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Dual Genetic Etiologies in a Child Presenting with Acute Pancreatitis: Concurrent PRSS1 and SPTB Pathogenic Variants

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ABSTRACT

Hereditary pancreatitis is a rare genetic disorder most commonly associated with pathogenic PRSS1 variants, while hereditary spherocytosis is an inherited hemolytic anemia that may predispose to biliary pancreatitis through chronic hemolysis and pigment stone formation. We report a 13-year-old male who presented with acute pancreatitis. Initial findings suggested biliary pancreatitis secondary to hereditary spherocytosis. However, further evaluation with whole exome sequencing identified a likely pathogenic SPTB variant confirming hereditary spherocytosis and a pathogenic PRSS1 variant associated with hereditary pancreatitis. This case highlights the diagnostic challenge posed by the coexistence of two hereditary disorders capable of independently contributing to pancreatitis and underscores the value of genetic testing in pediatric patients with atypical or unexplained pancreatitis.

Keywords: Hereditary pancreatitis; PRSS1; Hereditary spherocytosis; SPTB; Dual molecular diagnosis; Pediatric pancreatitis.

INTRODUCTION

Acute pancreatitis is an uncommon but increasingly recognized condition in the pediatric population, with etiologies ranging from infections, trauma, and metabolic disorders to structural and genetic abnormalities. [1] Among the genetic causes, hereditary pancreatitis is a rare autosomal dominant disorder most commonly associated with pathogenic variants in the PRSS1 gene, which encodes cationic trypsinogen. [2] Gain-of-function mutations in PRSS1 promote premature intrapancreatic trypsin activation, predisposing affected individuals to recurrent episodes of acute pancreatitis and eventual progression to chronic pancreatitis. [2, 3] Early identification of hereditary pancreatitis is important because of its implications for long-term surveillance, recurrence risk, and genetic counseling. [3]

Hereditary spherocytosis (HS) is the most common inherited hemolytic anemia and results from defects in erythrocyte membrane proteins such as spectrin, ankyrin, band 3, and protein 4.2. Variants in the SPTB gene encoding β-spectrin are among the established causes of autosomal

dominant hereditary spherocytosis. [4] Chronic hemolysis in HS predisposes patients to pigment gallstone formation and biliary sludge, which may in turn contribute to the development of biliary pancreatitis. [5] Although pancreatitis secondary to gallstone disease is a recognized complication of HS, the coexistence of HS with a genetically confirmed predisposition to hereditary pancreatitis is exceedingly rare and poses a diagnostic challenge.

While hereditary pancreatitis and hereditary spherocytosis are individually well-described entities, the coexistence of pathogenic PRSS1 and SPTB variants in the same individual appears to be exceedingly uncommon. Both disorders may independently contribute to pancreatobiliary pathology, creating diagnostic uncertainty regarding the underlying etiology of pancreatitis. To the best of our knowledge, reports describing the coexistence of genetically confirmed PRSS1-associated hereditary pancreatitis and SPTB-associated hereditary spherocytosis in the same patient have not been previously reported in the available literature.

In the present case, we report a 13-year-old male with acute pancreatitis in whom whole exome sequencing revealed pathogenic variants in both PRSS1 and SPTB. The coexistence of these disorders created diagnostic uncertainty, as pancreatitis could be attributed either to hereditary pancreatitis or to hepatobiliary complications of hereditary spherocytosis

CASE PRESENTATION

A 13-year-old male presented with complaints of abdominal pain and vomiting for 5 days. The abdominal pain was of acute onset, localized to the epigastric region, continuous, severe in intensity, and aggravated by oral intake. Vomiting was non-bilious, non-blood stained, and occurred four to five times daily. The patient's mother also noted yellowish discoloration of the eyes of the patient for the past two days. Family history was significant for hereditary spherocytosis in the patient's elder brother, who had previously undergone cholecystectomy for gallstone disease. The patient's past medical and personal history were otherwise unremarkable.

On examination, the patient was thin-built and noted to have pallor and icterus. Vital signs revealed tachycardia (110 beats/min), while the respiratory rate, blood pressure and oxygen saturation were within normal limits. Abdominal examination revealed epigastric tenderness. Other systemic examinations were otherwise unremarkable.

