ist hour and 133 mg/L, respectively).

A fine-speckled antinuclear antibody pattern at a diution of 1:640 was found in the first serological analysis. The complete ENA profile later revealed positive Smith antibody (1+), positive SS-A and Ro52 kd antibody (3+), positive Ku antibody (1+), positive nucleosomes (1+), positive RNP (3+). C3 level was 72 mg/dL, and C4 level was 6 mg/dL. Anti MPO - 0.20 (Negative) and anti proteinase 3 antibodies - <0.01 (Negative). Serology for HIV, hepatitis B, and hepatitis C was negative. The levels of vitamin B12 and thyroid-stimulating hormone (TSH) were within normal limits. The laboratory investigations are summarised in Table I.

The nerve conduction study supported the presence of axonal sensorimotor neuropathy.

Skin biopsy was taken from the site of purpuric rash, which revealed proliferation of small to medium-sized blood

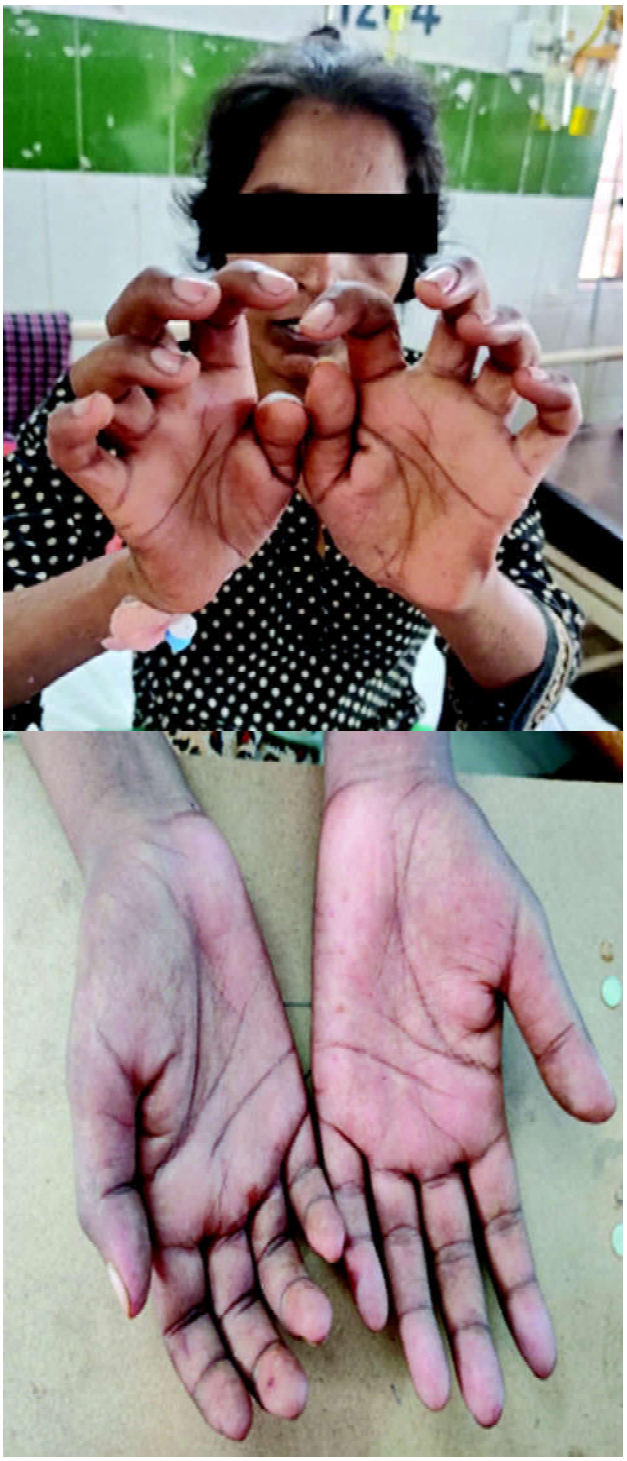

Fig. 2: *Ulnar claw hand with wasting of thenar and hypothenar muscles.*

vessels with perivascular infiltration of neutrophils. Focal destruction of blood vessels, extravastion of RBCs, and fibrinoid necrosis was also seen. These findings were consistent with cutaneous small vessel vasculitis (Fig. 3).

Nerve biopsy was also planned in our patient due to high suspicion for vasculitis. However, as it would have added little to what we already knew from clinical, biochemical and histopathological findings of skin biopsy, we deferred this procedure.

The patient also complained of dry eyes and dry mouth. Schirmer's test was also done, which showed a tear film up to 4 mm in both eyes. Tear filar breakup time was 20 seconds in both eyes.

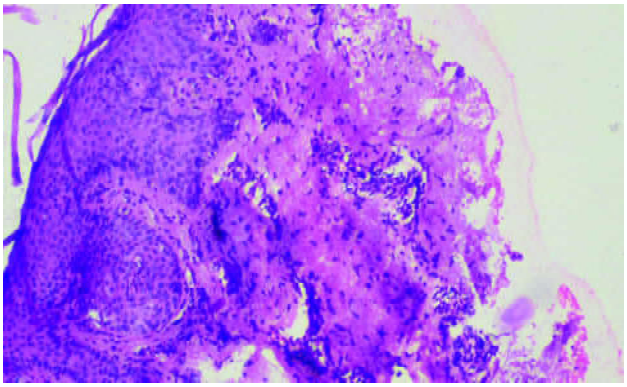

Fig. 3: *Examined section of skin biopsy slide in H & E staining showing perivascular inflammatory infiltrates consistent with vasculitis.*

Table I: Investigations

Total leukocyte count	7700/mm^3
Haemoglobin	8.6 g/dL
Platelet count	3,65,000/mm^3
BUN	13 mg/dL
S. creatinine	0.8 mg/dL
S. sodium	136 meq/L
S. potassium	4.2 meq/L
AST	31U/L
ALT	15 U/L
ALP	95 U/L
Urine routine microscopy	No protein
ANA (Indirect Immunofluorescence)	**1:640 (fine speckled)**
Anti smith	1+
Anti U1 RNP	**3+ (>200 U/mL)**
Anti-SSA	**3+**
Anti-SSB	**3+**
Anti-dsDna	**Negative**
ESR	65 mm Ist hour
CRP	133 mg/L
C3	72 mg/dL (90 - 180 mg/dL)
C4	6 mg/dL (10 - 40 mg/dL)

Differential Diagnosis

The patient presented with acute onset weakness and numbness in all four limbs involving predominantly distal muscles. History of dragging of feet, slipping of slippers, weakness of handgrip along with burning sensation and numbness in all four limbs since 10 days was suggestive of symmetric sensorimotor neuropathy or polyradiculopathy. Neuropathies with acute and subacute presentations include demyelinating neuropathy like Guillain Barré syndrome (GBS), vascultitis, radiculopathies related to diabetes, infective pathology like leprosy, lyme disease, Syphilis or any toxin exposure. The possibility of metabolic causes like vitamin B_{12} deficiency and niacin deficiency were also kept. The pattern was symmetrical, predominantly distal weakness associated with sensory loss. There was no history suggestive of any toxin or drug exposure. Acute motor sensory axonal neuropathy (AMSAN) variant of GBS was ruled out by the presened of deep tendon reflexes and absence of cytoalbuminological dissociation in CSF analysis. The patient also did not have any evidence of skin lesions or thickening of nerves suggestive of leprosy, neither any evidence of leprosy was found in skin biopsy. Metabolic causes were ruled out by normal vitamin B_{12} level and absence of clinical manifestation of niacin deficiency. Diabetic neuropathy was ruled out by normoglycaemia. MRI spine also did not show any features of radiculopathy.

The ANA profile report was strongly positive with a fine-speckled antinuclear antibody pattren (1:640) along with raised ESR and CRP levels.

The patient's presentation of polyneuropathy with vasculitic rash, lab results indicating antinuclear antibody (ANA) and anti-Smith Ab positivity, low complement level, electrodiagnostic studies revealing axonal sensorimotor neuropathy, and biopsy showing changes of vasculitis led to the diagnosis of severe sensorimotor polyneuropathy secondary to vasculitis associated with SLE.

Treatment

The patient was administered pulse intravenous steroids and an induction regimen of cyclophosphamide, given the organ-threatening complication of polyneuropathy. She was discharged on prednisone 40 mg, gabapentin, and nortriptyline for pain.

Discussion

Peripheral neuropathy is a known and underestimated complication in SLE, which may take several different forms. Patients usually present with generalised sensory or sensorimotor polyneuropathy. Some patients may present with burning pain and paraesthesiae with normal reflexes, suggesting small fiber neuropathy. In contrast, other patients may present with less common syndromes, including multiple mononeuropathies and acute or chronic demyelinating polyradiculopathy[6]. In our case, the patient presented with weakness of distal muscles and sensory loss of both upper limbs and lower limbs, which was consistent with symmetrical sensorimotor polyneuropathy.

Histopathological studies of the peripheral nerves in SLE have revealed axonal degeneration, inflammatory changes, and vasculitis. The primary characteristic of SLE vasculitic neuropathy is blood vessel wall inflammation, which leads to ischaemic nerve damage and axonal loss. According to Mawrin *et al*, vessel wall damage may be linked to the upregulation of matrix metalloproteinase-3[7] and matrix metalloproteinase-9 in the pathophysiology of peripheral neuropathy in SLE, leading to a chronic combined axonal and demyelinating type of SLE-PN.

In our case, we diagnosed vasculitic neuropathy based on skin biopsy and nerve conduction study findings, as nerve biopsy would be invasive and may lead to neurological complications. Histological findings of nerve biopsy would have been helpful only in difficult circumstances where nerve conduction studies and other non-diagnostic investigations were non-diagnostic.

Meanwhile, the clinical and laboratory manifestations of the patient also satisfied the ACR-EULAR 2016 classification criteria for Sjögren's disease with a score of 4 (Schirmer's test <5 mm and positive anti-SSA/SSB antibodies). Sjögren's disease can also be complicated by neuropathy most commonly axonal sensorimotor neuropathy followed by ganglionopathy which is characterised by sensory loss in the extremities. In our patient, this may have also contributed to neuropathy.

