CASE REPORT

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Severe Hypercalcaemia and Hepatosplenic Granulomas: A Rare Presentation of Multisystemic Sarcoidosis

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Abstract

Sarcoidosis is an orphan disease characterised by non-caseating granulomas with predominant pulmonary involvement, heterogeneous presentations, and variable incidence and prevalence. Here we are presenting the case of a 60-year-old female with multisystemic sarcoidosis who presented with chronic gastrointestinal manifestations and severe hypercalcaemia. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from subcarinal and paratracheal lymph nodes revealed non-caseating epithelioid cell granuloma which was negative for acid-fast bacilli and tuberculosis PCR. The diagnosis of sarcoidosis is difficult, especially in tuberculosis-endemic countries.

Key words: Sarcoidosis, EBUS-TBNA, hypercalcaemia, non-caseating granuloma.

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown aetiology with different phenotypic as well as biochemical presentations[1]. It is a global disease with a variable prevalence of 3.68 cases per 1,00,000 people in Eastern Europe to 40 cases per 1,00,000 people in Northern Europe[2]. The incidence seems to be higher among Blacks than Whites. In India, sarcoidosis incidence is estimated to be 10 to 12 cases/1,000 new registrations annually at the respiratory unit at Kolkata and 61.2/1,00,000 new cases seen at Vallabhbhai Patel Chest Institute, Delhi[3]. The exact prevalence is not well studied in India due to inadequate epidemiological data and under-reporting due to lack of awareness, scarce invasive diagnostic tests, and frequent misdiagnosis as tuberculosis due to strong clinico-radiological resemblance[1]. The exact cause is unknown and multiple factors like genetics, environmental, and infectious triggers leading to immune-mediated inflammatory response have been postulated. Around 25 - 30% of patients have extrapulmonary involvement in the skin, eyes, musculoskeletal system, kidneys, heart, central nervous system, and exocrine glands. But hepatosplenic involvement is around 3 - 4%[4].

Case report

A known diabetic, hypertensive, hypothyroid 60-year-old lady presented with pain abdomen, loss of appetite, constipation, weight loss, and grade 1 - 2 breathlessness according to Modified Medical Research Council grading from the last 3 years which got aggravated in the last 2 months. On examination, bilateral fine crackles were present in both infra-scapular areas, and hepatosplenomegaly was also present. Laboratory investigations are depicted in Table I. Abdominal ultrasonography revealed hepatosplenomegaly with multiple hypoechoic areas in the spleen. Contrast-enhanced computed tomography (CECT) of abdomen (Fig. 1a) confirmed ill-defined nodules in the spleen and liver with retroperitoneal lymphadenopathy suggestive of granulomatous disease. CECT chest (Fig. 1b) also suggested multiple nodules in all lobes of both lungs with tree-in-bud appearance and mediastinal lymphadenopathy. Bronchoscopy showed no endobronchial lesions; and EBUS-guided transbronchial needle aspiration (EBUS-TBNA) from subcarinal and paratracheal lymph nodes showed non-caseating epithelioid cell granuloma which was negative for acid-fast bacilli and tuberculosis PCR. Complete blood counts, renal function tests, serum glutamic-pyruvic transaminase, and serum glutamic-oxaloacetic transaminase, serum albumin, and ECG were normal. Viral markers, sputum for Cartridge Based Nucleic Acid Amplification Test (CBNAAT), urine, and blood culture were negative. She responded well to fluid resuscitation, salmon calcitonin, and oral steroids along with supportive care. The corticosteroid-sparing medication methotrexate with folic acid were added as it was difficult to taper steroids and associated co-morbidities. The patient is doing well on follow-up at 18 months.

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Table I: Laboratory investigations.