The patient was admitted with a provisional diagnosis of acute pancreatitis of unknown etiology pending further evaluation. Laboratory investigations revealed marked leukocytosis, suggestive of an acute inflammatory response. Hematological evaluation demonstrated an elevated mean corpuscular hemoglobin concentration (MCHC), a characteristic finding associated with hereditary spherocytosis. Liver function tests showed hyperbilirubinemia with a predominantly indirect component, suggestive of ongoing hemolysis, along with elevated hepatic transaminases indicating associated hepatobiliary involvement. Serum amylase and lipase levels were markedly elevated, supporting the diagnosis of acute pancreatitis. Serum triglyceride levels were within normal limits, thereby excluding hypertriglyceridemia as a potential etiological factor. The laboratory findings are summarized in Table 1.

Infectious etiologies were evaluated and found to be negative, including scrub typhus serology, Widal test, HAV IgM, HEV IgM, HBsAg, and anti-HCV. Direct Coombs test was negative, thereby excluding autoimmune hemolytic anemia. In the setting of acute pancreatitis, the presence of indirect hyperbilirubinemia, elevated MCHC, and a positive family history raised suspicion of an underlying hemolytic disorder contributing to the clinical presentation, prompting further hematological and etiological evaluation. Ultrasonography of the abdomen demonstrated a distended gall bladder

containing biliary sludge without evidence of gallstones, while the common bile duct appeared normal. Contrast-enhanced CT of the abdomen revealed mild diffuse enlargement of the pancreas with minimal peripancreatic and subhepatic free fluid collections, findings consistent with acute interstitial pancreatitis. No pancreatic calcifications, intraductal calculi, pancreatic necrosis, vascular complications, or other local complications were identified (Figure 1).

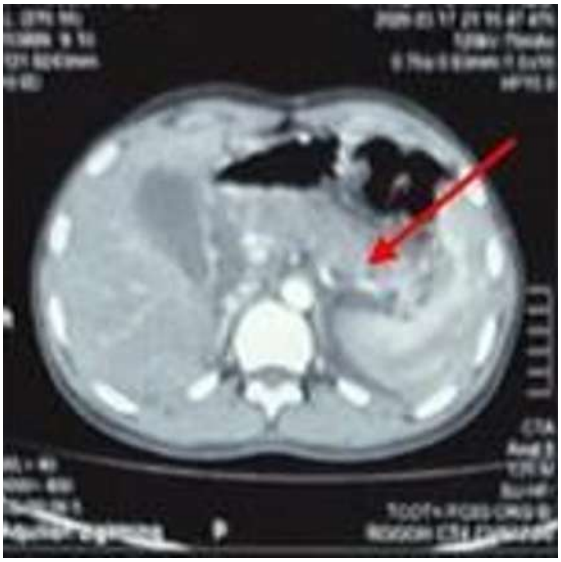

Figure 1: Contrast-enhanced CT abdomen showing mild diffuse enlargement of the pancreas (arrow) with adjacent peripancreatic inflammatory changes, consistent with acute interstitial pancreatitis.

Osmotic fragility testing was positive, supporting the diagnosis of hereditary spherocytosis. Peripheral smear examination demonstrated a normocytic normochromic blood picture with spherocytes and neutrophilic leukocytosis. Taken together, the clinical, biochemical, hematological, and radiological findings suggested biliary pancreatitis occurring in the setting of hereditary spherocytosis.

Given the clinical suspicion of biliary pancreatitis in the setting of hereditary spherocytosis, magnetic resonance cholangiopancreatography (MRCP) was performed. It demonstrated mild enlargement of the pancreatic head and body with minimal peripancreatic fat stranding, consistent with acute pancreatitis. Mild hepatomegaly and moderate splenomegaly were also noted. Although the common hepatic duct and common bile duct appeared prominent (Figure 2), no choledocholithiasis, biliary stricture, pancreatic ductal abnormality, or mass lesion was identified. These findings failed to demonstrate a definitive obstructive biliary etiology for the pancreatitis despite the presence of biliary sludge on prior ultrasonography.