A subset of SLE, SSc, and polymyositis clinical characteristics are incorporated into MCTD. A high level of anti-U1 RNP, a particular autoantibody, distinguishes it. Since a high titer of anti-U1 RNP is frequently associated with the sequential occurrence of the distinctive overlapping features of SLE, SSc, and inflammatory myopathy, the diagnosis frequently becomes challenging[8]. Anti-U1 RNP titers in our patient were extremely high, but there were no features like puffy fingers, Raynaud's phenomenon, myalgia, or synovitis. The patient even fulfilled the SLICC classification criteria 2012. Thus, the patient was eventually diagnosed with SLE with neuropathy as a result of the same disease process.

In a patient presenting with neuropathy, one should suspect a connective tissue disease when the patient presents with progressive sensory symptoms and weakness in the extremities, sometimes associated with burning pain and paraesthesiae. Such patients can also

present with multiple mononeuropathies or their presentation can also mimic GBS or chronic inflammatory demyelinating polyneuropathy CIDP. These are often associated with fever, polyarthralgia or other constitutional symptoms.

Peripheral neuropathy usually develops in the advanced stages of SLE and very rarely from the outset. Previous studies revealed that patients with SLE-related PN had an essentially higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K, which is a marker of disease activity and chronic inflammation[9-11]. In contrast to these studies, our patient presented with peripheral neuropathy early in the course of the disease, even before the development of other manifestations of active disease such as fever, mucocutaneous involvement, arthritis, or myositis. The disease activity, according to SLEDAI, was also low in our patient. However, our patient had unusually aggressive peripheral neuropathy in the form of bilateral distal sensory loss, bilateral distal muscle weakness along with muscle atrophy and ulnar claw hand deformity.

Since neuropsychiatric SLE can manifest as organ-threatening peripheral neuropathy, she was prescribed high-dose pulse methylprednisolone, i.v., for 3 days with cyclophosphamide 500 mg, i.v., monthly for 6 months for induction therapy. After being discharged on oral prednisolone, she was subsequently prescribed hydroxychloroquine. In the follow-up, the patient had significant improvement in the neuropathic pain; weakness improved from power 1/5 to 3/5.

Conclusion

Patients of SLE any have neurological symptoms. Although peripheral neuropathy does not pose a threat to life, it is linked to significant morbidity and has a substantial impact on the quality-of-life, particularly in younger individuals. The diagnosis of vasculitic neuropathy can be made without invasive procedures like nerve biopsies on the basis of serological profile alone. SLE should be considered as one of the differential diagnoses in all patients with polyneuropathy to aid in timely diagnosis and prompt initiation of treatment.

Declaration of patient consent

The author certifies that all appropriate patient consent forms have been obtained. In the form, the patient consented to her images and other clinical information being reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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CASE REPORT

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Olanzapine-Associated Preterm Delivery in a Woman with Intellectual Disability

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Abstract

Psychiatric management during pregnancy requires careful balancing between maternal and mental health needs and potential risks to the fetus. Antipsychotic medications, particularly second-generation agents such as olanzapine, are frequently prescribed but carry significant metabolic and obstetric risks. We describe a 23-year-old woman with mild intellectual disability who presented at 32 weeks of gestation with bilateral pitting oedema, decreased fetal movements, progressive weight gain, hyperglycaemia, and oligohydramnios. She was on Olanzapine 2.5 mg daily following discontinuation of risperidone due to psychiatric deterioration with recurrent hypertension and worsening oligohydramnios. An emergency caesarean section was performed for fetal compromise, resulting in the delivery of a preterm neonate weighing 1.8 kg with APGAR Score of 6 and 7. No congenital malformations were observed. Postoperative complications included fluid overload with mild pleural and pericardial effusions, which resolved with conservative management. This case underscores the complexity of managing antipsychotic therapy during pregnancy, particularly in women with intellectual disability. It highlights the risks of olanzapine-associated metabolic and obstetric complications, and emphasizes the importance of gradual dose adjustment, pharmacist-led medication review, and coordinated multidisciplinary care to optimize maternal and fetal outcomes.

Key words: Olanzapine, intellectual disability, preterm birth, oligohydramnios.

Introduction

Pregnancy in women with intellectual disabilities (ID) presents a distinct set of clinical, social, and ethical challenges. Cognitive limitations may impede their ability to seek timely prenatal care, understand medical advice, and communicate symptoms effectively, thereby increasing the risk of adverse maternal and fetal outcomes[1]. Moreover, many women with ID have coexisting psychiatric disorders, such as schizophrenia, mood disorders, or behavioral dysregulation, which necessitates long-term pharmacological management[2].

Second-generation antipsychotics (SGAs), such as olanzapine, are commonly prescribed to these patients because of their efficacy in stabilizing mood and managing psychotic symptoms, with a relatively favourable side-effect profile compared to first-generation agents. However, the use of SGAs during pregnancy is concerning[3]. Olanzapine, in particular, is associated with metabolic disturbances, including excessive weight gain, gestational hypertension, hyperglycaemia, and oligohydramnios. These conditions are known contributors to obstetric complications such as preterm labor, preeclampsia, and increased rates of caesarean section[4].

It's use during pregnancy, also raises concerns regarding potential teratogenicity and perinatal outcomes. Current literature suggests that while olanzapine crosses the placenta, most studies have not demonstrated a significant increase in major congenital malformations. A review of observational studies and case series indicates that olanzapine exposure *in utero* may be associated with risks, such as low birth weight, gestational diabetes, and neonatal adaptation syndrome, although these findings are not consistent across all studies[5]. Overall, the available evidence supports a relatively favourable safety profile compared to other antipsychotics, but caution and individualised risk-benefit assessment remain crucial. The World Health Organisation (2023) estimates that approximately 10% of pregnant women experience mental health disorders globally, underlining the importance of integrating psychiatric care into obstetric management. In recent years, the increasing use of antipsychotics among pregnant populations reflects the growing recognition of the need to treat maternal mental illness, but it also demands careful monitoring and interdisciplinary collaboration to ensure the safety of both the mother and fetus[6].

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This case report details the clinical course of a 23-year-old pregnant woman with mild intellectual disability who developed complications, including oligohydramnios, weight gain, and hypertension during the third trimester while on olanzapine therapy, ultimately resulting in preterm delivery via emergency caesarean section. This case highlights the complex interplay between psychiatric stabilisation and obstetric risk in this vulnerable population and emphasizes the importance of individualised multidisciplinary care.

Case report

A 23-year-old woman had a history of mild intellectual disability (IQ score: 65) and behavioural disturbances over the past six years. Her psychiatric condition had been previously managed with risperidone (2 mg once daily), which was discontinued during the first trimester of her current pregnancy. Following this, she experienced deterioration in her mental health and was subsequently started on olanzapine 20 mg once daily at 29 weeks of gastation. Additional medications included folic acid, calcium, vitamin B complex, and iron supplements. Obstetrically, she was gravida 2, para 2, living 1, with no history of abortions (G2P2L1A0). She had received tetanus toxoid doses and had a regular menstrual history with moderate flow till her pregnancy. Her pre-pregnancy weight was 73 kg, which increased to 79 kg on admission, with a BMI of 33.2 kg/m^2, categorizing her as class I obesity. At 32 weeks of gestation, the patient complained of bilateral pitting oedema persisting for four days, along with decreased fetal movements and noticeable weight gain. Furthermore, obstetric ultrasound showed a significant reduction in the amniotic fluid index (AFI) from 10 to 5 cm, consistent with oligohydramnios, a condition linked to fetal compromise and a known risk factor for preterm labor.

Investigations

Laboratory investigations revealed several abnormalities at admission. Peripheral smear analysis indicated moderate macrocytic anaemia, which is typically associated with nutritional deficiencies such as vitamin B12 or folate, both of which are critical during pregnancy. Although the exact haemoglobin level was 11.4 g/dL, the presence of macrocytic anaemia suggested a suboptimal haematologic status. Additionally, the patient exhibited fasting hyperglycaemia, with a blood glucose level of 170 mg/dL, exceeding the normal range (70 - 100 mg/dL), indicating impaired glucose control. These findings collectively reflect the physiological stress and complications that contribute to high-risk pregnancies.

Management and outcome

During hospitalisation, the patient underwent multiple clinical interventions to manage the psychiatric and obstetric complications. On Day 3, the insulin dose was increased from 5 to 7 units owing to elevated fasting blood glucose (170 mg/dL). On Day 9, she developed adverse effects of olanzapine, including weight gain, hypertension, oligohydramnios, and decreased fetal movement, prompting emergency cesarean section. She also experienced a hypersensitivity reaction to ampicillin, presenting with facial puffiness and rashes. An urgent cesarean section was done at gestational week 32 due to preeclampsia. The newborn's birth weight was 1,800 g, and the APGAR scores at 1 and 5 min were 6 and 7, respectively. No growth restriction or developmental abnormalities were observed at birth.

Post-operatively, a medication error involving prolonged intravenous fluid administration led to mild pleural and pericardial effusions, which resolved after the fluid was stopped. On Day 16, tramadol was replaced with paracetamol to address opioid-induced headache. Throughout her stay, the patient received antenatal steroids (dexamethasone) for fetal lung maturity, and pharmacist-led interventions ensured safe medication use, dose adjustments, ADR monitoring, and proper counselling for postnatal and psychiatric follow-up.

Table I: Timeline of Drug treatment.

Gestational age (week + days)	29	29 + 6	30 + 5	**32 (admission)**
Tapering of olanzapine	Olanzapine - 20 mg - OD	Olanzapine - 15 mg - OD	Olanzapine - 15 mg - OD	Olanzapine - 2.5 mg - OD

Discussion

This case highlights the complexities of managing psychiatric disorders in pregnant women with intellectual disabilities and underscores the clinical challenges posed by antipsychotic medications such as olanzapine[7,8]. One of the most significant observations in this case was the abrupt switch from risperidone to olanzapine, which led to complications including weight gain, oligohydramnios, hypertension, and ultimately, preterm labor[9,10].

Tapering antipsychotics during pregnancy should be performed with extreme caution. Sudden discontinuation or rapid dose reduction, as observed with risperidone in this case, increased the risk of withdrawal symptoms and relapse of psychiatric illness[11]. According to evidence-based guidelines, a gradual tapering schedule, with close monitoring, is crucial, particularly during the perinatal period. A multidisciplinary approach involving obstetricians,

psychiatrists, and clinical pharmacists is vital for optimizing maternal and fetal outcomes[12].