Parameters	Results	Reference range
CRP	12 mg/L	0 - 5.0 mg/L
ESR	32 mm/hr	4 - 12 mm/hr
Alkaline phosphatase	602.4 U/L	46 - 116 U/L
Corrected Calcium	15 mg/dL	8.4 - 10.4 mg/dL
Serum Phosphate	2.32 m/dL	2.5 - 4.5 mg/dL
25-Hydroxy-Vitamin D	18.3 ng/mL	30 - 100 ng/mL
Se. Parathyroid Hormone Intact	7.40 pg/mL	14 - 72 pg/mL
Se. Angiotensin Converting Enzyme	208 U/L	8 - 52 U/L
HbA1C	7.1%	6.5%
Thyroid profile	FT3 2.76pg/mL, FT4 1.24 ng/dL, TSH 7.91 mIU/L	2.45 - 5.93 pg/mL 0.78 - 2.19 ng/dL 0.46 - 4.68 mIU/L
Anti-thyroid peroxidase antibody	>1,300 U/mL	<60.00 U/mL

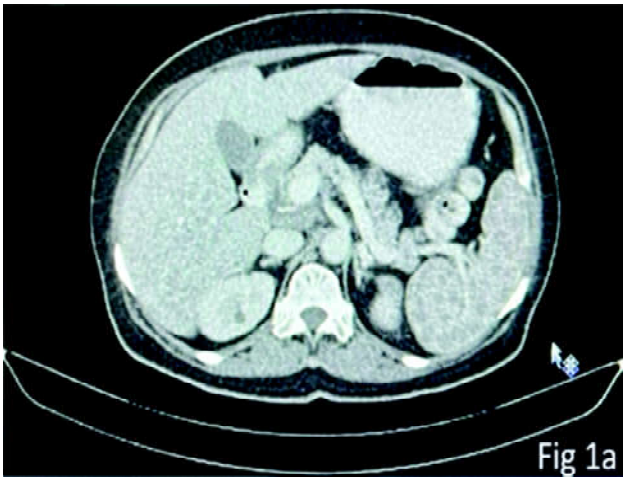

Fig. 1.a: *CECT abdomen showing Ill-defined nodules in spleen and liver.*

Discussion

Sarcoidosis incidence is more in the 4th decade with a second peak occurring around 65 years of age[2]. Female predominance is well documented with more ocular and neurological manifestations. Some Indian studies have found no gender predominance[4]. Non-caseating granulomas are the hallmark of this disease. Immunopathogenetic mechanisms triggering T-cell antigen stimulate a cascade of events leading to non-caseating granuloma formation. First-degree relatives have an increased risk of developing the disease by five-fold. Certain HLA alleles are associated with increased susceptibility like HLA-DRB1*03, *11, *12, *14, *15, and with certain phenotypes like HLA-DRB1*1101 with cardiac sarcoidosis[2].

