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A Rare Case Report Having Compound Heterozygous CFTR Mutation in an Indian Patient with Cystic Fibrosis

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Abstract

Background: Cystic fibrosis (CF) is caused by mutations in the CFTR gene, with delF508 accounting for ~70% of alleles in Caucasian populations but only ~27% in Indian cohorts, reflecting substantial regional genotypic heterogeneity. The nonsense mutation R1162X (c.3484C>T) is generally associated with a mild-to-moderate pulmonary phenotype when homozygous, attributed to residual CFTR mRNA expression.

Case Presentation: A 20-year-old Indian male presented with chronic productive cough since infancy, failure to thrive, and acute abdominal pain. Examination revealed severe malnutrition (BMI 12.4 kg/m^2) and Grade 3 digital clubbing. Investigations showed markedly elevated sweat chloride (>175 mEq/L), severe obstructive-restrictive pulmonary disease (FEV1 23%, FVC 42%, DLCO 31% predicted), chronic *Pseudomonas aeruginosa* colonization, hepatobiliary involvement (elevated transaminases, ALP, and bilirubin with negative viral hepatitis screening), pancreatic involvement, chronic pansinusitis, and reduced bone mineral density at multiple skeletal sites. Genetic testing, negative for delF508, revealed compound heterozygosity for CFTR c.3718-2477C>T (intron 22) and c.3484C>T/p.Arg1162Ter (exon 22) — a combination not previously reported.

Conclusion: Despite the comparatively mild phenotype reported for R1162X in the homozygous state, our patient exhibited severe multisystem disease, suggesting the paired deep intronic variant may confer a more severe loss-of-function effect than previously characterized R1162X genotypes. This case highlights the genotypic heterogeneity of CF in India, the limitations of genotype-based severity prediction from single-mutation reports, and the need for comprehensive CFTR sequencing and heightened clinical suspicion in Indian patients with unexplained multisystem disease.

Keywords: Paroxysmal Nocturnal Hemoglobinuria(PNH), Hemolytic Anemia, PIGA Gene Mutation, Misdiagnosis

Introduction

Cystic Fibrosis(CF) is an autosomal recessive genetic disorder, occurring due to mutations in Cystic Fibrosis Transmembrane Regulator(CFTR) gene located on chromosome-7q31.2, which functions as a chloride and other ion transporter across the epithelial cell membranes [1]. Malformation of this transporter protein results in abnormal transport of ions across the membrane resulting in highly viscous secretions on the luminal surface of lungs, pancreas and abnormal electrolyte composition in sweat [2].

The most common type of mutation worldwide found in CF patients is delF508, accounting for approximately 70% of CFTR alleles in Caucasian populations but only around 27% in Indian cohorts [3, 4]. A lower frequency of delF508 does not indicate that CF is rare in India, but rather that the remaining alleles are spread across a much more heterogeneous set of mutations-a recent South Indian cohort identified 55 distinct CFTR variants, including six novel ones, among just 120 patients [1]. Both the mutation diversity and low clinical awareness contribute to significant diagnostic delay in India. This heterogeneity underscores the importance of comprehensive CFTR sequencing, rather than targeted panels, in Indian patients with clinical presentation suggestive of CF [1,3,4].

We describe a case of a 20-year-old Indian male diagnosed with CF, negative for delF508 with a compound heterozygous for two CFTR mutations, comprising c.3718-2477C>T(intron 22) on one allele and c.3484C>T/p.Arg1162Ter(exon 22) on the other. This compound heterozygous combination has not, to our knowledge, been previously described, though both variants have been

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individually reported in Indian cohorts[1]. Notably, both mutations are individually associated with comparatively milder pulmonary disease in prior reports, whereas our patient presented with a severe form of disease [5].

Case Presentation

A 20-year-old male, born from non-consanguineous parents presented with complaints of diffused abdominal pain for 20 days. The pain was insidious in onset, mild in intensity, non-radiating, persistent, aggravated by coughing and vomiting, and relieved by bending forward and resting. He also reported intermittent productive cough since childhood which was gradually progressive over the years, with yellowish-white, non-foul-smelling sputum and no hemoptysis. Symptoms were predominantly seen in the early morning, aggravated during winter and relieved on medication based on purely clinical examination. He also had a history of failure to thrive during childhood and decreased appetite for 10 years.