Several case reports and reviews in the literature support an association between olanzapine metabolism abnormalities and neuropsychiatric symptoms, particularly in individuals with underlying vulnerabilities. For instance, elevated homocysteine levels, often linked to olanzapine metabolism, have been correlated with an increased risk of schizophrenia and other psychotic disorders[13]. Similar cases have reported the emergence or exacerbation of psychosis following the excessive intake of olanzapine or related compounds. In terms of antipsychotic management, while the chosen regimen in the current case may have been effective, alternative options could have included atypical antipsychotics, such as aripiprazole or lurasidone, which offer a more favourable metabolic profile and lower risk of extrapyramidal symptoms. These agents could be considered especially in patients with concerns about long-term side-effects or co-morbid metabolic conditions[14].

Conclusion

This case highlights the delicate balance required to treat pregnant women with psychiatric co-morbidities. When necessary, antipsychotic medications must be prescribed and tapered based on clinical judgment to prevent maternal and fetal complications. This case reinforces the importance of integrating clinical pharmacy services into obstetric care teams, particularly for high-risk pregnancies involving complex medication regimens.

Declaration of patient consent

Written informed consent was obtained from the patient representative for publication of this case report. The patient's identity was protected and no identifiable information was disclosed.

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CASE REPORT

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An Uncommon Cause Of Dysphagia

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Abstract

Swallowing difficulties are frequently attributed to intrinsic esophageal or neuromuscular disorders. However, in select cases, subtle extrinsic anatomical factors may underlie progressive dysphagia, requiring vigilant clinical and radiological assessment. We present the case of a young adult with non-specific gastrointestinal symptoms whose underlying diagnosis revealed a rare anatomical variant. A 20-year-old man with Type 1 Diabetes Mellitus and congenital scoliosis presented with a three-month history of dysphagia, followed by acute abdominal pain and vomiting. Initial evaluation revealed diabetic ketoacidosis, which was managed conservatively. Further diagnostic workup, including barium swallow and CT angiography, uncovered an unusual cause of esophageal compression. The patient underwent definitive surgical intervention involving a minimally invasive sternotomy, dissection of the arch vessels, and strategic revascularization of the compressing structure. Post-operative recovery was uneventful, and symptoms markedly improved. This case underscores the importance of considering rare congenital anomalies in young patients with unexplained dysphagia. Early imaging and targeted surgical management can lead to excellent outcomes, especially when embedded within a multidisciplinary approach.

Key words: Dysphagia, vascular anomalies, scoliosis.

Introduction

Dysphagia in young adults is often dismissed or attributed to benign gastrointestinal conditions. However, the intersection of subtle symptoms with unexpected anatomical findings can make for a challenging diagnostic journey. Esophageal obstruction secondary to extrinsic compression, while rare, demands a heightened index of suspicion – especially when routine investigations yield inconclusive results.

This case exemplifies one such diagnostic complexity. A young man, with well-documented endocrine and musculoskeletal co-morbidities, developed progressive difficulty swallowing alongside acute gastrointestinal distress. What began as a straight forward metabolic crisis evolved into an intricate investigation, with imaging ultimately revealing a congenital vascular anomaly previously unrecognised in the patient.

Surgery offered resolution for both an anatomical diagnosis and symptomatic relief, reinforcing the need to look beyond conventional causes in cases of persistent dysphagia. The following report delineates the clinical course, diagnostic process, and surgical management of this unusual presentation – reminding clinicians that sometimes, the clue lies just outside the esophageal wall.

Case

A 20-year-old man, previously in good health, presented with a three-month history of progressively worsening difficulty in swallowing, which initially affected solids more than liquids. Over the past three days, he also developed diffuse abdominal pain and recurrent episodes of vomiting occurring within minutes after eating. The vomiting was watery, occurred multiple times, and was not associated with blood. He had type 1 diabetes mellitus for the past six years, well controlled on insulin. His past medical history was also significant for congenital scoliosis and chronic gastritis associated with *Helicobacter pylori* infection. He consumed a mixed diet and had no history of substance abuse, and normal bladder and bowel habits with a preserved sleep cycle.

On examination, the patient's vital signs were stable, with a blood pressure of 102/60 mmHg, pulse rate of 100/min, respiratory rate of 14/min, oxygen saturation of 96% on room air, and a body temperature of 99° F. General and systemic examinations revealed no significant findings. Initial laboratory investigations, including complete blood count, liver and kidney function tests, serum electrolytes, thyroid profile, and coagulation parameters, were within normal limits. Cardiac markers, serum vitamin B12, and folate levels were also normal. However, his HbA1c was elevated at 8.72%, indicating suboptimal long-term glycaemic control. Additional findings included a mildly elevated urine ketone (1+), a metabolic acidosis pattern on arterial blood gas analysis, and a D-dimer level of 173 ng/mL with a fibrinogen level of 304 mg/dL. Echocardiography showed a preserved ejection fraction of 55 - 60% without structural abnormalities.

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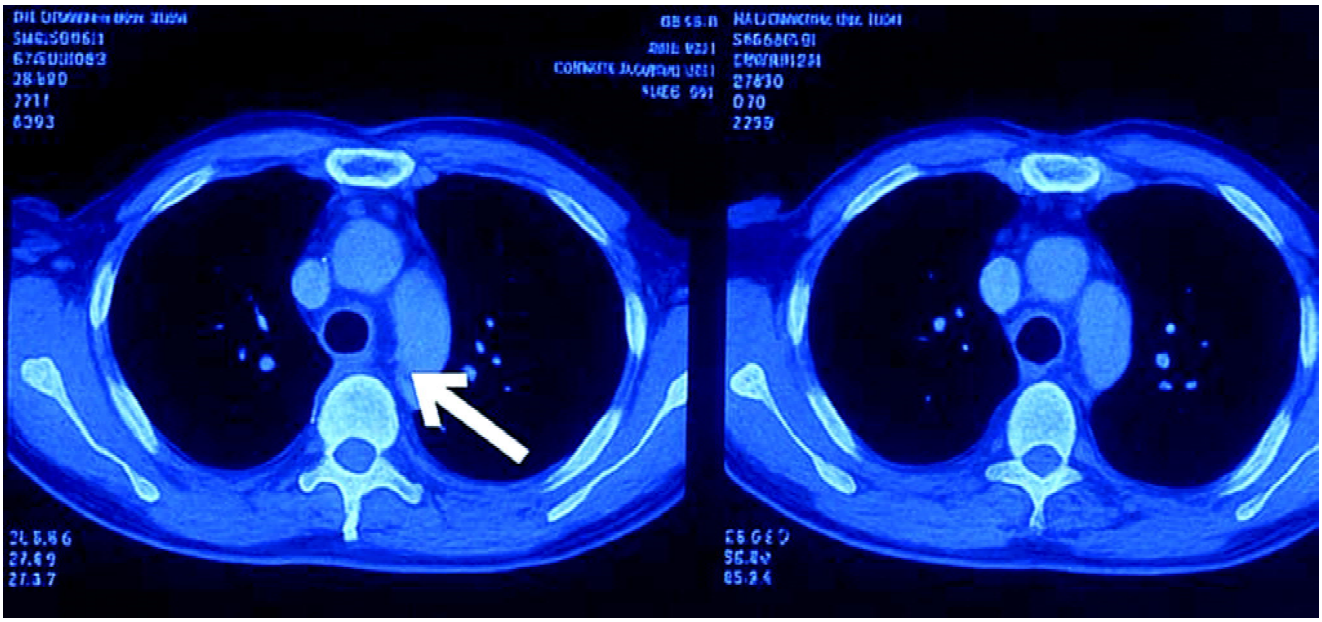

Fig. 1: *CT chest images showing the aberrant right subclavian artery.*

An abdominal ultrasound revealed a liver of normal size and texture, a normal portal vein, spleen, and gallbladder without biliary calculi or dilatation. A barium swallow demonstrated the classic "bird-beak" appearance, raising suspicion of a compressive esophageal pathology. Subsequent contrast-enhanced CT angiography confirmed the presence of an aberrant right subclavian artery (ARSA) coursing posterior to the esophagus, a vascular anomaly known to cause dysphagia lusoria.

Initially, the patient was managed conservatively for diabetic ketoacidosis with intravenous fluids and insulin therapy. Once metabolic parameters stabilised, surgical intervention was planned. Through an upper mini-sternotomy approach, the surgical team dissected the innominate vein and aortic arch

