Original Research Paper

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General Medicine

SPINK 1 MUTATION IN IDIOPATHIC RECURRENT PANCREATITIS

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ABSTRACT Hereditary chronic pancreatitis associated with a mutation in the serine protease inhibitor, Kazal Type-1 (SPINK-1 gene) is extremely rare. The SPINK1 mutation results in trypsinogen activation which predisposes to chronic pancreatitis predominately when combined with CFTR gene mutations. It presents as either chronic or recurrent acute pancreatitis. Symptom control and management of complications is important. Active surveillance with cross-sectional imaging for pancreatic malignancy in individuals with hereditary pancreatitis is advocated due to individuals being high risk. Here we present a case of recurrent acute pancreatitis in a 26-year-old male.

KEYWORDS : Hereditary pancreatitis, SPINK1 mutation, atypical presentation, hypofibrinogenemia

INTRODUCTION

Mutation in the serine protease inhibitor, Kazal type-1 (SPINK1 gene) increases the chance of an individual developing chronic pancreatitis 12-fold [1]. Inheritance is autosomal recessive due to the need for mutations in both copies of the SPINK1 gene, thus one mutant copy is inherited from each parent who are unaffected carriers. Mutations in the SPINK1 gene lead to premature trypsinogen activation and resultant pancreatitis [2-4]. SPINK mutation associated pancreatitis is extremely rare, with under 1% of carriers proceeding to develop pancreatitis [5]. Other commonly identified genes whose mutations are associated with chronic pancreatitis include the cationic trypsinogen gene (PRSS1) and Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR), with the later gene being the most common genetic variant to co-exist with SPINK1 mutations [2, 3].

Case Presentation

A 26 year old male was admitted to tertiary care center in solapur with complaints of abdominal distention, breathlessness and loss of appetite. An initial evaluation revealed severe anemia and deranged coagulation profile. Diagnosis of chronic liver disease was made.

Patient was born of nornal vaginal delivery with increase bleeding from umbilical cord at the time of birth. At 18 month of age patient presented with prolong bleeding from lips and Hematoma on lateral aspect of thigh (vaccine injection site). On evaluation Coagulation studies- Platelet count was 250000/mm^2 , Bleeding time was >20 min, Clotting time was >20 min (blood did not clot even after 4 hrs), Adhesion Test was Positive, Prothrombin time was 180+ sec (control-18 sec), Partial Thromboplastin Time with Kaolin(PTTK) was 200+ sec (control- 38 sec),(PTTK correction- ½ patient plasma + ½ control plasma-30 sec, ½ patient plasma + ½ aged serum – 180 sec, ½ patient plasma+ ½ adsorbed plasma – 46 sec), Factor Inhibitor were Absent, Thrombin test was 180+ sec (control- 16 sec), Fibrinogen was 40 mg%%(Normal 150-450 mg%). Diagnosis of Factor I (Fibrinogen) Deficiency was made. 6 cryoprecipitates were transfused. Patient was treated with ayurvedic medications for next 1 and ½ years.

At age of 13 years, patient was admitted with complaints of abdominal pain with c vomiting. On evaluation serum amylase was 21 IU/L, serum lipase was 4648 U/Lf. Abdominal ultrasound showed bulky pancreas with increased echogenicity and locculated margins, which was suggestie of acute pancreatitis. Moderate ascites was also detected. Patient was diagnosed with Acute Pancreatitis and treated conservatively.

In the last 1 and 1/2 years, patient has been admitted three more times, each time with similar complaints. On present admission, patient had abdominal distention with respiratory distress and loss of appetite. On examination he also had severe pallor. On investigation

Investigations	Results
Haemoglobin	5.5 gm/dl
Total count of WBC	11000/mm2
Platelet count	127000/mm2
Creatinine	1.3 mg/dl
ALT (SGPT)	69 U/L
S. Lipase	3263 U/L
S. Amyalse	56 U/l
S. Calcium	09.2 mg/dl
S. Alkaline Phosphatase	183 U/L
S. Parathyroid Hormone (PTH)	50.2 pg/dl
S. Magnesium	1.5mg/dl
S. Inorganic Phosphate	2.5mg/dl
Prothrombin Time	23 sec
Activated Partial Thromboplastin Time	>1 min

Contrast enhanced triple phase abdominal CT revealed liver cirrhosis with regenerative nodules; portal vein cavernoma with dilated porto-caval tributaries; severe pancreatic atrophy with pancreatic parenchymal calcification; bulky spleen with calcification in anterero-inferior part of spleenic parenchyma. Large right renal calculus in renal pelvis causing mild obstructive uropathy in right kidney with cortical scarring was also seen along wiith moderate ascites.