There was a history of recurrent respiratory infections since the 28th day of life, for which he had been previously diagnosed with bronchiectasis and asthma and treated with Ayurvedic medications and nebulization. There was no history of fever, diarrhea, hemoptysis, altered sensorium, or burning micturition.

On examination, the patient was severely malnourished(BMI-12.4 kg/m^2).Patient was vitally stable with Grade-3 bilateral clubbing. Respiratory examination revealed bilateral lower-zone coarse crepitations with equal air entry. Abdominal examination revealed mild epigastric tenderness without any organomegaly; the rest of the systemic examination was unremarkable. Routine and radiological investigations are shown in Table 1 and 2 respectively.

Viral hepatitis screens, including HBsAg and anti-HCV, were negative. Given the constellation of chronic bronchiectasis, failure to thrive, severe digital clubbing, pancreatic involvement, and hepatobiliary involvement; CF was suspected. Sweat chloride testing was performed, revealing markedly elevated levels at >175mEq/L(diagnostic threshold ≥60 mEq/L), and genetic testing revealed compound heterozygosity for CFTR c.3718-2477C>T (intron 22) and c.3484C>T/p.Arg1162Ter (exon 22), confirming our diagnosis of CF.

Treatment given to him was Inj-Cefosulbactam, ursodeoxycholic acid, pancreatic enzymes capsules, multivitamins, folic acid, zinc, calcium, and vitamin-D supplementation. Nebulization with salbutamol, ipratropium, budesonide, and ambroxol was administered. Chest physiotherapy and airway-clearance measures were explained, and inhaled formoterol and beclomethasone via Rotahaler were prescribed at discharge. He was counselled regarding a high-protein diet to improve nutritional status.

Discussion

The Genetic variation found in our patient is consistent with the underlying pattern a seen in Indian CF cohorts[1]. Unlike the Caucasian population, where delF508 accounts for approximately 70% of CFTR alleles[4]. Whereas, Indian cohort showing a markedly lower frequency of delF508 around 27%, with the remaining disease-causing alleles which are distributed across a wide and largely distributed [1,3]. A recent study by Varkki et al. on south indian population reveals 55 distinct CFTR variants, including six novel mutations, demonstrating that no single targeted panel can reliably capture the diversity of CF-causing allele in the population [1]. Our patient, on contrary has negative delF508 and is compound

Table 1: Routine Investigations

Investigation	Patient's values	Normal values	Interpretation
Hemoglobin	**12.4 g/dL**	13–17 g/dL	Mildly reduced
Platelet count	**142,000/cmm**	150,000–450,000/cmm	Mild thrombocytopenia
Aspartate Transaminase	**130 IU/L**	~10–40 IU/L	Markedly elevated
Alanine Transaminase	**517 IU/L**	~7–56 IU/L	Markedly elevated
Alkaline Phosphatase	**165 IU/L**	40–120 IU/L	Elevated
Serum Albumin	**2.9 g/dL**	3.5–5.0 g/dL	Hypoalbuminemia
Total Protein	**4.9 g/dL**	6.0–8.3 g/dL	Hypoprotenemia
Serum Amylase	**328.36 IU/L**	~30–110 IU/L	Elevated
Serum Lipase	**64 IU/L**	~0–60 IU/L	Borderline elevated
Serum IgE	**21.72 IU/ml**	<100–150 IU/mL	Normal level ruling out allergic bronchopulmonary aspergillosis (ABPA)
C-Reactive Protein	**13.5 mg/L**	<5 mg/L	Elevated
Sweat chloride test	**>175 mEq/L**	<30 mmol/L	Diagnostic range for CF
Diffused Lung Carbon Monoxide Test	**31%**	~75–140% predicted	Reduced
Total Lung Capacity	**Decreased**	~80–120% predicted	Reduced
Spirometry	***FEV$_1$(23%)/ FVC(42%)** ratio = 49%**	~75–85% in adults	Reduced
CBNAAT for MTB	**Not Detected**	-	No active TB infection found
Culture Growth	**Pseudomonas colonies growth seen**		

