CASE REPORT

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Atypical Adult-Onset Cystic Fibrosis in a Patient with Type 1 Diabetes Mellitus: Diagnostic Challenges with Multisystem Involvement

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Abstract

Cystic fibrosis (CF) is a multisystem autosomal recessive disorder most commonly found in the Caucasian populations, typically diagnosed in childhood. Adult-onset presentations are rare and often misdiagnosed due to overlapping features with other chronic respiratory or gastrointestinal diseases. We present the case of a 19-year-old Indian male who presented with prolonged weight loss, chronic diarrhoea, persistent fever, productive cough, and progressive dyspnoea. His past medical history included type 1 diabetes mellitus, and he was being treated for pulmonary tuberculosis. Clinical evaluation revealed signs of malnutrition, bilateral hearing impairment, and persistent hypokalaemia unresponsive to supplementation. Imaging showed patchy lung consolidation, bronchiectasis, and fibrotic changes. Barter and Gitelman syndromes were suspected due to the unexplained and refractory hypokalaemia but its presence with type 1 diabetes, recurrent pulmonary infections, sensorineural hearing loss, raised suspicion of cystic fibrosis, which was confirmed through genetic testing. This case underscores the importance of considering possibility of cystic fibrosis in the differential diagnosis of chronic respiratory and systemic symptoms in adult patients, particularly in regions where the disease is considered uncommon.

Introduction

Cystic fibrosis is a life-limiting genetic disorder caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, resulting in defective chloride ion transport across epithelial membranes[1,2]. Although it is most frequently diagnosed in early childhood among Caucasians, there is growing recognition globally of adult-onset cystic fibrosis, especially with improved diagnostic awareness and access to genetic testing[3,4]. In adults, clinical manifestations can be atypical and are often misattributed to other more common illnesses, such as asthma, bronchiectasis of other aetiologies, or tuberculosis, particularly in resource-limited settings[5]. Adult patients may present with subtle or single-organ involvement, which delays diagnosis and appropriate intervention[6,7]. This case report discusses an unusual presentation of cystic fibrosis in a young adult male from India, where the disease is underreported and frequently overlooked as it is uncommon in the region[3,5,8].

Case Description

A 19-year-old male presented to our hospital with a one-year history of significant weight loss amounting to 15 kilograms. Over the previous three months, he had been experiencing chronic diarrhoea and, in the last week, reported passage of blood in stool. For the past ten days, he complained of fever associated with night sweats, along with a productive cough yielding yellow sputum and increasing shortness of breath. His dyspnoea had progressed to Modified Medical Research Council (MMRC) grade 3 and was worse in the supine position. His medical history revealed that he had been diagnosed with type 1 diabetes mellitus five years earlier and was on insulin therapy. He had also been diagnosed with pulmonary tuberculosis and was on anti-tubercular therapy, specifically ethambutol and levofloxacin, for the past one month. Social history revealed that he was a chronic smoker and a habitual tobacco chewer.

On examination, the patient appeared cachexic and undernourished. He was afebrile at presentation, with a pulse rate of 92 beats per minute and blood pressure of 102/68 mmHg. Auscultation of the chest revealed bilateral early and mid-inspiratory coarse crepitations along with diffuse rhonchi. Neurologically, the patient reported decrease in hearing, which was confirmed through pure tone audiometry showing severe sensorineural hearing loss in the right ear and mixed severe hearing loss in the left ear.

Laboratory investigations including a complete blood count were within normal limits, with a haemoglobin level of 11.2 g/dL, a white cell count of 7,200/mm^3, and a platelet

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count of 170,000/mm^3. However, serum electrolytes revealed significant hypokalaemia with a potassium level of 2.9 mmol/L, while sodium was 141 mmol/L and chloride was 113 mmol/L. Despite intravenous potassium supplementation, the patient's serum potassium level remained low, and repeated testing on the second day showed potassium at 2.9 mmol/L with sodium at 132 mmol/L and chloride at 109 mmol/L. Further evaluation of hypokalaemia revealed a urine osmolality of 300 mOsm/kg and a serum osmolality of 261 mOsm/kg, with urinary sodium at 113 mmol/L, urinary potassium at 19 mmol/L, urinary chloride at 13 mmol/L,24-hour urinary protein excretion of 70 mg and C-peptide levels as 0.46 ng/mL.