Genetic testing was done

Gene & Transcript	Location	Variant	Zygosity/ Inheritance	OMIM Phenotype
FGB(+) NM_005141.5	Exon 8	c.1391G>A (p.Gly464Asp)	Homozygous /Autosomal Recessive	Hypofibrinogenemia, congenital
SPINK1(-) NM_003122.5	Exon 4	c.101A>G (p.Asn34Ser)	Heterozygous /Autosomal Dominant	Pancreatitis, hereditary

DISCUSSION

Hereditary pancreatitis is a rare cause of chronic pancreatitis, with mutations in PRSS1, SPINK1, and CFTR genes being the most common genetic causes. Hereditary pancreatitis significantly increases the risk of pancreatic malignancy [2-5]. While up to 2% of the *general population* carry SPINK1 mutations, the actual number of individuals with SPINK1 associated pancreatitis is extremely rare, with less than 1% of carriers going on to developing pancreatitis [6]. Despite this, carrying the SPINK1 mutation increases an individual's risk of developing chronic pancreatitis 12-fold. The prevalence of SPINK1 mutations in *patients* with idiopathic chronic pancreatitis has been reported as between 16-23%, with a case series reporting that SPINK1 mutations were 16.9% more common in patients with chronic and recurrent acute pancreatitis than controls [1, 5, 7].

The most common variant of the SPINK1 mutation is the N34S variant. However, there are also reports of another variant called the NM_003122.5 variant, SPINK1 encodes a pancreatitis secretory trypsin inhibitor which is released by pancreatic acinar cells when there is inflammation. Mutation in the SPINK1 gene leads to trypsin being uninhibited which increases the risk of pancreatitis [9]. Most patients have heterozygous SPINK1 mutations leading to complex inheritance patterns, although SPINK1 variants have also been associated with autosomal recessive familiar pancreatitis, alcoholic pancreatitis and tropical pancreatitis [10]. Clinically, hereditary pancreatitis presents as either chronic pancreatitis or recurrent acute pancreatitis and normally presents before the age of 20. It classically presents with epigastric abdominal pain radiating to the back, steatorrhea secondary to malabsorption and pancreatic diabetes due to islet cell damage [11]. The diagnosis of hereditary pancreatitis is based on a combination of factors including genetic testing, history, physical examination, laboratory results and radiographic imaging [4]. Treatment of hereditary pancreatitis is the same as the management of other causes of chronic pancreatitis and primarily involves administration of analgesia, pancreatic enzymes, fat-soluble vitamins, sometimes insulin and avoidance of alcohol and tobacco, as well as a

low-fat diet. In severe cases, pancreatectomy with islet cell transplantation can be considered [12-14]. Lifetime risk of developing pancreatic cancer in hereditary chronic pancreatitis is approximately 40%. Screening with EUS or MRCP is recommended in hereditary chronic pancreatitis, however, exact interval is undefined due to its cost effectiveness and sensitivity of these tests [15].

CONCLUSION

Our case of SPINK mutation associated pancreatitis is extremely rare. This case is made even more unique by the atypical presentation of the severe chronic pancreatitis, and associated hypofibrinogenemia. This case highlights the importance that clinicians should have a high index of suspicion that hereditary pancreatitis may be the underlying cause of chronic pancreatitis in younger patients. It is vital that patients who test positive for hereditary pancreatitis, including the SPINK1 mutation undergo active surveillance for pancreatic malignancy due to them being in a high-risk group. This will allow early treatment and ensure the best prognosis in these rare cases of hereditary pancreatitis.
The corelation between the two genetic defect is yet to be studied.

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