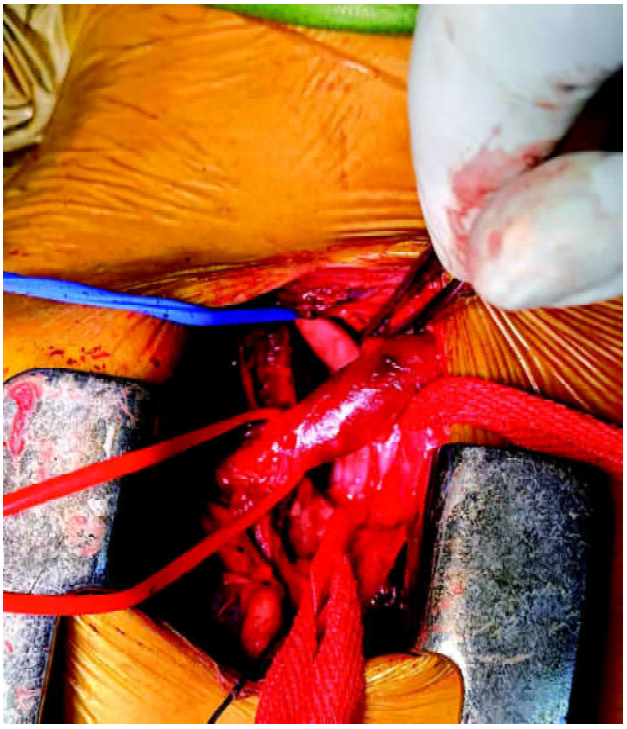

Fig. 2: *Vascular structures separated and aberrant artery identified.*

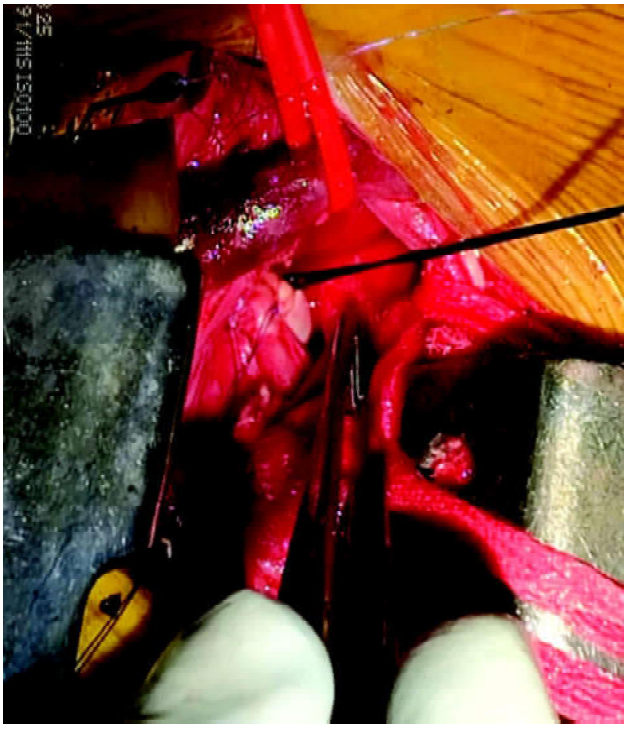

Fig. 3: *Artery was dissected and stump was made.*

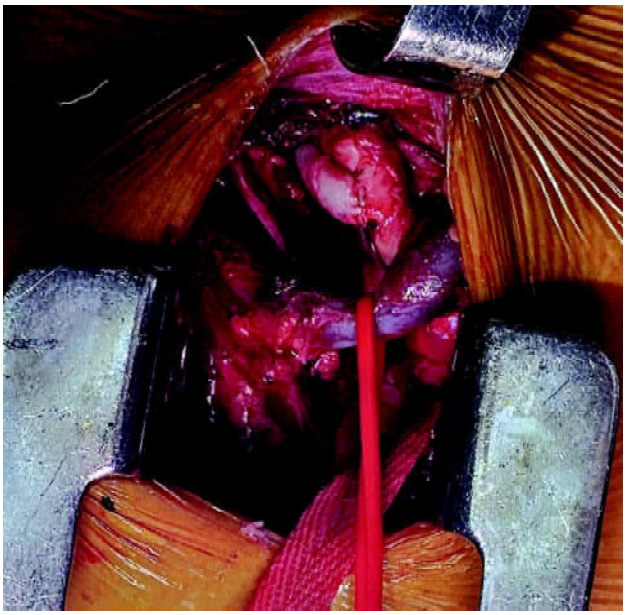

Fig. 4: *Aberrant artery was sutured to the Right Common Carotid Artery.*

vessels. The aberrant right subclavian artery was identified posterior to the esophagus, clipped, transfixed, and reimplanted anteriorly into the right common carotid artery using an end-to-side anastomosis. Hemostasis was secured, and the chest was closed with a right pleural drain in place.

This case exemplifies dysphagia lusoria, a rare but important vascular cause of esophageal compression, which should be considered in patients presenting with unexplained dysphagia. The diagnosis was clinched through characteristic imaging findings, and definitive surgical correction led to resolution of symptoms. The case also highlights the importance of managing co-existing metabolic derangements, such as diabetic ketoacidosis, before undertaking major surgical procedures.

Discussion

Dysphagia lusoria is a rare congenital vascular anomaly that results in difficulty swallowing (dysphagia) due to an aberrant course of the right subclavian artery. The term was first coined by David Bayford in 1761, who described a case of progressive dysphagia due to an unusual vascular structure, referring to it as a *"lusus naturae"* (freak of nature), hence the term "lusoria[1]". Bayford identified an aberrant right subclavian artery (ARSA) that traversed anterior to the esophagus, causing significant compression and ultimately contributing to emaciation and death in the patient he studied. This vascular anomaly is now broadly defined to include any congenital vascular abnormality that compresses the esophagus. The condition has an incidence of approximately 0.4 - 2% in the general population[2]. Symptoms often do not manifest until adulthood, usually triggered by atherosclerotic or aneurysmal changes in the aberrant vessel.

Embryologically, by the fifth week of fetal development, six aortic arches form. The left 4th aortic arch develops into the arch of the aorta and the proximal portion of the left subclavian artery. In contrast, the right 4th aortic arch, right dorsal aorta, and right 7th intersegment artery contribute to the formation of the right subclavian artery. If the distal part of the right dorsal aorta persists and the right 4th arch regresses, an aberrant right subclavian artery can form, typically passing behind the esophagus (retro-esophageal).

Dysphagia lusoria is sometimes associated with other congenital anomalies, often grouped under the acronym VACTERL[3]. This includes:

- V: Vertebral anomalies such as hemivertebrae or spina bifida.
- A: Anal atresia (absence or blockage of the anal opening).
- C: Cardiac defects, including VSD (ventricular septal defect), ASD (atrial septal defect), and PDA (patent ductus arteriosus).
- T: Tracheoesophageal fistula-an abnormal connection between the trachea and esophagus.
- E: Esophageal atresia-where the esophagus ends in a blind pouch.
- R: Renal anomalies like renal agenesis or vesicoureteral reflux (VUR).
- L: Limb anomalies such as radial or thumb aplasia and syndactyly.

Conclusion

Dysphagia lusoria, although uncommon, should remain a consideration in young patients presenting with unexplained dysphagia. Timely diagnosis through appropriate imaging modalities and prompt surgical correction can result in complete symptom resolution. This case underscores the critical role of a multidisciplinary approach and highlights the importance of addressing coexisting co-morbidities to optimise outcomes. The patient's co-existing scoliosis also raises the possibility of underlying syndromic associations, such as VACTERL. Accordingly, a high index of suspicion should be maintained for evaluating additional congenital anomalies in similar presentations.

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CASE REPORT

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The Silent Strain: A Rare Case of Charcot-Marie-Tooth 4H

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Abstract

Charcot-Marie-Tooth disease 4H (CMT4H) is an autosomal recessive demyelinating form of CMT caused by FGD4/FRABIN mutations. CMT4H is typically characterised by early onset and a slow progression of motor and sensory deficits, particularly in the distal extremities, along with foot deformities. Here, we report a patient with CMT4H who presented with gradually worsening flaccid paraparesis. This case represents the second reported instance of CMT4H in an Indian patient, harboring a novel homozygous 1880T >C (p.Phe627Ser) mutation in the FGD4 gene. This case emphasizes the importance of genetic testing in the diagnosis of rare neuromuscular disorders, particularly when clinical findings suggest a hereditary neuropathy with atypical progression.

Introduction

Charcot-Marie-Tooth disease (CMT) is a diverse group of genetically and clinically varied heterogeneous peripheral neuropathies, characterised by the progressive degeneration of distal muscles and loss of sensory function. CMT type 4 (CMT4) is an autosomal recessive demyelinating form of CMT, distinguished by an earlier onset of symptoms. CMT4 is further classified into several subtypes, CMT4A to CMT4J, based on clinical manifestations and genetic causes. Mutations in over 10 different genes, including GDAP1, MTMR2, SBF1, SBF2, NDRG1, HK1, MPZ, EGR2, SH3TC2, PRX, FGD4, FIG4, and SURF1, have been identified as causes of CMT4[1]. CMT type 4H, caused by mutations in the FGD4 gene, typically presents in the first decade of life with slow progression, areflexia, and foot deformities[2]. While most cases of CMT4H have been reported in the Mediterranean region, it is rarely seen in other areas. In this report, we describe a case of CMT4H in an Indian patient.

Case Presentation

A 17-year-old girl presented with a long-standing history of weakness in both lower limbs, which began at the age of 1.5 years. She was born via normal vaginal delivery at 9 months, with early development progressing normally. The symptoms first appeared when she started walking at the age of 1.5 years, with complaints of knee buckling and frequent falls, particularly on uneven surfaces. By school age, she had difficulty climbing stairs and required support to board the bus. At the age of 7 to 8 years, she found it challenging to descend the bus independently and had trouble participating in physical activities, such as running. By the age of 9-10 years, she voluntarily stopped dancing due to a fear of falling. Over time, the weakness has gradually worsened. From the age of 11 years, she initially needed minimal support to squat and stand up. However, in the last seven months, her condition progressed to the point where she now required two-person assistance to rise from a squatting position. In the past year, she also struggled with wearing slippers, having difficulty reaching her feet to place them on and experiencing slippage.

The patient denied any sensory disturbances such as tingling, numbness, paresthesias, or burning sensations. There was no history of autonomic disturbances, including tachycardia, palpitations, flushing, or urinary abnormalities. She reported no sensorimotor complaints in the upper limbs or any signs of cranial nerve involvement. There was no family history of similar complications over the past three generations (Fig. 1).

Physical examination revealed a *pes cavus* deformity (Fig.

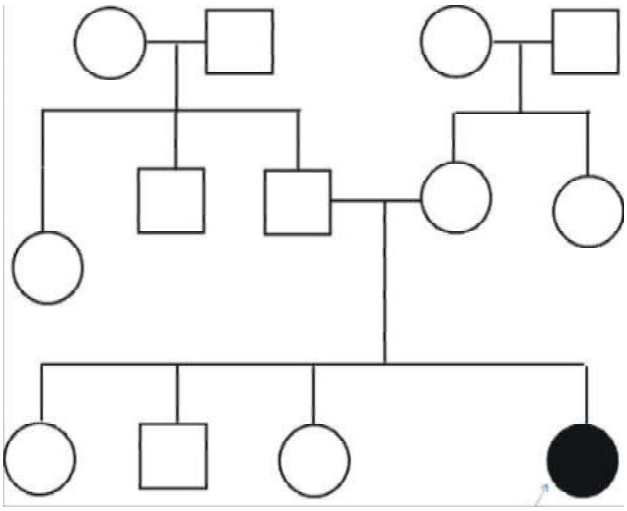

Fig. 1: *Family tree of the patient.*

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2), but the rest of the examination was unremarkable. The central nervous system (CNS) examination showed normal higher mental functions and cranial nerve findings. Motor examination demonstrated generalised hypotonia. Muscle strength in the upper limbs was 4/5 at the shoulders, elbows, and wrists. In the lower limbs, muscle strength was as follows: hip flexion 3/5, hip extension, abduction, and adduction 4/5, knee flexion 3/5, knee extension 4-/5, ankle plantar flexion 2/5, and ankle dorsiflexion 3/5. On sensory examination, the patient showed normal responses to fine touch, crude touch, and pain-temperature sensations in both lower limbs. However, proprioception was impaired up to the knee joints symmetrically in the lower limbs and up to the elbow joints symmetrically in the upper limbs.