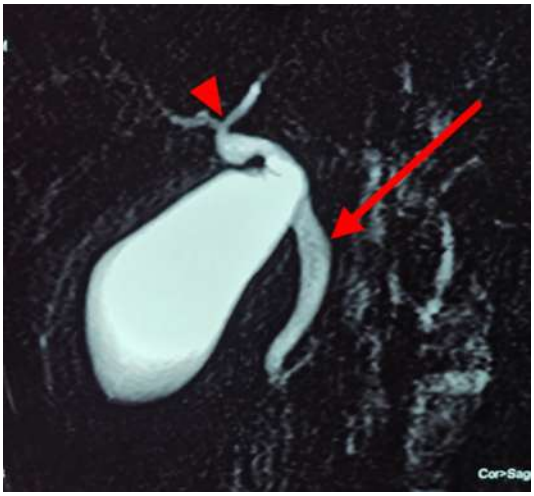

Figure 2: Magnetic resonance cholangiopancreatography demonstrating prominence of the common hepatic duct (arrowhead) and common bile duct (arrow) without evidence of choledocholithiasis or biliary stricture.

Upper gastrointestinal endoscopy was subsequently performed in view of persistent upper gastrointestinal symptoms and revealed Los Angeles Grade D reflux esophagitis with pangastritis. The stomach contained significant bile-stained contents and showed diffuse erythematous mucosa. These findings were managed conservatively and were not considered sufficient to account for the patient's pancreatitis.

At this juncture, given the patient's young age, the absence of a definitive obstructive pancreatobiliary lesion on MRCP, and the coexistence of hereditary spherocytosis with acute pancreatitis, whole exome sequencing (WES) was performed for further etiological evaluation. WES identified a heterozygous

likely pathogenic splice-site variant in the SPTB gene [c.1183-1G>A], consistent with autosomal dominant hereditary spherocytosis (type 2) (Table 2). In addition, a heterozygous pathogenic missense variant in the PRSS1 gene [c.86A>T; p. Asn29Ile] was detected, a well-established mutation associated with autosomal dominant hereditary pancreatitis. These genetic findings provided molecular confirmation of hereditary spherocytosis while simultaneously establishing a genetic predisposition to pancreatitis, thereby redefining the clinical picture from presumed biliary pancreatitis secondary to hereditary spherocytosis to hereditary pancreatitis occurring in a patient with concurrent hereditary spherocytosis.

Table 1 – Routine investigatory findings

Parameter	Admission	Day 9	Reference Range
Hemoglobin (g/dL)	14.8	10.9	12.0–16.0
Total Leukocyte Count (/µL)	29,700	6,400	4,000–11,000
MCHC (g/dL)	36.5	35.7	32–36
Total bilirubin (mg/dL)	18.4	4.6	0.2–1.2
Direct bilirubin (mg/dL)	5.3	1.4	0–0.3
AST (U/L)	213	29	10–40
ALT (U/L)	190	40	7–56
ALP (U/L)	290	270	100–390
Serum amylase (U/L)	693	145	30–110
Serum lipase (U/L)	1873	195	13–60
Triglycerides (mg/dL)	75	72	<150

Reference ranges may vary according to age, sex, and laboratory methodology. Pediatric reference ranges were considered where applicable.

Table 2 – Whole exome sequencing findings

Gene	Variant	Zygosity	Classification	Phenotype	Inheritance
SPTB	c.1183-1G>A	Heterozygous	Likely pathogenic	Hereditary spherocytosis type 2	Autosomal dominant
PRSS1	c.86A>T (p. Asn29Ile)	Heterozygous	Pathogenic	Hereditary pancreatitis	Autosomal dominant

The patient was managed conservatively with bowel rest, intravenous fluids, and supportive care. Medical management included intravenous antibiotics, analgesics, antiemetics, proton pump inhibitors. Surgical gastroenterology opinion was obtained, and interval cholecystectomy with splenectomy was advised following stabilization. Serial laboratory evaluation (Table 1) demonstrated improvement in inflammatory markers, liver function tests, and pancreatic enzymes, although hemoglobin levels declined during hospitalization, likely reflecting the underlying hemolytic process. The patient showed gradual symptomatic improvement with reduction in abdominal pain and vomiting and was discharged in stable condition with advice for regular follow-up and definitive surgical management. Table 3 summarizes the diagnostic workup of the case.