(**FEV$_1$/FVC:* forced expiratory volume in the first second/forced vital capacity (*FEV$_1$/FVC*) ratio)

heterozygous for a well-characterised non-sense mutation(R1162X) and a rare deep intronic variant, representing this pattern and supporting the case for comprehensive CFTR sequencing over targeted mutation panels when the clinical suspicion for CF is high in Indian patients, regardless of delF508 status.

The R1162X(c.3484C>T) mutation has been individually well characterized and is generally associated with a comparatively mild pulmonary phenotype. In a cohort of nine Italian patients who were homozygous for R1162X, all had pancreatic insufficiency, yet the pulmonary manifestation was mild to moderate and the onset of respiratory symptoms were seen after the first year of life and favourably long-term radiographic scores relative to other CF genotypes [5]. R1162X mutation creats a premature stop codon; however, some of the CFTR mRNA remains intact, leading to formation of small amount of functional CFTR protein This residual CFTR function may contribute to a relatively milder pulmonary phenotype compared with mutations such as R553X and W1316X, which are associated with markedly reduced CFTR mRNA levels and consequently more severe disease [2].

Whereas, in a study by Shao et al. (2020), R1162X was reported in a Chinese sibling pair in a compound heterozygous state with a distinct missense variant and was associated with a considerably more severe pulmonary phenotype, including bronchiectasis with FEV1 as low as 24.3% predicted and congenital bilateral absence of the vas deferens [6]. This demonstrates that the clinical presentation due to R1162X mutation is not the same in every patient, but depends upon the other CFTR variant present. Our patient's presentation — severe

Table 2: Radiological Investigations.

Radiological investigation	Findings
Ultrasonography of Abdomen	• Mild-to-moderate ascites with free fluid around the liver; splenomegaly (13.2 cm) • Distended gallbladder containing echogenic material with wall thickening (6.3 mm) and mild-to-moderate pericholecystic edema • Mildly edematous and heterogeneous pancreas • 2-mm concretion in the upper calyx of the left kidney
Ultrasonography of Chest	Bilateral pleural effusion (right: 150–170 cc; left: 110–120 cc) with air bronchograms in the underlying lung
High-Resolution Computed Tomography(HRCT) scan of Chest	• Bilateral bronchiectatic changes were noted • Bilateral upper-lobar pneumonia • Bilateral moderate pleural effusion with subpleural atelectasis and mild fissural extension • smooth interlobular and intralobular septal thickening; mild cardiomegaly • mild prominence of the main pulmonary artery; mild pericardial effusion • features of cardiac congestion and bilateral peribronchial cuffing
Paranasal sinus CT scan	Bilateral chronic pansinusitis, non-pneumatized frontal sinuses, hypopneumatized sphenoid sinuses
Abdominal CT scan	hepatomegaly (~16 cm), Gall Bladder wall thickening/edema, omental caking, mesenteric haziness/peritoneal thickening, ascites; note pancreas reported as normal on CT (vs. inflamed on USG same period)
Magnetic Resonance Imaging(MRI) of Lumbosacral spine	Disc desiccation, reduced disc spaces, multiple Schmorl's nodes, and disc bulges involving almost the entire lumbar, dorsal, and lower cervical spine.
Dual-Energy X-ray Absorptiometry (DEXA) spine scan	Reduced bone mineral density with a Z-score of −1.8
DEXA Hip scan	Left hip results comprising an overall Z-score of −1.9 and an intertrochanteric score of −2.4, complementing the aforementioned lumbar spine measurements (Z −1.8)

obstructive-restrictive pulmonary disease (FEV1 23% predicted, FVC 42% predicted, DLCO 31% predicted), chronic Pseudomonas aeruginosa colonization, hepatobiliary involvement, and reduced bone mineral density at multiple skeletal sites — is considerably more severe than that reported for R1162X homozygotes, and instead parallels the severe phenotype described when R1162X is paired with a second pathogenic variant.