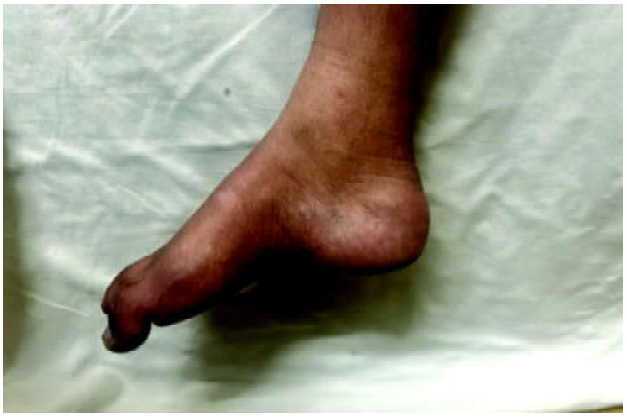

Fig. 2: *pes cavus and hammer toes with distal atrophy of lower limbs.*

Investigations revealed normal creatine kinase levels, along with normal electrolytes, renal function tests, liver function tests, thyroid profile, and haemogram. The HbA1c was 5.2%. Cerebrospinal fluid was normal. Nerve conduction studies (NCS) showed non-recordable motor and sensory conduction velocities, distal latencies, and amplitudes in the median, ulnar, radial, common peroneal, and tibial nerves on both sides (Table I).

The nerve biopsy was not performed as consent was not provided. Whole exome sequencing, revealed a homozygous variation c.1880T>C (p.Phe627Ser) affecting exon 11 of the FGD4 gene (Fig. 3).

Table 1: Nerve conduction studies showed non-recordable motor conduction velocities, distal latencies, and amplitudes in the right median, common peroneal, and tibial nerve.

Nerve	Latency	Amplitude	Duration m/s	Velocity m/s
MNC				
Right Median - APB				
Wrist	NR	NR	NR	
Elbow	NR	NR	NR	NR
Right Peroneal				
Ankle	NR	NR	NR	
Knee	NR	NR	NR	NR
Right Tibial				
Ankle	NR	NR	NR	
Knee	NR	NR	NR	NR

Treatment

Physical and occupational therapy was started.

Discussion

CMT4 is an autosomal recessive form of CMT and mutation in the *FGD4* gene is implicated as the cause of this disease. FGD4 encodes a protein called frabin, which belongs to the family of Rho guanine nucleotide exchange factors (RhoGEFs) that activate Rho GTPases, such as Cdc42 and Rac1, by catalysing the exchange of GDP for GTP[3]. Mutations in FGD4 cause CMT4H by disrupting the normal function of frabin and impairing the signalling pathways that regulate the actin cytoskeleton and myelination in Schwann cells[2]. Mutations in FGD4 causes CMT4H by disrupting the normal function of frabin and impairing the signalling pathways that regulate the actin cytoskeleton and myelination in Schwann cells[4]. Our patient had foot deformities since childhood along with other typical neurological features which developed gradually. The proband had both motor and sensory involvement which was demonstrated by the electrophysiological studies. CMT4H is characterised by distal weakness at the onset of symptoms which was seen in our case as well[5]. We identified a homozygous variation c.1880T>C

Gene* (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
FGD4 **(+)** (ENST00000534526.7)	Exon 11	c.1880T>C **(p.Phe627Ser)**	Homozygous	Charcot-Marie-Tooth disease type 4H	Autosomal recessive	Uncertain Significance

Fig. 3: *Whole exome sequencing showing homozygous variation c.1880T>C (p.Phe627Ser) affecting exon 11 of the FGD4 gene.*

(p.Phe627Ser) affecting exon 11 of the FGD4 gene that has not been published in literature before.

Conclusion

The gradual and slowly progressive nature of the disease underscores the heterogeneity of CMT4H, and the findings highlight the importance of genetic testing for definitive diagnosis in cases where clinical features suggest a hereditary neuropathy. This case emphasizes the significance of recognizing rare genetic mutations in the differential diagnosis of childhood-onset neuropathies and the value of early intervention with physical and occupational therapy to manage symptoms and improve quality-of-life. The report also contributes to the growing body of knowledge on CMT4H, encouraging further research and awareness in diverse populations.

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ANNOUNCEMENT

Mrs. Uma Bansal – Prof. B.C. Bansal Best Paper Award (Journal - 2025)

Best Original Article: "Infarction Patterns among Patients with Tuberculous Meningitis: An Entity with Diversity in Itself" – Dr. Himanshu Kaushal, Dr. Gaurav Goyal, Dr. Mukesh Kumar Sarna, Dr. Sudha Sarna, Dr. Abhishek Sandhya, Department of General Medicine, Mahatma Gandhi Medical College and Hospital, Jaipur - 302 022, (Rajasthan).

Best Review Article: "Demystifying the Cluster Differentiation (CD) System and Clinico-Pathological Implication" – Dr. Prerna Arora, Dr. Reena Tomer, Department of Pathology, Hematopathology, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi - 110 002.

Best Case Reoprt: "Human Herpes Virus-6 Meningoencephalitis in an Immunocopetent Peripartum Lady" – Dr. Anusha Uddandam, Dr. Sonali Bhattu, Dr. SH Talib, Dr. Abdulla Ibji, Dr. Amjad Syed Ali, Department of Medicine, MGM Medical College, Chhatrapati Sambhaji Nagar - 421 003, (Maharashtra).

CASE REPORT

JIACM 2025; 26 (4): 234-36

Coexistence of G6PD Deficiency and Hereditary Spherocytosis: Challenges in Diagnosis and Management

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency and hereditary spherocytosis (HS) are distinct haematological disorders with differing genetic causes. Their coexistence is rare and presents diagnostic and therapeutic challenges. We report the case of a 38-year-old Indian man with a known history of G6PD deficiency since childhood, who presented with progressive fatigue, jaundice, and dark-coloured urine over a one-week period. Laboratory investigations revealed spherocytes on peripheral blood smear, increased osmotic fragility, and elevated mean fluorescence intensity on the eosin-5'-maleimide (EMA) binding test, confirming the diagnosis of coexisting G6PD deficiency and hereditary spherocytosis. The patient was managed with inpatient supportive care including intravenous hydration, and close laboratory monitoring. The patient showed clinical improvement and was advised lifestyle modifications and follow-up. This case emphasizes the need for considering overlapping genetic disorders in haemolytic anaemia and highlights the utility of advanced diagnostics like the EMA binding test.

Key words: G6PD deficiency, hereditary spherocytosis, haemolytic anaemia, genetic disorders, jaundice.

Introduction

G6PD deficiency is the most common enzyme deficiency seen in humans[1]. It tends to be asymptomatic throughout life except in situations associated with oxidative stress when a haemolytic crisis may ensue. In some patients a mild-severe, chronic haemolysis has been described[1]. Hereditary spherocytosis arises from mutations in genes coding for red cell membrane proteins such as spectrin, ankyrin, and band 3, which result in spheroidal red cells with reduced deformability and premature destruction in the spleen[2]. Both disorders independently cause haemolytic anaemia, but their simultaneous occurrence is exceedingly rare and complicates diagnosis and treatment[3]. This report describes such a case with a focus on the diagnostic process and clinical management.

Case Description

A 38-year-old Indian man presented to the emergency department with progressive fatigue, yellowish discoloration of the skin and eyes (jaundice), and dark-coloured urine for one week. The patient reported experiencing similar but intermittent episodes of jaundice since childhood, often associated with infections or minor illnesses. He was diagnosed with G6PD deficiency during childhood after an episode of acute haemolysis triggered by an infection. The patient had no prior history of blood transfusion, chronic illnesses, or other haematological disorders. He denied any recent drug intake, fava bean consumption, or exposure to known oxidative agents. His family history was unremarkable, with no relatives diagnosed with hereditary blood disorders.

On physical examination, the patient appeared mildly icteric, with stable vital signs. Abdominal examination revealed mild splenomegaly without hepatomegaly or palpable lymphadenopathy. There were no signs of heart failure or other systemic involvement. Initial laboratory investigations revealed a haemoglobin level of 8.2 g/dL, an elevated reticulocyte count at 12.6%, and normal mean corpuscular volume (MCV) of 78.8 fL. The peripheral blood smear demonstrated prominent spherocytes and anisocytosis, along with occasional polychromasia. Biochemical tests showed elevated total bilirubin at 5.3 mg/dL (predominantly indirect), elevated lactate dehydrogenase (LDH) at 517 IU/L, and markedly decreased haptoglobin levels (<10 mg/dL), indicating ongoing haemolysis. Vitamin B12 and folic acid levels were within normal range. The direct Coombs test was negative, ruling out immune-mediated haemolysis. A dye decolourisation method test was done which showed that decolourisation had not occurred even after 3 hours (Range in normal subjects: 30 - 60 minutes) indicating the presence of G6PD deficiency. The osmotic fragility test revealed increased fragility of red blood cells. The Eosin-5'-maleimide (EMA) binding test was performed, demonstrating a mean fluorescence intensity (MFI) of 0.84, suggestive of hereditary

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spherocytosis (normal >0.85).

Upon admission, the patient was carefully monitored and treated with intravenous hydration to maintain renal perfusion and prevent haemoglobinuria-related complications. The patient received supportive care for mild splenomegaly. Genetic counselling was provided, where the patient was informed about the autosomal dominant inheritance pattern of hereditary spherocytosis and the X-linked inheritance of G6PD deficiency. He was advised regarding the risk of transmitting these conditions to offspring, the importance of avoiding oxidative triggers such as fava beans and sulfonamides, and the need for regular follow-up. The patient's clinical condition gradually improved over the course of hospitalisation. At discharge, his haemoglobin was 9.2 g/dL, total bilirubin dropped to 4.8 mg/dL, and LDH normalised to 440 IU/L.