Table 3 – Diagnostic workup

Investigation	Finding
Peripheral smear	Normocytic normochromic blood picture with spherocytes and neutrophilic leukocytosis
Osmotic fragility test	Positive
Direct Coombs test	Negative
CT abdomen	Mild diffuse pancreatic enlargement with minimal peripancreatic and subhepatic free fluid collections, consistent with acute interstitial pancreatitis; no pancreatic necrosis, calculi, vascular complications, or ductal abnormalities

Upper gastrointestinal endoscopy	Los Angeles Grade D reflux esophagitis with pangastritis; bile-stained gastric contents and diffuse erythematous gastric mucosa
MRCP	Mild hepatomegaly, moderate splenomegaly, and prominence of the common hepatic and common bile ducts; no choledocholithiasis, biliary stricture, pancreatic ductal abnormality, or mass lesion
Whole exome sequencing (WES)	Heterozygous likely pathogenic *SPTB* c.1183-1G>A variant and heterozygous pathogenic *PRSS1* c.86A>T (p. Asn29Ile) variant

DISCUSSION

Acute pancreatitis in children is a heterogeneous condition with etiologies that differ substantially from those encountered in adults. While biliary tract disease, trauma, infections, medications, metabolic abnormalities, and structural anomalies remain important causes, genetic factors account for a significant proportion of pediatric pancreatitis, particularly in recurrent, idiopathic, or early-onset cases. [1] Hereditary pancreatitis is a rare autosomal dominant disorder most commonly associated with pathogenic variants in the PRSS1 gene, which encodes cationic trypsinogen. [2, 3] Mutations in PRSS1 disrupt the tightly regulated process of trypsinogen activation, resulting in premature intrapancreatic trypsin activity and subsequent pancreatic autodigestion. [6] This mechanism predisposes affected individuals to recurrent episodes of acute pancreatitis beginning in childhood and may ultimately progress to chronic pancreatitis with exocrine and endocrine insufficiency. [3, 6, 8]

The present case was diagnostically challenging because the patient initially possessed several features strongly suggestive of biliary pancreatitis secondary to hereditary spherocytosis. He presented with hyperbilirubinemia, elevated MCHC, a positive osmotic fragility test, a family history of hereditary spherocytosis, and biliary sludge on ultrasonography. Collectively, these findings appeared to provide a plausible explanation for the development of pancreatitis. Chronic hemolysis in hereditary spherocytosis results in excessive bilirubin production, predisposing affected individuals to pigment stone formation and biliary sludge. [4,5] These hepatobiliary complications may subsequently lead to biliary obstruction, cholangitis, or acute pancreatitis. [9-12] Indeed, pancreatitis secondary to gallstones or biliary obstruction has been previously reported in patients with hereditary spherocytosis and is a recognized complication of long-standing hemolytic disease. [10-12]

Hereditary spherocytosis is most commonly caused by defects in erythrocyte membrane proteins including spectrin, ankyrin, band 3, and protein 4.2. [4] Variants in the SPTB gene, which encodes β-spectrin, impair membrane stability and deformability, resulting in premature splenic sequestration and destruction of erythrocytes. [13, 14] The resultant chronic hemolysis manifests clinically as anemia, jaundice, splenomegaly, and an increased risk of pigment gallstone formation. [4,5] In the present patient, the diagnosis of hereditary spherocytosis was supported by characteristic hematological findings, a positive osmotic fragility test, the presence of spherocytes on peripheral smear examination, and subsequent identification of a likely pathogenic SPTB variant on whole exome sequencing.

Despite the compelling evidence supporting a biliary etiology, certain aspects of the patient's clinical course remained difficult to reconcile with a purely obstructive mechanism. Although ultrasonography demonstrated biliary sludge, MRCP failed to identify choledocholithiasis, biliary strictures, pancreatic ductal abnormalities, or other structural causes capable of definitively explaining the pancreatitis. Furthermore, contrast-enhanced CT findings were consistent with acute interstitial pancreatitis without evidence of gallstone-related complications or persistent biliary obstruction. These findings introduced

diagnostic uncertainty and prompted consideration of an alternative underlying predisposition.

Although biliary sludge likely contributed to the patient's presentation, the identification of a pathogenic PRSS1 variant suggests that the threshold for pancreatic injury may have been lowered by an underlying genetic susceptibility. Consequently, pancreatitis in this patient may have resulted from the interplay between biliary factors related to hereditary spherocytosis and an intrinsic genetic predisposition to pancreatic inflammation.