The mechanism underlying this severity in our patient may be related to the nature of second allele in our patient, ie c.3718-2477C>T, which is a deep intronic variant and may disturb normal mRNA splicing resulting in abnormal CFTR protein production, potentially contributing to the patient's severe clinical presentation. If this variant results in significantly reduced or absent functional CFTR transcript, it would be expected to behave as a severe loss-of-function allele in trans with R1162X, rather than the partially compensatory relationship that can occur when R1162X is paired with a mild, residual-function variant such as R347P [5]. This is consistent with the broader principle that R1162X functions as a severe loss-of-function allele whose ultimate phenotypic expression is recessive to, or dependent upon, the functional status of the paired allele. Functional splicing studies, such as minigene assays, would be required to confirm the precise molecular consequence of this intronic variant; in the absence of such data, this mechanistic explanation remains hypothetical.

The hepatic disease, chronic pansinusitis, and early skeletal involvement illustrates multisystem involvement in our patient. Further elaborating the extra pulmonary burden of clever CF genotype are the gallbladder wall thinking, biliary sludge, elevated ALT, AST, ALP and elevated bilirubin in our patient, the absence of Hepatitis B and C is consistent with CF-associated hepatobiliary disease, a well-known complication, resulting due to biliary duct obstruction by viscous secretions [7].

Notably, the diagnostic delay to age of 20 years old, despite having symptoms onset in the neonatal period shares similarities with a case of delayed CF diagnosis in a child from the Indian subcontinent with an initially gastrointestinal-predominant presentation [7] reinforcing that, the low clinical suspicion for CF outside its classically described Caucasian phenotype [4] remains a barrier to timely diagnosis in South Asian patients. Similarly, our patient's reduced bone mineral density at both the lumbar spine (Z-score −1.8) and left hip (Z-score −1.9, intertrochanteric −2.4) reflects the multifactorial etiology of CF-related bone disease, which includes malnutrition, pancreatic insufficiency, chronic inflammation, and vitamin D deficiency [8]. Given the patient's severe malnutrition(BMI 12.4 kg/m^2) and unassessed vitamin D status, these osteopenic changes are biologically plausible manifestations of CF-related bone disease occurring at an unusually young age, though a pre-existing lumbar spine MRI performed two years prior to CF diagnosis had attributed similar findings to Scheuermann disease, and the relative contribution of each process to this patient's skeletal phenotype cannot be firmly disentangled from the available data.

There are several limitations in this case. As a single case, it cannot establish a definitive genotype-phenotype correlation, and the pathogenicity of the intronic variant is inferred from its classification and reported the associations rather than confirmed through functional splicing studies in this patient. Several biochemical evaluations relevant to a complete etiological picture were not performed, including fecal elastase-1 (limiting formal biochemical grading of pancreatic insufficiency), gamma-glutamyl transferase, and 25-hydroxyvitamin D, the last of which is particularly relevant given the patient's osteopenia. The exact bilirubin value was not retrievable from available records. Segregation analysis was not possible, as the patient's brother, who also reported recurrent respiratory symptoms, has not undergone sweat chloride or genetic testing to date; such testing would help clarify whether he shares this genotype and could support future genetic counseling for the family.

Conclusion

We report to our knowledge, that the first described instance of compound heterozygosity for CFTR c.3718-2477C>T and c.3484C>T (p.Arg1162Ter) in a patient with cystic fibrosis. Despite the individually mild pulmonary phenotype reported for R1162X in homozygous state, our patient presented with severe multisystem disease, suggesting that the deep intronic variant may confer a more severe loss-of-function effect than previously characterized R1162X-associated genotypes. This case underscores the substantial genotypic heterogeneity of CF in the Indian population, the limitations of

relying on genotype-based severity predictions derived from single-mutation reports, and the continued need for comprehensive CFTR sequencing and heightened clinical suspicion for CF in Indian patients presenting with unexplained multisystem disease.

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