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**Case Report**

# Hereditary stomatocytosis vs elliptocytosis presenting recurrent pancreatitis

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## ABSTRACT

Hereditary stomatocytosis is a rare autosomal dominant genetic disorder due to an abnormality of red cell permeability to monovalent cations resulting in alteration in water content of red cells. Hereditary elliptocytosis is autosomal dominant disorder caused by inherited mutations in genes encoding red cell membrane. Patient may show up with symptoms of varying severity. We present a case of 35-year-old male with recurrent episodes of abdominal pain, yellowish discolouration of eyes and skin, nausea and vomiting since 2015. He was treated symptomatically earlier but cause was still obscured. Patient underwent liver biopsy and multiple blood examinations but etiology was still not determined. In 2024 patient was again diagnosed with acute pancreatitis and acute kidney injury, evaluated for hyperbilirubinemia and MRCP was suggestive of cholelithiasis without cholecystitis. With a suspicion of hemolytic anemia, peripheral smear of the patient was done which revealed stomatocytosis vs elliptocytosis. Meanwhile Patient was stabilized and referred for genetic testing.

**Keywords:** Acute pancreatitis, Cholelithiasis without cholecystitis, Hemolytic anemia, Hyperbilirubinemia, Stomatocytosis and elliptocytosis.

## INTRODUCTION

Hereditary spherocytosis is the most common congenital haemolytic anaemia seen in caucasians, with an estimated prevalence ranging from 1:2,000 to 1:5,000. Hereditary elliptocytosis is an autosomal dominant disorder, with presence of elliptically shaped red cells on peripheral blood smear, more common in malaria endemic regions in West Africa (prevalence 2%).[1] There is no direct correlation between elliptocytic morphology and clinical severity. We present a case with patient presenting with recurrent pancreatitis and diagnosed with cholelithiasis without cholecystitis secondary to hemolytic anemia.

## CASE REPORT

A 35-year-old male patient came in April, 2024 with complaints of severe abdominal pain, yellowish discolouration of skin, eyes, and urine and nausea and vomiting since, 10 days. On probing, gave history of blood transfusion in 2008 and repeated similar symptoms since 2015 and was evaluated with pancreatitis at every admission at various hospitals in Maharashtra but etiology was not known. Patient had no other comorbidities and no addictions. In 2018, patient was referred to Government hospital in Mumbai due to similar complaints; his blood reports revealed hemoglobin 12.9, MCV 84, WBC 17000, total bilirubin 7.5, indirect bilirubin 6.3, SGOT 235, SGPT 47, ALP 241, KFT WNL, lipase 15771, INR 1.1, HHH neg, Hb electrophoresis normal, serum ceruloplasmin 35, IgG (total) 1190, ANTI LKM 1, ASMA, ANA negative, KF ring negative, DCT/ICT negative and; retic count 2%. CECT revealed acute interstitial pancreatitis with mild left pleural effusion and ascites and mild splenomegaly; selective hepatobiliary scan revealed no abnormality but patient underwent a liver biopsy which revealed mild intrahepatic cholestasis with normal liver histology.

In April 2024, patient had similar complaints and thus was admitted in GMCH Aurangabad, on examination patient was conscious, apprehensive, restless, oriented, febrile vitals–BP 110/70 mmHg, RR 22/min, pulse 107/min, temperature 101-degree Fahrenheit, icterus ++, grade 3 spleenomegaly, liver span 20cm. When investigated MRCP revealed acute pancreatitis with peripancreatic fat stranding and mild peripancreatic fluid, cholelithiasis without cholecystitis, hepatosplenomegaly-spleen 16.7, liver 19 cm. Blood investigations revealed Hb 10.8, MCV 82, TLC 14600, total bilirubin – 32, indirect bilirubin 23, SGOT 150, SGPT 100, amylase 1141, lipase 1069, urine for free Hb negative, iron studies- iron 247, ferritin 594, TIBC 234, transferrin 159, DCT/ICT negative, retic count 10%, LDH 1180, creatinine- 6.8, urea 110, urine output 250 ml/24 hours. Patient was started on optimum treatment and was initiated for Hemodialysis to treat acute kidney injury. His family history revealed his brother has similar complaints since, 2 years but was never evaluated. On examination, his brother also had grade-3 spleenomegaly. His mother died at early age, but father was absolutely normal.