He was instructed to follow-up at the haematology clinic for long-term monitoring, with emphasis on lifestyle modifications, early recognition of haemolytic crises, and periodic blood tests.

Table I: Laboratory investigations.

Parameter	At Admission	At Discharge	Reference Range
Haemoglobin (g/dL)	**8.2**	9.2	13.5 - 17.5
Reticulocyte Count (%)	**12.6**	–	0.5 - 2.5
Mean Corpuscular Volume (fL)	78.8	87	80 - 100
Total Bilirubin (mg/dL)	**5.3**	4.8	0.3 - 1.2
Indirect Bilirubin (mg/dL)	**4.5**	4.1	0.2 - 1.0
Lactate Dehydrogenase (IU/L)	**517**	440	140 - 280
Haptoglobin (mg/dL)	**<10**	–	30 - 200
EMA Binding Test MFI	**0.84**	–	>0.85 (Normal)

Differential Diagnosis

Given the clinical presentation of haemolytic anaemia, jaundice, dark urine, and splenomegaly, several differential diagnoses were considered before concluding the coexistence of G6PD deficiency and hereditary spherocytosis. Autoimmune haemolytic anaemia (AIHA) was an important consideration due to the presence of spherocytes, but the negative direct Coombs test ruled out immune-mediated haemolysis. No history of autoimmune disorders, drug exposure, or other triggers supported AIHA. Thalassaemia and hereditary elliptocytosis (HE) were also considered. Thalassaemia typically presents with microcytic anaemia and abnormal haemoglobin electrophoresis patterns, which were absent in this patient. He would have manifested primarily with elliptocytes on the peripheral smear, unlike the spherocytes observed here. Other enzymopathies such as pyruvate kinase deficiency were excluded based on enzyme assay results and the clinical picture. The definitive diagnosis was supported by history of G6PD deficiency, elevated osmotic fragility, and abnormal EMA binding test findings.

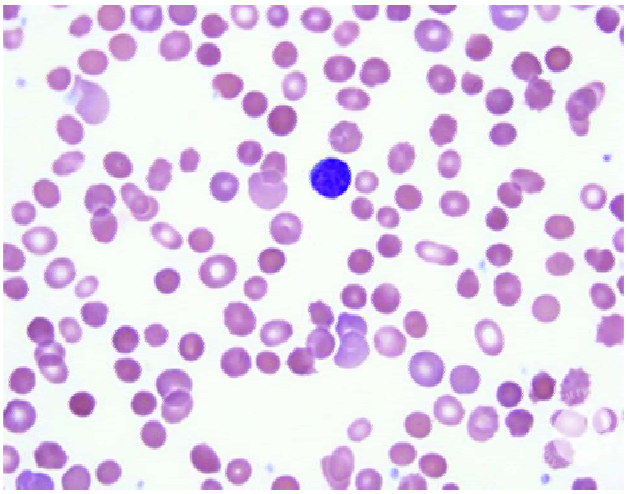

Fig. 1: *Spherocytes in Peripheral blood film.*

Discussion

This case highlights the coexistence of combined intra and extravascular haemolysis mechanisms, i.e., hereditary spherocytosis which is primarily extravascular (splenic destruction), and G6PD deficiency which is intravascular (oxidative stress-mediated). The diagnostic complexity was posed by the rare coexistence of G6PD deficiency and hereditary spherocytosis[3]. Both disorders independently lead to haemolytic anaemia, jaundice, and splenomegaly, but their combination may obscure a clear diagnosis without comprehensive evaluation. The EMA binding test has demonstrated higher sensitivity than traditional osmotic fragility testing and serves as a useful tool in such complex presentations[4]. Genetic testing for specific mutations in ANK1, SPTA1, SPTB, or G6PD could further confirm the diagnosis and guide family screening but was not performed due to logistic constraints[5].

Management of this patient focused on supportive care during the acute haemolytic crisis. Intravenous hydration was prioritised to prevent renal damage from haemoglobinuria[6]. Serial laboratory monitoring guided ongoing management. A multidisciplinary approach ensured tailored care, and genetic counselling provided clarity on inheritance patterns and the importance of preventive measures[3,6]. The role of splenectomy was discussed but deferred, as it is typically reserved for severe or refractory cases of hereditary spherocytosis[3,6]. The patient was discharged with clear advice to avoid haemolytic triggers, maintain regular follow-up, and monitor for early

signs of haemolytic episodes. Chronic haemolysis in dual pathology may lead to pigment gallstones, pulmonary hypertension, iron overload, or leg ulcers and renal dysfunction which was currently not present in the patient[7]. Periodic ferritin and abdominal ultrasound evaluations are recommended.

spherocytosis is a rare but significant diagnostic entity. A structured diagnostic approach including the EMA binding test and consideration of genetic analysis is crucial to avoid misdiagnosis. A multidisciplinary team-based management strategy ensures optimised care, and long-term follow-up focuses on patient education, lifestyle modifications, and

Table II: Drugs/conditions, which can lead to haemolysis in patients with G6PD deficiency[8].

Category	Examples	Remarks / Severity
Drugs – High-Risk	Primaquine, Chloroquine, Hydroxychloroquine, Quinine	Antimalarials. Primaquine is the most classic and severe
	Sulfonamides (Sulfamethoxazole, Sulfadiazine, Sulfasalazine), Dapsone	Very common cause; avoid in all G6PD patients
	Nitrofurantoin	Often prescribed for UTI; strong haemolytic trigger
	Rasburicase	Very high risk; contraindicated in G6PD deficiency
	Methylene blue	For methemoglobinemia '! dangerous in G6PD deficiency
Drugs – Moderate/Reported Risk	Chloramphenicol, Nalidixic acid, Ciprofloxacin (older FQs), Phenazopyridine	Less common but documented
	High-dose Aspirin, Vitamin K analogues	Rare, dose-dependent
Food	Fava beans (Broad beans)	Classic favism; can cause severe acute haemolysis
Infections	Bacterial: Pneumonia, Sepsis, Typhoid, UTI	Most common real-world trigger of haemolysis
	Viral: Hepatitis, Influenza, CMV	Viral oxidative stress worsens haemolysis
	Parasitic: Malaria	Dual effect: parasite + treatment (primaquine/quinine)

Review of Literature

G6PD deficiency is a common X-linked enzymopathy affecting over 400 million people globally, especially in Asian, Mediterranean, and African populations[1]. It impairs the pentose phosphate pathway, reducing NADPH production, and making red cells vulnerable to oxidative damage from infections, drugs, or fava beans[8]. Hereditary spherocytosis is the most common inherited haemolytic anaemia in Northern Europe but occurs worldwide, caused by mutations in red cell membrane proteins such as spectrin, ankyrin, and band 3[2]. This leads to reduced deformability of red blood cells and premature splenic destruction[2].

The coexistence of G6PD deficiency and hereditary spherocytosis is exceptionally rare, with only a few case reports in the literature[3]. Their overlapping clinical features can complicate the diagnosis. Advanced tests such as the EMA binding test have improved the diagnostic process, particularly in cases with ambiguous osmotic fragility results[4]. Management remains supportive during acute haemolytic crises, while genetic counselling is essential for patient education regarding inheritance patterns and family planning[3,6].

Conclusion

The coexistence of G6PD deficiency and hereditary preventive strategies, contributing to a favourable prognosis.

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CASE REPORT

JIACM 2025; 26 (4): 237-39

Cutaneous Mucinosis and Anti-Jo-1 Dermatomyositis: An Atypical Case

Gurinder Mohan, Hargurdas Singh**, Ranjeet Kaur****

Abstract

Dermatomyositis (DM) is a type of idiopathic inflammatory myopathy (IIM) with an incidence of 9.63/million, characterised by muscle weakness, typical cutaneous features, and myositis-specific and myositis-associated antibodies. Cutaneous mucinosis is a heterogeneous group of excess mucin deposition in the dermis leading to the waxy appearing papules, plaques, or nodules, ranging from self-healing mucinosis to severe forms like scleromyxoedema. Significant mucinosis is a well-known entity in systemic lupus erythematosus, but is much less reported in dermatomyositis. We are reporting an interesting atypical case of significant mucinosis in a patient with dermatomyositis.

Key words: Dermatomyositis, scleromyxoedema, mucinosis, anti-Jo1-antibody.

Introduction

Dermatomyositis (DM) is a rare autoimmune disease characterised by proximal muscle weakness, distinctive cutaneous manifestations, and the presence of myositis-specific and myositis-associated autoantibodies leading to distinctive phenotypic pattern, prognosis, and organ involvement[1]. The classic dermatological features include Gottron's papules, V-like sign, shawl sign, and heliotrope rash. However, atypical presentations can make the diagnosis difficult. Cutaneous mucinosis is characterised by excess mucin deposition within the dermis, leading to waxy appearing papules, plaques, or nodules[2]. But it is rarely reported in dermatomyositis. This article highlights an atypical case of significant cutaneous mucinosis in a patient with anti-Jo-1 dermatomyositis, underscoring the diagnostic complexities and the importance of integrating clinical, histopathological, and immunological findings for accurate disease characterisation and management.

Case Discussion

A 69-year-old woman presented with complaints of a hyperpigmented rash on both legs, arms, and abdomen, weakness of proximal muscles of lower limbs and upper limbs, generalised malaise, and low-grade fever from 8 - 10 months. Examination showed diffuse erythematous scaly plaques on the abdomen, both arms, and legs. Her ANA by immunofluorescence assay showed Nuclear speckled pattern with an end titre of 1:320, and the ENA reflex showed positive anti SS-B antibody. Anti-Jo-1 Myositis-specific antibody came out to be positive. Magnetic resonance imaging of bilateral thighs showed patchy areas of oedema in bilateral gluteus maximus, proximal thigh, long head of biceps femoris, vastus lateralis, and right vastus medialis and intermedius. Electromyography showed an abnormal myopathic pattern. Muscle biopsy showed mild endomysial inflammation. Skin biopsy showed perivascular lymphocytic infiltrate, interface dermatitis, and mucin deposition. The erythrocyte sedimentation rate (ESR) was 28 mm/hr, and C-Reactive Protein (CRP) level was 12 mg/L. Computed tomography of showed a few soft tissue density nodules and no evidence of interstitial lung disease or malignancy. Thyroid profile, creatine kinase, bilirubin, transaminases, serum proteins, protein electrophoresis, and renal function tests were normal. Rheumatoid factor, anti-CCP antibody, and viral markers were negative. A workup for paraproteinaemia and malignancy was negative. 2017 EULAR/ACR classification criteria score for IIM was 10.1 s/o Definite IIM. According to the clinical profile, histopathological, and radiological imaging, a diagnosis of dermatomyositis with cutaneous mucinosis seemed most likely. She was given pulse steroid therapy followed by high-dose oral steroids and methotrexate along with supportive care and showed improvement in cutaneous and myopathic features.