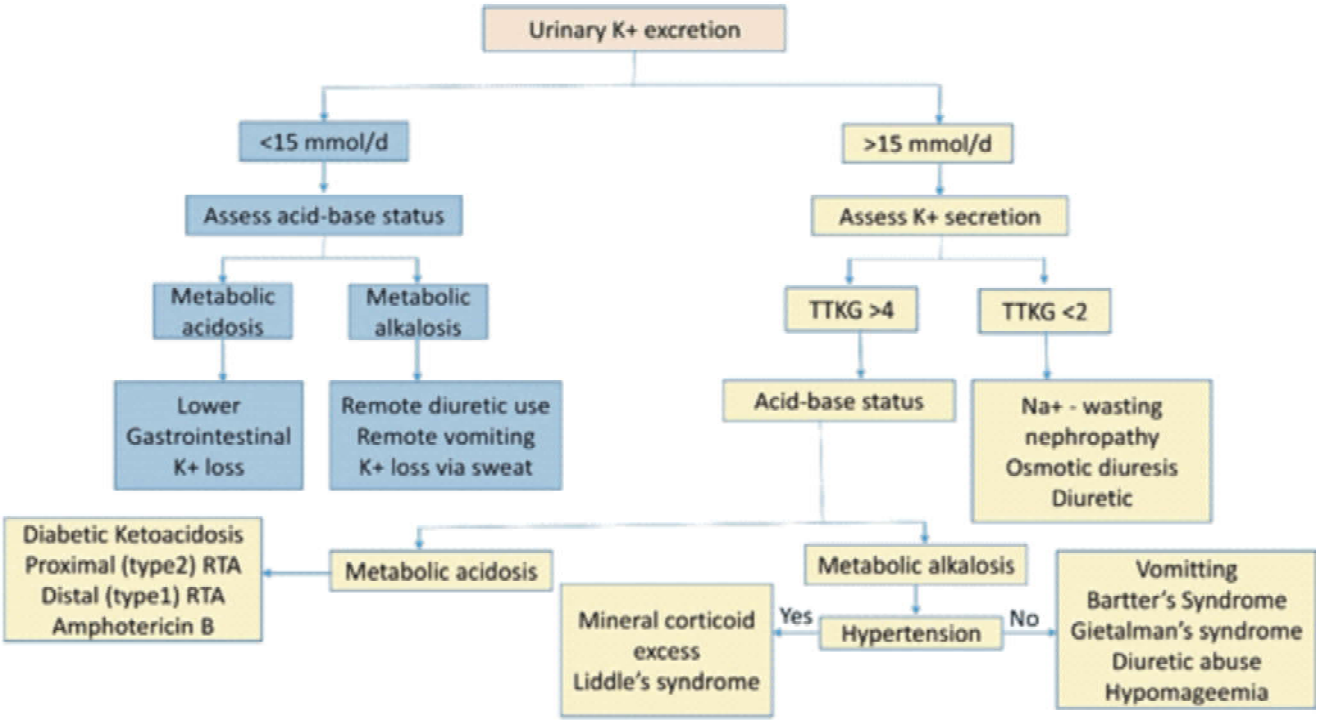
Due to the presence of chronic respiratory symptoms and history of tuberculosis, a chest X-ray AP view was performed. The imaging demonstrated patchy areas of consolidation and collapse in the right upper and bilateral middle lung lobes suggestive of an infective process, along with fibrotic opacities in the upper lobes and evidence of bronchiectatic changes in both lower lobes. This radiological picture, along with clinical findings, suggested a chronic suppurative pulmonary process. The combination of type 1 diabetes mellitus, chronic productive cough, recurrent respiratory infections, and unexplained refractory hypokalaemia led to a suspicion of cystic fibrosis. The presence of sensorineural hearing loss further supported a multisystem disease process.

The patient's urinary potassium excretion was checked and found to be more than 15 mmol/day. Therefore, to proceed with further workup, the trans tubular potassium gradient (TTKG) was calculated by dividing the urine potassium concentration by the ratio of urine to plasma osmolality, which was found to be greater than four. An arterial blood gas analysis was subsequently advised, which revealed metabolic alkalosis. Given the presence of hypokalaemia, urinary potassium excretion greater than 15 mmol/day, a TTKG greater than four, metabolic alkalosis, and a normotensive status, the patient was suspected to have either Gitelman or Bartter syndrome (Flow chart 1).

To confirm the diagnosis, genomic sequencing was conducted, which confirmed the presence of mutations in the CFTR gene, thereby establishing the diagnosis of cystic fibrosis and ruled out Gitelman or Bartter syndromes.

The patient was managed conservatively for hypokalaemia, intravenous cycles of potassium chloride (KCl) were given. After the serum potassium level reached 3.4 mmol/L, he was switched to oral potassium supplementation. For pulmonary tuberculosis, the patient was started on a six-month course of anti-tubercular therapy. For type 1 diabetes mellitus, insulin therapy was continued. In view of sensorineural hearing loss, the patient was advised to use a

Flow chart 1: Clinical approach to Hypokalaemia



hearing aid. Following the confirmation of a diagnosis of cystic fibrosis, Ivacaftor (a CFTR potentiator, improving the function of protein in the body to decrease the build-up of thick mucus in lungs and improving the symptoms of cystic fibrosis) twice daily was initiated. Additionally, chest and limb physiotherapy, along with cough expectorants, were administered.