Due to indirect hyperbilirubinemia and family history, we suspected RBC membrane defects or enzyme defects with autosomal dominant inheritance; Upon investigating the peripheral smear, detected RBC: anisopoikilocytosis ++, elliptocytes ++, polychromasia, few stomatocytes+, WBC no abnormal cells, Platelet adequate; which prompted us to consider hereditary membrane defects disorders as the diagnosis. Meanwhile patient was shifted to MICU in view of metabolic encephalopathy and started on higher antibiotics and continued hemodialysis.

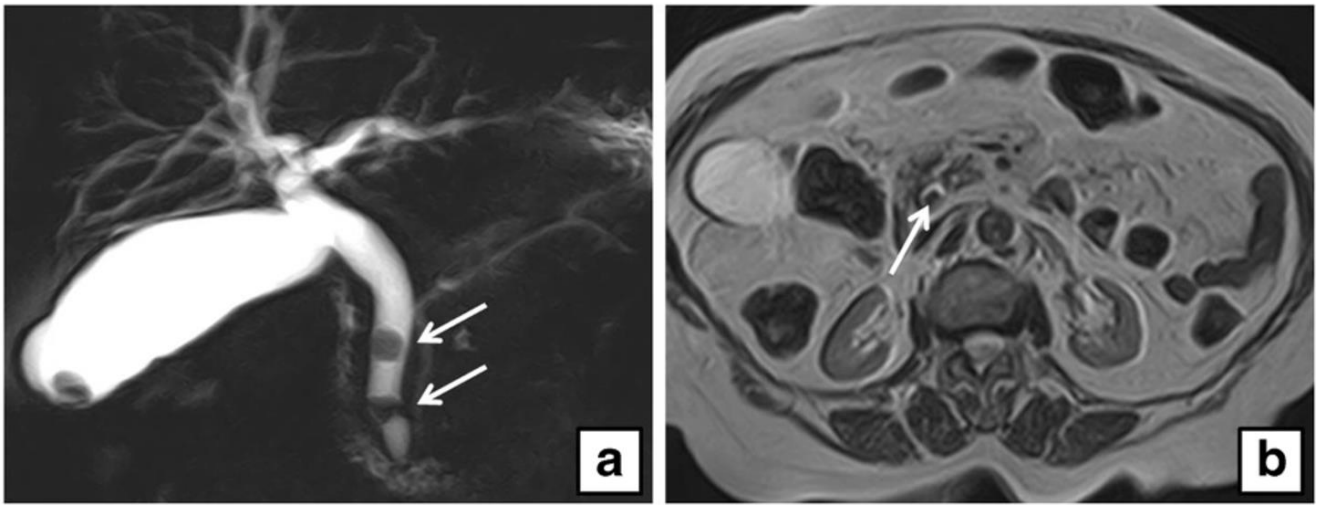


**Figure 1 (a and b): MRCP.**

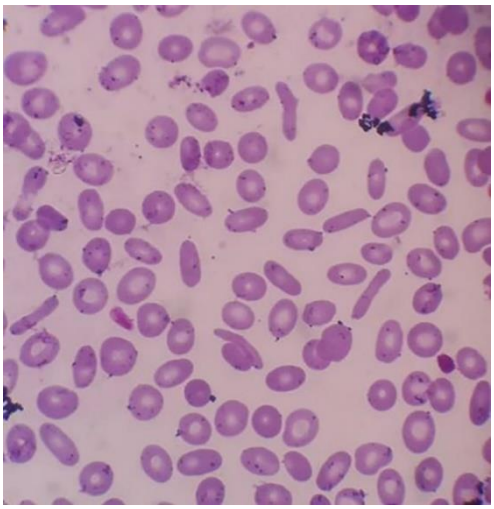

**Figure 2: Peripheral smear.**

After 20 days patient was stabilised and referred for further genetic studies. Patient underwent red cell enzyme and membrane study suggested red cell enzymes like pyruvate kinase, G6PD, glucose phosphate isomerase are within normal limits, but flow cytometric analysis using Eosin 5 maleimide revealed result of 58967.15 MCF that is decreased (normal 65000 to 95000 MCF) which suggests presence of red cell membrane protein defect.