Case Discussion

Dermatomyositis can have varied presentations ranging from amyopathic to severe muscle weakness, severe lung involvement, and cutaneous features. Myositis-specific antibodies are directed against antigens of protein synthesis pathways like Jo-1 and MDA-5. They have high specificity

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and a temporal link with malignancy, especially anti-TIF1-gamma (TIF1-γ) or anti-NXP2[1]. The typical cutaneous features of DM include Gottron's papule, Gottron's sign, heliotrope rash, shawl sign, holster sign, linear erythema, and mechanic hands, but all were absent in this patient. Mucinosis can be primary cutaneous or secondary, but the exact definitions and criteria are still lacking. Kauffman *et al*, 1998 reported similar atypical plaque-like mucinosis with dermatomyositis[3], Launay *et al* 2001 reported a case of scleromyxoedema associated with DM and treated with prednisone, azathioprine, and methotrexate. The muscular weakness and cutaneous features of DM improved, but not scleromyxoedema[4]. Perel-Winkler *et al* 2014 reported diffuse cutaneous mucinosis in a patient with DM and stated that secondary mucinosis is when mucin deposition is present in addition to some primary clinicopathological settings like connective tissue diseases, viral infections, and thyroid disorders[5]. Vysakha *et al* 2019 reported a case of a 38-year-old woman with myopathy and scleromyxoedema having characteristic mucin deposition and treated with intravenous immunoglobulin, oral prednisolone, and thalidomide[6]. The annular type of Lichen myxedematosus (LM) has also been reported in dermatomyositis[7]. However, in primary mucinosis, mucin deposition is the primary pathology. However, many extra-cutaneous features are well documented with primary mucinosis, like paraproteinaemia, multiple myeloma, dermato-neuro syndrome, dysphagia, cardiomyopathies, proximal myopathy, etc. So, it is difficult to ascertain the types, especially in the absence of standard classification or diagnostic criteria. The exact pathogenesis is not yet known, but it is postulated that cytokines like Interleukin-1, Interleukin-6, TNF-alpha, TGF-beta, and autoantibodies upregulate glucosaminoglycan synthesis from fibroblasts. Most of the earlier case reports did not specify myositis-specific antibodies, while recently, a case of Anti-MJ/NXP2 antibody-positive adult-onset dermatomyositis with LM and endometrial carcinoma which responded to resection of comorbid malignancy and prednisolone, was reported[8]. Although workup for malignancy was negative in our patient, but ovarian, gastric, endometrial, and nasopharyngeal carcinomas have been reported. Perel Winkler *et al* 2014 reported that around 30% (3 out of 12) DM with cutaneous mucinosis patients had associated

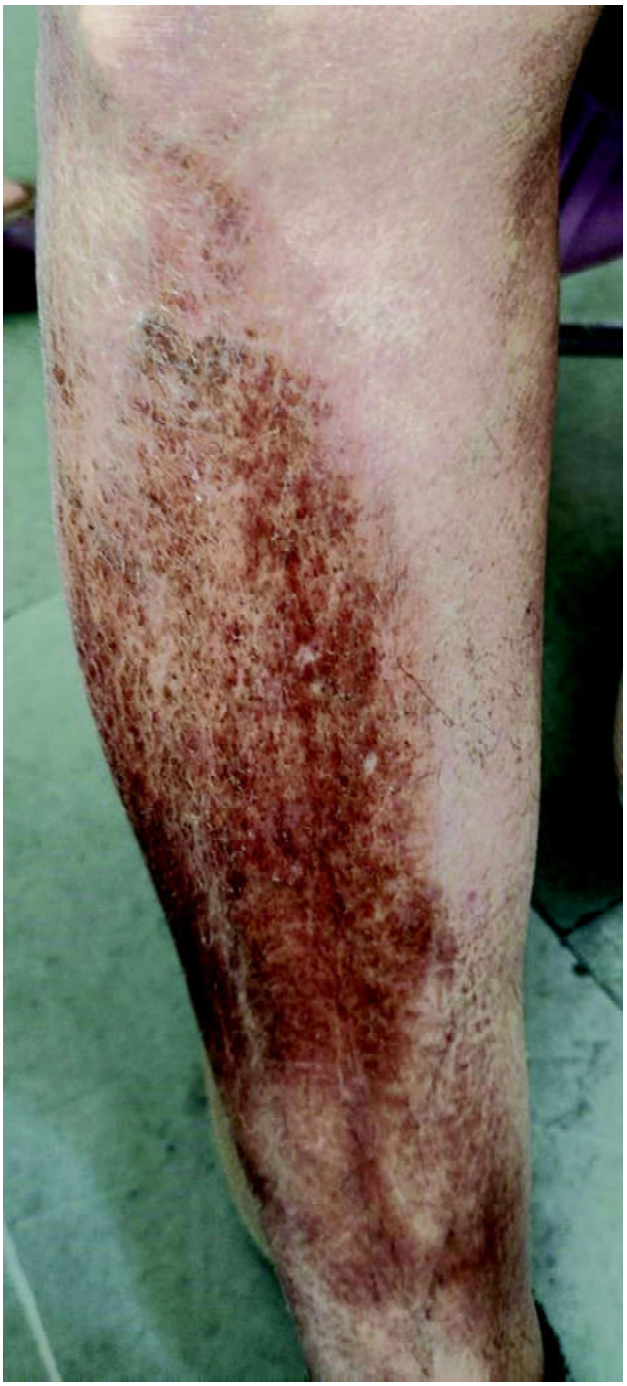

Fig. 1: *Scaly, waxy erythematous rash on the right leg.*

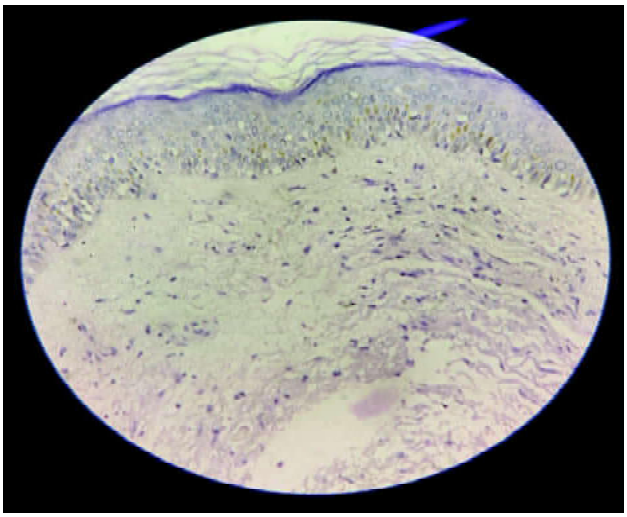

Fig. 2: *Perivascular lymphocytic infiltrate, interface dermatitis, and mucin deposition shown in skin biopsy.*

malignancy, which was similar to dermatomyositis alone[5]. LM is also reported in other connective tissue diseases like rheumatoid arthritis and mixed connective tissue disease[9]. Our patient responded well to high-dose steroid therapy along with a steroid-sparing agent; however, intravenous immunoglobulin is of some benefit in resistant cases. The presence of significant diffuse mucinosis in a setting of connective tissue disease can lead to atypical presentations and pose a diagnostic challenge. We need to evaluate the clinical relevance of mucinosis in connective tissue diseases, especially dermatomyositis. Primary and secondary mucinosis must be differentiated, as management, associations, and prognosis differ. Primary mucinosis can have systemic involvement and is also associated with paraproteinaemia and malignancy. A strict close follow-up is warranted because of the temporal association with malignancy. The systemic features do respond early with partial or complete resolution of cutaneous features. We need more studies and data to understand the spectrum of this disease and formulate standard nomenclature and classification criteria.

Conclusion

Dermatomyositis (DM) can present with atypical features of significant cutaneous mucinosis, making diagnosis and management challenging. A multidisciplinary approach is required to differentiate primary and secondary mucinosis because of distinct prognostic and therapeutic implications. Limited data is available for mucinosis and myositis-specific antibodies, like the Anti-Jo-1 antibody. Close follow-up is required to monitor disease progression and assess the risk of malignancy. Further studies are required to refine diagnostic criteria and management guidelines for mucinosis in connective tissue diseases.

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CASE REPORT

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Autoimmune Nodopathy Masquerading as Guillain-Barré Syndrome

Pravesha Chandrasekaran, Satish Janardhan Wagh***

Abstract

Autoimmune Nodopathies are characterised by antibody-mediated damage of the nodes of Ranvier, thereby affecting the propagation of action potential. We present the case of a 42-year-old woman who initially presented with acute flaccid quadriparesis. Based on clinical and electrophysiological findings, a diagnosis of Guillain-Barré Syndrome (GBS) was made, and the patient was started on intravenous immunoglobulin therapy. However, her condition worsened, and the patient developed bilateral Lower Motor Neuron facial paresis and bulbar weakness, prompting a diagnostic reevaluation. Repeat nerve conduction studies showed absent responses, and cerebrospinal fluid analysis revealed a rising protein level. A nodopathy panel revealed anti-neurofascin-140 antibody positivity, confirming autoimmune nodopathy. The patient responded dramatically to plasmapheresis and was subsequently maintained on rituximab therapy with sustained clinical remission. This case highlights the importance of considering autoimmune nodopathies in patients with atypical or treatment-resistant GBS-like presentations.

Key words: Bulbar palsy, ascending flaccid paralysis, neurofascin, autoimmune nodopathy, Guillain-Barré syndrome.