The patient was discharged with these medications. On follow-up after 7 days, the serum potassium level had improved, but blood glucose levels remained uncontrolled, which was further managed by adjusting the insulin dose. On the next follow-up after 1 month, the patient's serum potassium levels and blood glucose levels were checked again, and an X-ray was repeated, which showed improvement in serum potassium levels and control of blood glucose levels, along with improvement on the X-ray. The patient was continued on the same medication.

Case Discussion

This case highlights the diagnostic complexity and clinical significance of atypical presentations of cystic fibrosis (CF), particularly in a young adult male from India – a region where CF is considered rare and often underdiagnosed[3,5,8]. Traditionally viewed as a pediatric disease with early-onset symptoms, CF is increasingly being recognised in adolescents and adults due to better diagnostic techniques and improved clinical awareness[3,4]. However, late-diagnosed cases often have milder or non-classical presentations, making diagnosis challenging, especially in areas with high prevalence of diseases that mimic CF, such as tuberculosis[4,5].

The patient's initial clinical presentation raised a broad range of diagnostic possibilities. He had constitutional symptoms including chronic weight loss, low-grade fever, productive cough, and breathlessness. These findings, combined with radiologic features such as consolidation and fibrotic changes, led to a preliminary diagnosis of pulmonary tuberculosis. This was a reasonable first impression given his demography and the high endemicity of tuberculosis in the region[5]. The patient had also been on a course of anti-tubercular therapy which caused ATT-induced hepatitis, so patient was started on Ethambutol and Levofloxacin, but his lack of clinical improvement and the persistent progression of symptoms prompted further investigations. However, tuberculosis alone could not explain the full spectrum of his systemic symptoms. Chronic diarrhoea, persistent hypokalaemia, and sensorineural hearing loss pointed to a more complex and multisystem pathology. Inflammatory bowel disease and celiac disease were considered due to the gastrointestinal symptoms and nutritional deficiencies. Yet, neither accounted for the patient's respiratory involvement or persistent metabolic derangements.

Renal tubulopathies such as Bartter or Gitelman syndromes were also explored due to the recurrent, treatment-resistant hypokalaemia and trans tubular potassium gradient (TTKG) more than four. These conditions are known to cause potassium and chloride wasting, metabolic alkalosis, with normotension. But, the biochemical profile did not fully align, and these syndromes do not typically present with concurrent pulmonary, gastrointestinal, and endocrine abnormalities. Moreover, the patient's serum and urine osmolality values and urinary electrolytes suggested renal salt loss in the context of a systemic condition rather than an isolated renal disorder.

Another consideration was a mitochondrial cytopathy, given the constellation of diabetes, hearing loss, and multisystem involvement. However, the absence of neurological signs, lactic acidosis, or maternal inheritance pattern made a mitochondrial disorder less likely. Primary immuno-deficiencies, such as common variable immunodeficiency (CVID), can present with recurrent respiratory infections and gastrointestinal symptoms. Still, there was no history of frequent infections in early life or laboratory evidence of immune deficiency, making this diagnosis unlikely.

Ultimately, a unifying diagnosis was achieved with CFTR gene mutation testing, confirming cystic fibrosis[3,6]. This diagnosis brought clarity to the patient's complex presentation. The gastrointestinal complaints and malnutrition were attributable to pancreatic exocrine insufficiency, a classic but sometimes overlooked feature of CF, particularly in adults[1,2,6]. His diabetes was consistent with cystic fibrosis-related diabetes (CFRD), which is distinct from type 1 and type 2 diabetes. CFRD arises from pancreatic islet cell destruction and insulin resistance due to chronic inflammation and fibrosis. This patient had low C-peptide levels and elevated HbA1c levels and in CFRD C-peptide levels are either elevated or normal and HbA1c levels are either low or normal. Therefore, the patient was labelled as having type 1 diabetes mellitus[1]. CFRD affects approximately 40 - 50% of adults with CF and is associated with worse pulmonary function and nutritional outcomes[1].

The hypokalaemia, which was refractory to oral supplementation, was explained by a salt-losing syndrome secondary to CF[2,6]. The defect in chloride transport results in renal and sweat gland salt wasting. Diarrhoea, insulin use, and malabsorption compounded these losses, as reflected in his abnormal urinary and serum electrolyte levels. Persistent hypokalaemia in young patients, especially when associated with multisystem findings, should prompt evaluation for CF, particularly when more common causes have been excluded[6].