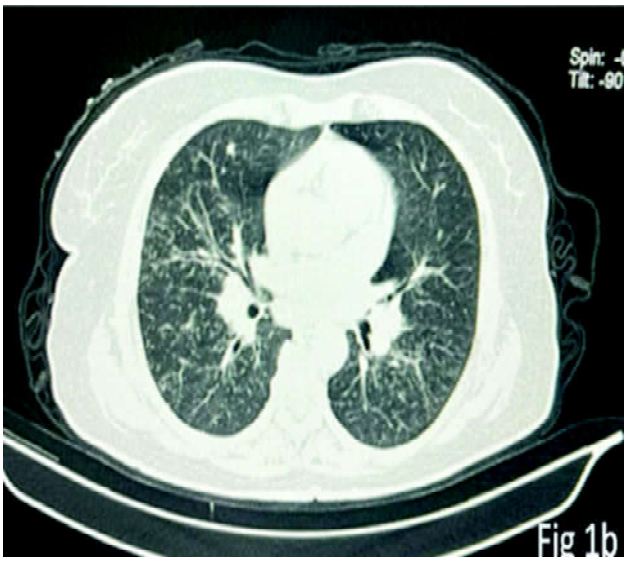

Fig. 1b: *CECT thorax showing perilymphatic micronodular opacities.*

Nath *et al* 2019 did a retrospective study from January 2014 to December 2018 and found gastrointestinal involvement in eight patients (6.67%) out of 120 with only 4 having hepatosplenomegaly with hypodense lesions[5]. Graf *et al* (2021) found hepatic sarcoidosis in 4.2% patients, 62 out of 1476 sarcoidosis patients diagnosed between 2004 to 2020 in 5 German centres, and cirrhosis was found in 9 patients[6]. The most common presentation is the cholestatic pattern with raised alkaline phosphatase and gamma-glutamyl transferase as seen in our patient. If untreated and not diagnosed in time, can lead to portal hypertension, end-stage liver disease, and cirrhosis. Madan *et al* (2022) found only 1.5 - 3% hepatosplenic involvement and 3.8 % hypercalcaemia on ambispective analysis of 327 sarcoidosis patients at AIIMS, New Delhi diagnosed between 2013 to 2019[4]. Also, 12.2% had hypothyroidism and nearly 30% had received anti-tubercular treatment[4]. Autoimmune thyroid disease with positive autoantibodies has been associated with sarcoidosis and hypothyroidism being more common as in our patient[7]. There can be direct granulomatous infiltration of the thyroid gland or an associated autoimmune process. Sarcoidosis patients have higher levels of thyroid peroxidase antibodies and/or thyroglobulin antibodies. It is a major co-morbidity that should be diagnosed and treated in time. Serum ACE levels are raised in around only 50% of cases as in our patient and normal levels do not rule-out sarcoidosis. The ACE levels can also be raised in tuberculosis, lymphoma, or atypical mycobacterial infection. As hypercalcaemia can be due to infective or non-infective granulomatous disease or malignancy, it becomes a diagnostic challenge to rule out these. The patient also had severe hypercalcaemia with a corrected calcium level of 15 mg/dL. As hypercalcaemia

can be due to infective or non-infective granulomatous disease or malignancy, it becomes a diagnostic challenge to rule-out these, especially in developing countries like India. Anand *et al* 2015 reported a case of a 35-year-old lady with isolated abdominal sarcoidosis presenting with hypercalcaemic crisis[8]. Although asymptomatic hypercalcaemia is more common. The index patients had primarily gastrointestinal symptoms for a long time due to sarcoidosis as well as hypothyroidism which remained undiagnosed and later aggravated leading to severe hypercalcaemia. Even though bronchoscopy, BAL, EBUS-TBNA, and lung biopsy are invasive and costly, but very helpful to delineate the exact aetiology and rule out neoplasm as well as other infective aetiologies, especially tuberculosis. Because of its clinical heterogeneity, learning about varied presentations is crucial to avoid missed or delayed diagnoses. Pulmonary involvement is the most common cause of morbidity and mortality in sarcoidosis patients. The true burden of sarcoidosis is not known because of underreporting, varied presentation, and inaccurate diagnosis. The treatment goal is to decrease granuloma formation and progression, thus decreasing the risk of morbidity, mortality and improving quality-of-life[9]. Many patients undergo spontaneous remission on their own but some follow a more chronic progressive course. Mortality increases with time due to disease or treatment complications. Treatment is considered for those with high symptom burden and/or organ damage with more aggressive approach in case of hypercalcaemia, neurological, cardiac, or ophthalmic involvement. The first-line treatment is corticosteroids; 20 - 40 mg/day prednisolone maintained over 1 to 3 months and then gradually tapered to 5 - 10 mg/day over 6 months to 1 year. Corticosteroid-sparing medication like methotrexate, azathioprine, leflunomide, and mycophenolate mofetil is used when inability to taper steroids below 10 mg/day or relapse or increased complications or side effects[9]. The biologics like Tumour Necrosis Factor-alpha (TNF-a) inhibitors infliximab, adalimumab, and rituximab are given in case of non-remitting disease or relapse according to the systemic involvement[10].

Take home message

Sarcoidosis is not as rare as earlier thought in tuberculosis-endemic countries like India but still not much reported and diagnosed in time. Bronchoscopy and EBUS-TBNA play an important diagnostic role. Extrapulmonary and gastrointestinal manifestations can be the first presenting features. Autoimmune thyroid disease should be ruled-out.

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