Introduction

The nodes of Ranvier are specialised unmyelinated segments of axons essential for the rapid conduction of action potentials via saltatory conduction. Flanked by paranodes, these nodes are densely populated with voltage-gated sodium channels and anchoring proteins that stabilise the membrane and secure the membrane protein to the underlying cytoskeleton[1]. One such anchoring protein is Neurofascin[2]. Autoantibodies directed against anchoring proteins such as Contactin, Neurofascin and Gliomedin disrupt the structural and functional integrity of nodes, impairing action potential conduction[3]. Over time, Neurofascin antibodies have been implicated in atypical presentations of Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyneuropathy[4]. Although initially thought to represent a variant of chronic inflammatory demyelinating polyneuropathy, autoimmune nodopathy is now recognised as a distinct entity due to its unique pathophysiology[5].

We present the case of a 42-year-old woman who developed acute-onset flaccid quadriparesis. A provisional diagnosis of Guillain-Barré Syndrome was made based on clinical findings and supporting evidence from nerve conduction studies and cerebrospinal fluid analysis, which showed albuminocytological dissociation. The patient was treated with intravenous immunoglobulin at 2 g/kg. However she deteriorated, and developed bilateral lower motor neuron facial palsy and bulbar weakness. The Nerve Conduction Study showed further worsening. Repeat Cerebrospinal fluid analysis showed an elevated protein level despite completion of the Intravenous immunoglobulin course. Given her treatment-resistant course, the possibility of autoimmune nodopathy was suspected. A Nodopathy antibody panel revealed positive neurofascin - 140 IgG antibodies, confirming the diagnosis. The patient responded dramatically to plasmapheresis and was subsequently maintained on rituximab therapy (every 6 months), achieving sustained remission. She currently performs all activities of daily living independently. This case underscores the importance of early reconsideration of diagnosis in patients with atypical or treatment-refractory Guillain-Barré syndrome presentations.

Case Presentation

A 42-year-old woman with no known co-morbidities presented with a history of difficulty walking for two days and weakness in both upper limbs for one day before admission. She was admitted to the ward with the above complaints.

On examination, hypotonia was present in all four limbs. Muscle power was Medical Research Council (MRC) grade III in the proximal and distal muscles of both lower limbs.

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On examination, hypotonia was present in all four limbs. Muscle power was Medical Research Council (MRC) grade III in the proximal and distal muscles of both lower limbs. Muscle power was MRC grade IV in both upper limbs. Generalised areflexia was noted. Sensory examination revealed absent joint position and vibration sense, with intact pain and temperature sensation. Based on these findings, a provisional diagnosis of polyradiculoneuropathy was considered. Nerve conduction studies (NCS) of all four limbs and cerebrospinal fluid (CSF) analysis were planned to assess for albumino-cytological dissociation. On the second day of admission, the patient's weakness worsened in all four limbs, accompanied by flaccid dysarthria and bilateral lower motor neuron (LMN) facial paresis. Given the progressive course, she was transferred to the medical ICU. The initial NCS showed generalised demyelinating polyradiculoneuropathy with conduction block (Table I).

Table I: Nerve conduction study prior to Intravenous immunoglobulin.

Nerve	Latency (ms)	Amplitude (mV)	Conduction Velocity (m/s)	Interpretation
Left Median (Wrist)	11.25	2.5	54.92	Demyelinating changes with conduction block
Left Median (Elbow)	15.63	1.5	–	Demyelinating changes with conduction block
Left Ulnar (Wrist)	5.31	4.0	58.55	Demyelinating changes with conduction block
Left Ulnar (Elbow)	9.58	3.7	—	Demyelinating changes with conduction block
Right Peroneal (Ankle)	14.27	2.3	35.18	Demyelinating changes with conduction block
Right Peroneal (Knee)	23.65	0.5	—	Demyelinating changes with conduction block
Left Peroneal (Ankle)	21.04	1.9	32.64	Demyelinating changes with conduction block
Left Peroneal (Knee)	31.15	1.0	—	Demyelinating changes with conduction block
Right Tibial (Ankle)	11.56	3.1	35.35	Demyelinating changes with conduction block
Right Tibial (Knee)	21.46	0.8	—	Demyelinating changes with conduction block
Left Tibial (Ankle)	8.65	4.1	—	Demyelinating changes with conduction block

Abbreviations: ms = Milliseconds, mV = Millivolts, m/s = Meters per second.*

CSF analysis revealed elevated protein (84 mg/dL) with no cells, consistent with albumino-cytological dissociation.

A diagnosis of Guillain-Barré syndrome (GBS) was made, and intravenous immunoglobulin (IVIG) was initiated at 400 mg/kg/day for five days. On the third day of admission, the patient developed dysphagia to liquids and solids, along with orthopnoea. She was electively intubated for bulbar symptoms. Supportive measures included physiotherapy, a high-protein diet, and symptomatic medications. Despite completing the IVIG course, no significant clinical improvement was noted. She remained on invasive ventilation and subsequently underwent tracheostomy for prolonged airway support. Repeat NCS performed 10 days after completing IVIG course demonstrated worsening with no recordable potentials in all four limbs (Table II).

Table II: Nerve conduction study post-intravenous immunoglobulin.

Nerve	Latency (ms)	Amplitude (mV)	Conduction Velocity (m/s)	Interpretation
Left Median (Wrist)	–	NR	–	No recordable response
Left Median (Elbow)	–	NR	–	No recordable response
Left Ulnar (Wrist)	–	NR	–	No recordable response
Left Ulnar (Elbow)	–	NR	–	No recordable response
Right Peroneal (Ankle)	–	NR	–	No recordable response
Right Peroneal (Knee)	–	NR	–	No recordable response
Left Peroneal (Ankle)	–	NR	–	No recordable response
Left Peroneal (Knee)	–	NR	–	No recordable response
Right Tibial (Ankle)	–	NR	–	No recordable response
Right Tibial (Knee)	–	NR	–	No recordable response
Left Tibial (Ankle)	–	NR	–	No recordable response

Abbreviations: ms = Milliseconds, mV = Millivolts, m/s = Meters per second.*

Repeat CSF analysis showed a further increase in protein concentration to 270 mg/dL, with no cells present.

Given the patient's rapidly progressive course and poor response to IVIG, the possibility of nodopathy was considered. A CSF nodopathy antibody test was sent, and plasma exchange (PLEX) was initiated, with five cycles on alternate days. Following the initiation of PLEX, gradual improvement was observed in both limb weakness and bulbar symptoms. The patient was subsequently weaned from ventilatory support and initiated on oral feeding. The CSF nodopathy test result was positive for neurofascin - 140 antibodies (Table III).

Table III: Neurofascin 140 antibody - ELISA method.

Test	Result	Reference range	Unit
Neurofascin 140 IgG antibody (ELISA)	342	0 - 233	ng/mL

**Abbreviations: ELISA = Enzyme-linked immunosorbent assay.*

Based on these findings, Rituximab 375 mg/m^2 (two doses, 15 days apart) was initiated. By three weeks of admission, the patient was walking with minimal support. The

tracheostomy was decannulated at an outpatient follow-up. At her most recent visit, she remained functionally independent in daily activities while on a 6-monthly rituximab maintenance course.

Discussion

This case highlights a presentation of autoimmune nodopathy, initially thought to be Guillain-Barré syndrome, due to overlapping clinical features. The patient, a 42-year-old woman, exhibited classical signs of acute inflammatory demyelinating polyneuropathy, including bilateral lower limb weakness, leading to the initial suspicion of GBS. Initially, the NCS suggested generalised demyelinating polyradiculoneuropathy, consistent with GBS, while the CSF analysis revealed albumino-cytological dissociation, a hallmark of this syndrome. However, the absence of response to intravenous immunoglobulin therapy and the subsequent worsening of neurological deficits, as evidenced by deterioration in the nerve conduction study, prompted a re-evaluation of the diagnosis. The increasing trend of CSF proteins and bulbar features further strengthened the suspicion of widespread damage beyond typical GBS[6,7]. Hence a possibility of autoimmune nodopathy was considered. In autoimmune nodopathy, antibody-mediated damage to the nodes of Ranvier results in destruction and detachment of the ion channels, thereby disrupting the depolarisation of the successive nodes. Neurofascin, a critical cell adhesion molecule at the nodes of Ranvier, plays a vital role in stabilising sodium channels essential for proper nerve conduction[8,9].

The nodal and paranodal antibodies primarily belong to the IgG4 class of immunoglobulins, which have a poor affinity for Fc receptors and thus are unable to activate complement[7]. Hence, the patient showed no improvement following the completion of the IVIG course.

The discovery of autoantibodies targeting neurofascin highlights a distinct autoimmune process that can lead to neuropathy with features similar to GBS and CIDP, but diverges in pathophysiology and treatment response[10]. Earlier, autoimmune nodopathy was thought to be a variant of CIDP. However, the acute onset and rapid progression of the disease, coupled with lack of inflammation and macrophage-mediated demyelination, led to the conclusion of Autoimmune nodopathy being a different entity[11].

In this patient's case, after transitioning to plasmapheresis therapy, we observed a significant clinical improvement. The gradual recovery of limb and bulbar strength following plasmapheresis underscores the critical role of timely and appropriate therapeutic interventions in improving outcomes for patients with autoimmune-mediated nerve injuries[9].

The identification of specific autoantibodies can further guide management strategies and provide insight into prognosis. In this case, the follow-up treatment plan included consideration for Rituximab therapy. Rituximab is a chimeric monoclonal antibody against the CD20 antigen primarily found on pre-B and mature B lymphocytes[12]. In patients with nodopathy associated with IgG4 autoantibodies, rituximab has emerged as an effective approach to achieve remission. Rituximab depletes these CD20+ B cells, thereby interrupting the generation of new plasmablasts and reducing the production of IgG4 antibodies[13]. This mechanism is particularly relevant since IgG4 antibodies are functionally monovalent, do not activate complement, and tend to exert pathogenicity via disruption of the paranodal axo-glial junctions, rather than through inflammatory demyelination[13].

This case highlights how early diagnostic reconsideration, particularly in patients presenting with atypical or treatment-resistant forms of demyelinating polyradiculoneuropathy, can lead to a significant shift in management and markedly improved patient outcomes.

Conclusions

Autoimmune Nodopathies are rare, yet important differential diagnoses in patients with atypical or treatment-refractory presentations of Guillain Barré Syndrome. This case highlights the need for timely reconsideration of diagnosis, especially when traditional management fails. Early identification of Autoimmune Nodopathies can significantly influence treatment decisions and underscores the importance of long-term immunotherapy planning to achieve sustained remission.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the consent form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity; however, anonymity cannot be guaranteed.

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