The sensorineural hearing loss observed in this patient is not a direct consequence of CF pathology but is an important clinical clue. CF patients often experience chronic otitis media due to Eustachian tube dysfunction or may develop hearing impairment secondary to ototoxic antibiotics, particularly aminoglycosides, which are commonly used to manage bacterial lung infections. In our patient, there is no history of aminoglycosides administration[7].

A striking aspect of this case is the diagnostic delay caused by geographic and epidemiologic biases. In South Asia, CF remains under-recognised due to its perceived rarity, lack of widespread new-born screening, limited access to sweat chloride testing, and a general underappreciation of adult-onset or atypical cases[3,5,8]. Furthermore, the genetic profile of CFTR mutations in South Asian populations differs from Western cohorts, with a lower prevalence of the common AF508 mutation and a higher frequency of rare or region-specific variants[3,8]. This genetic variability likely contributes to milder or variable phenotypes and complicates standard diagnostic pathways.

Several critical clinical lessons emerge from this case. Firstly, clinicians must suspect for CF in young or adults who present with type 1 diabetes mellitus, chronic productive cough, recurrent respiratory infections, and unexplained hypokalaemia. Secondly, the presence of persistent hypokalaemia should prompt consideration of systemic conditions like CF when more common renal, endocrine and gastrointestinal causes have been ruled-out[6]. Thirdly, the co-existence of chronic pulmonary disease and diabetes mellitus in a young patient should be a red flag, especially in the context of weight loss and malnutrition[1,6]. Finally, this case reinforces the value of molecular genetic testing in confirming CF, especially in atypical presentations or in resource-constrained settings where traditional diagnostics like sweat chloride testing may be unavailable or inconclusive[3,6].

In conclusion, this case not only broadens the clinical spectrum of adult-diagnosed CF but also serves as a reminder of the diagnostic challenges posed by systemic diseases with overlapping features. It underscores the importance of holistic patient evaluation, context-specific diagnostic algorithms, and the critical role of genetic testing in achieving diagnostic clarity. Heightened awareness and early recognition are essential to avoid delays in appropriate management and to improve long-term outcomes in patients with atypical CF[3,5].

Review of Literature

Cystic fibrosis (CF), historically considered a paediatric disease, is now increasingly recognised in adults due to greater awareness, improved diagnostic tools, and milder phenotypic variants. Barry and Simmonds (2023) emphasized that adult presentations are often atypical and may involve subtle or organ-specific symptoms such as recurrent sinusitis, pancreatitis, or male infertility. Delayed diagnosis in adults can be attributed to retained pancreatic function and less severe pulmonary manifestations, making comprehensive diagnostic workup – including sweat chloride testing, CFTR mutation analysis, and nasal potential difference studies – essential for confirmation[4].

A recent study by Vaidyanathan *et al* (2022) highlighted significant disparities in the diagnosis and treatment of cystic fibrosis (CF) among Asian populations, using data from major international CF registries. The authors found that Asian individuals are underrepresented in CF registries and frequently harbour rare or population-specific CFTR mutations not covered by standard Western mutation panels. This genetic diversity complicates diagnosis, leading to under diagnosis or misdiagnosis. Furthermore, limited representation in clinical trials restricts access to CFTR modulator therapies for many Asian patients. The study underscores the urgent need for inclusive genetic screening protocols, population-specific mutation databases, and equitable access to precision therapies across all ethnic groups[3].

Mandal *et al* (2015) examined the Indian context, highlighting that CF is often underdiagnosed or misdiagnosed due to limited awareness and access to diagnostic facilities. The clinical phenotype in Indian patients is typically severe, with earlier colonisation by Pseudomonas aeruginosa, significant malnutrition, and frequent vitamin deficiencies. The review also pointed out the relatively lower frequency of the AF508 mutation in the Indian population, complicating genetic confirmation of the disease[8].

The American Diabetes Association's 2010 standards provide comprehensive guidelines for the management of diabetes, including diagnostic criteria, glycaemic targets, and complication monitoring. While not CF-specific, these guidelines are highly relevant for managing cystic fibrosis-related diabetes (CFRD), a common comorbidity in adult CF patients, which requires an individualised approach due to overlapping features of both type 1 and type 2 diabetes[10].

Kabra *et al* (2003) presented data from a cohort of North Indian children with CF, underlining the burden of delayed diagnosis and associated complications such as severe malnutrition, fat-soluble vitamin deficiencies, and chronic respiratory infections. They stressed the need for increased clinical suspicion in children with recurrent respiratory or gastrointestinal symptoms, even in populations where CF is considered rare[11].

Collectively, these studies underscore the diagnostic and therapeutic challenges associated with CF in resource-limited settings and adult populations. They also highlight the importance of multidisciplinary care, especially in patients with overlapping co-morbidities such as diabetes and chronic infections.

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