Whole exome sequencing subsequently identified a heterozygous pathogenic PRSS1 variant, c.86A>T (p. Asn29Ile), confirming hereditary pancreatitis. The p. Asn29Ile (N29I) mutation is among the most extensively studied disease-causing PRSS1 variants and has been consistently associated with hereditary pancreatitis across multiple populations. [6, 7] Functional studies have demonstrated that this variant promotes inappropriate intrapancreatic trypsin activity through gain-of-function mechanisms, thereby increasing susceptibility to pancreatic inflammation and recurrent pancreatitis. [6] The identification of this mutation substantially altered the interpretation of the case. Rather than representing a straightforward example of biliary pancreatitis secondary to hereditary spherocytosis, the patient was found to harbor an independent genetic predisposition capable of causing pancreatitis in its own right.

The coexistence of hereditary spherocytosis and hereditary pancreatitis is particularly noteworthy because both conditions may independently contribute to pancreatobiliary pathology through entirely different mechanisms. In hereditary spherocytosis, pancreatic injury occurs indirectly through chronic hemolysis, hyperbilirubinemia, biliary sludge formation, and pigment gallstones. [4, 5, 11] In contrast, PRSS1-associated hereditary pancreatitis results from intrinsic dysregulation of pancreatic enzyme activation within the pancreas itself. [2, 6] Consequently, both disorders converge upon the same clinical endpoint of acute pancreatitis, despite fundamentally distinct pathogenetic pathways. This overlap creates considerable difficulty in determining the relative contribution of each disorder to an individual episode of pancreatitis.

A review of the available literature identified reports describing pancreatitis secondary to hereditary spherocytosis and biliary obstruction; however, reports documenting the coexistence of genetically confirmed SPTB-associated hereditary spherocytosis and PRSS1-associated hereditary pancreatitis appear to be exceedingly rare. Previously reported cases have largely attributed pancreatic inflammation to gallstones, biliary obstruction, or cholestatic complications of hemolytic disease. [10-12] In contrast, our patient possessed an additional molecularly confirmed predisposition to pancreatitis. The present case therefore expands the spectrum of pancreatobiliary manifestations associated with hereditary spherocytosis and highlights the potential for concurrent hereditary disorders to obscure etiological attribution.

This case also underscores the growing importance of genetic testing in the evaluation of pediatric pancreatitis. Current evidence supports genetic evaluation in children presenting with unexplained, recurrent, or atypical pancreatitis, particularly when conventional investigations fail to establish a definitive etiology. [1, 15] Whole exome sequencing proved instrumental in the present case by revealing a dual molecular diagnosis that would not have been apparent through routine clinical, laboratory, and radiological investigations alone. Beyond establishing the diagnosis, identification of a pathogenic PRSS1 variant carries important implications for long-term surveillance, recurrence risk assessment, family screening, and genetic counseling. [3, 7, 15]

In conclusion, this case illustrates the diagnostic complexity that may arise when

two independent hereditary disorders converge on a common clinical presentation. Although hereditary spherocytosis initially appeared to provide a sufficient explanation for the patient's pancreatitis through hemolysis-associated biliary pathology, whole exome sequencing revealed a concurrent pathogenic PRSS1 variant, establishing an additional and independent genetic predisposition to pancreatic disease. Whether the index episode was predominantly driven by biliary pathology, PRSS1-associated susceptibility, or a combination of both mechanisms cannot be determined with certainty. Nevertheless, this case highlights the importance of recognition of such dual molecular diagnoses for accurate etiological classification, appropriate counseling, and long-term management of pediatric patients presenting with pancreatitis.

CONCLUSION

This case describes a rare coexistence of SPTB-associated hereditary spherocytosis and PRSS1-associated hereditary pancreatitis in a 13-year-old male presenting with acute pancreatitis. While the presence of chronic hemolysis, hyperbilirubinemia, and biliary sludge initially suggested biliary pancreatitis secondary to hereditary spherocytosis, subsequent genetic evaluation revealed an independent hereditary predisposition to pancreatic disease.

The case highlights the importance of considering genetic etiologies in pediatric pancreatitis, particularly when conventional explanations do not fully account for the clinical presentation. Comprehensive genetic testing can play a crucial role in resolving diagnostic uncertainty, guiding long-term management, and facilitating appropriate family counseling.

Declaration by Authors

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