**Table 1: Investigation chart.**

| Test | Result |
|---|---|
| **Hb** | 10.8 |
| **MCV** | 82 |
| **Platelets** | 4 LAC |
| **RBC count** | 4.58 * 10^6 |
| **TLC** | 14600 |
| **Coomb** | neg |
| **Sickling** | neg |
| **Retic count** | 10% |
| **Bilirubin T** | 32 |
| **Bilirubin D** | 9 |
| **Bilirubin I** | 23 |
| **Sgot** | 150 |
| **SGPT** | 100 |
| **GGT** | 608 |
| **INR** | 1.1 |
| **Triglyceride** | 132 |
| **Bile acids** | 2.54 |
| **Albumin** | 4.69 |
| **Serum glucose** | 108 |
| **HHH** | neg |
| **Syphilis (VDRL)** | neg |
| **Amylase** | 1141 |
| **Lipase** | 1069 |
| **LDH** | 1180 |
| **ALP** | 194 |
| **BUN** | 20 |
| **Creatinine** | 6.8 |
| **Urea** | 110 |
| **Electrophoresis** | normal |
| **Ceruloplasmin** | 35 |
| **IgG total** | 1190 |
| **Anti LKM 1** | neg |
| **ASMA** | neg |
| **ANA** | neg |
| **KF ring** | neg |
| **Iron** | 247.9 |
| **Ferritin** | 594.7 |
| **TIBC** | 234.1 |
| **Transferrin** | 159.25 |

## DISCUSSION

As the patient had recurrent episodes of pancreatitis and MRCP revealed cholelithiasis without cholecystitis, it was certain that pancreatitis was secondary to cholelithiasis. Also, as patient had indirect bilirubin raised more than direct bilirubin along with raised LDH levels, decreased serum haptoglobin and his brother having similar complaints accompanied with spleenomegaly on examination, it was evident that gallstones are secondary to hemolysis. Hence peripheral smear was produced which revealed anisopoikilocytosis++, elliptocytes++, polychromasia, few stomatocytes+, WBC no abnormal cells, Platelet adequate, DCT/ICT negative pointing towards the diagnosis of hereditary membrane defects disorders. Hereditary stomatocytosis (HSt) consists of a group of hemolytic anemias where the red cells leak monovalent cations and there is a residual permeability of the red cell membrane to cations. The condition, which is extremely rare, was first described in 1961.[2] The disease has two forms, first being dehydrated form where MCV and MCHC both are on higher side with PIEZ01 or KCNN4 mutation and other being overhydrated form showing macrocytic picture as well but MCHC is decreased with RhAg, BAND3, GLUT 1 mutation.[3] Hereditary Elliptocytosis is dominantly inherited mutations in genes encoding red cell membrane proteins, α-spectrin, β-spectrin, and protein 4.1 result in hemolytic anemia. Two variants associated with elliptocytosis first South East Asian ovalocytosis where in frame deletion of 9 amino acid (SLCA41 gene) of band 3 seen and second hereditary pyropoikilocytosis where biallelic mutation of any one gene is seen.[4,5] Decreased membrane mechanical stability leads to cell fragmentation during the circulatory life span, with resultant increases in cell sphericity, which promotes splenic sequestration of the fragmented red cells. Clinical features of elliptocytosis includes hemolysis with infection, hypersplenism or vitamin B12 deficiency, gallstones, jaundice, aplastic crisis, extramedullary hematopoesis and hemochromatosis.[6] Diagnostic approach includes complete blood count, peripheral smear, reticulocytosis, raised serum LDH, and decreased haptoglobin levels. Testing for hemolysis should be carried out. A sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) for quantitation of protein 4.1 and spectrin analysis can be done. Osmotic gradient ektacytometry may be helpful and typically shows a decreased maximum of deformability.[7] The amount of spectrin and ankyrin is best assessed by RIA or EIA. Automated capillary gel electrophoresis system can be used to separate and quantify the erythrocyte membrane proteins and obviously genetic testing need to be done.[6] Treatment includes supportive and splenectomy in case of elliptocytosis. Spleen which is a site for RBC to be phagocytosed can cause thrombosis due to altered endothelial adherence due to membrane phospholipid asymmetry which makes them sticky and hence splenectomy is contraindicated in stomatocytosis as it may cause thromboembolic events.[8]

## CONCLUSION

Patients presenting with indirect hyperbilirubinemia, gallstones, pancreatitis, should be evaluated for hemolytic anemia as one of the differentials and a simple investigation like peripheral smear with a family history can provide a lead to the diagnosis for such a hereditary disease. Prognosis and outcome need to be explained to the patient and relatives.

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