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Multiple Causes Leading to Massive Splenomegaly in an Elderly Female

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ABSTRACT

Splenomegaly is defined as enlargement of the spleen measured by size or weight. The spleen is an essential site for hematopoiesis and immunosurveillance. Splenomegaly may be diagnosed clinically or radiographically using ultrasound, CT imaging or MRI. Splenomegaly may be a transient condition or may be due to serious underlying acute or chronic condition. A combination of clinical examination, serology and imaging may diagnose splenomegaly and the underlying cause. Derangement in the complete blood (cell) counts and morphology including WBC, RBC and platelets will vary based on underlying disease. Abnormalities in liver function tests, lipase, rheumatologic panels and disease-specific infectious testing help in ascertaining the cause of splenomegaly. We present here a rare case of massive splenomegaly which had multiple causes within the same patient contributing to a massive spleen and a diagnostic enigma.

Keywords: Splenomegaly, autoimmune hepatitis, autoimmune hemolytic anemia

Splenomegaly is the enlargement of the spleen as measured by size or weight. The spleen is an essential site for hematopoiesis and immunosurveillance. The major functions performed by the spleen include clearance of abnormal erythrocytes, removal of microorganisms and antigens as well as the synthesis of immunoglobulin G (IgG). Apart from that, one-third of circulating platelets are stored in the spleen. Spleen usually measures up to 11 cm in craniocaudal length. Splenomegaly may be diagnosed clinically or radiographically using ultrasound, computed tomography (CT) imaging or magnetic resonance imaging (MRI). Splenomegaly may be a transient condition or may be due to serious underlying acute or chronic condition.

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A combination of clinical examination, serology and imaging may diagnose splenomegaly and the underlying cause. Derangement in the complete blood (cell) counts and morphology including white blood cell (WBC), red blood cell (RBC) and platelets will vary based on underlying disease. Abnormalities in liver function tests, lipase, rheumatologic panels and disease-specific infectious testing help in ascertaining the cause of splenomegaly.

Imaging is useful in deciphering the underlying cause of splenomegaly. The spleen has a similar attenuation as the liver when measured on CT scan. Ultrasound is a useful imaging modality in measuring the spleen and spares the patient radiation from CT imaging. MRI, positron emission tomography (PET) scans, liver-spleen colloid scanning and splenectomy and splenic biopsy may be indicated in certain cases.

We present here a rare case of massive splenomegaly which had multiple causes of splenomegaly within the same patient, contributing to a massive spleen and a diagnostic enigma.

CASE SUMMARY

A 60-year-old female presented with fatigue for 6 months, dragging sensation in abdomen for 2 months and melena for 2 days. There was no history of shortness of breath, palpitation, high grade fever, rashes over the body, epigastric discomfort or hematemesis.

There was no previous evidence of trauma to abdomen, pain abdomen, diarrhea, hematochezia and constipation. There was a past history of yellowish discoloration of eyes 2 years back. On general examination, pulse rate was 92/min, blood pressure was 112/76 mmHg, severe pallor was present, icterus was absent; there was no lymphadenopathy or rashes. Jugular venous pressure (JVP) was not raised and there was no pedal edema.

Abdomen was soft and nontender. There was no fluid thrill or shifting dullness. Liver span was 11 cm. There was massive splenomegaly, 10 cm below the costal margin. The other systems were within normal limits.

The hemoglobin was 4.7 g%, total leukocyte count (TLC) was 4,400/mm^3, differential leukocyte count (DLC) was $P_{79}L_{19}E_{01}$, mean corpuscular volume (MCV) was 76.3 fl and platelet count was 64,000/μL. Blood urea was 22 mg/dL, serum creatinine was 0.79 mg/dL, blood sugar was 136 mg/dL. Serum aspartate aminotransferase (AST) was 17 IU/L, serum alanine aminotransferase (ALT) was 20 IU/L, total bilirubin was 4.5 mg/dL, direct bilirubin was 0.8 mg/dL and indirect bilirubin was 3.7 mg/dL. Reticulocyte count was 6%, serum albumin was 3 g/dL, serum globulin was 2.5 g/dL, A:G ratio was 0.7:1, prothrombin time was 18.6 seconds and INR was 1.7.

Ultrasound abdomen revealed massive splenomegaly with normal liver echotexture and normal portal vein. There was no ascites on ultrasonography. The general blood picture (GBP) was suggestive of moderate anisocytosis with few microspherocytes, polychromatophils, target cells, tear drop cells and nucleated RBCs (Figs. 1 and 2).

Based on the GBP findings, the following diagnosis was proposed: Hemolytic anemia with associated microcytic hypochromic anemia. An extensive work-up was done to find out the cause of hemolytic anemia. Serum lactate dehydrogenase (LDH) was normal, there was no evidence of hemoglobinuria, the hemoglobin electrophoresis was normal. However, indirect Coombs test was positive. Thus, a diagnosis of autoimmune hemolytic anemia (AIHA) was made. The cause of splenomegaly was proposed to be extravascular hemolysis as evidenced by a positive Coombs test. This explained all the findings in the patient and practically seemed the end of the case. However, there was something which needed further evaluation.

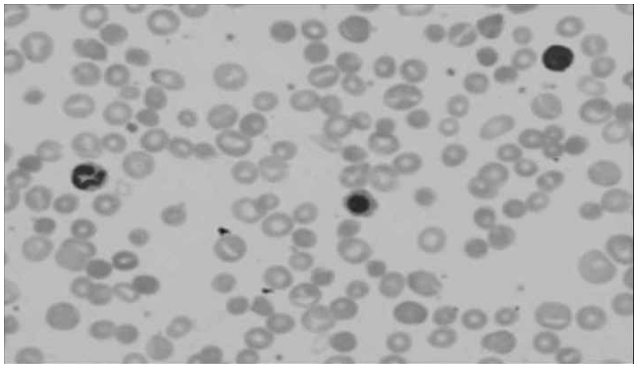

Figure 1. The general blood picture showing features of hemolysis.

The Unexplained Findings in this Case

Although severe anemia and splenomegaly could be explained with hemolysis in this patient, the cause of melena was not understood. Although, it was thought that thrombocytopenia due to hypersplenism or associated immune thrombocytopenic purpura (ITP) could be contributing to upper gastrointestinal bleeding and melena. However, to know the exact cause of melena, an esophagogastroduodenoscopy (EGD) was done. The EGD was suggestive of Grade II esophageal varices with portal hypertensive gastropathy (Fig. 3).

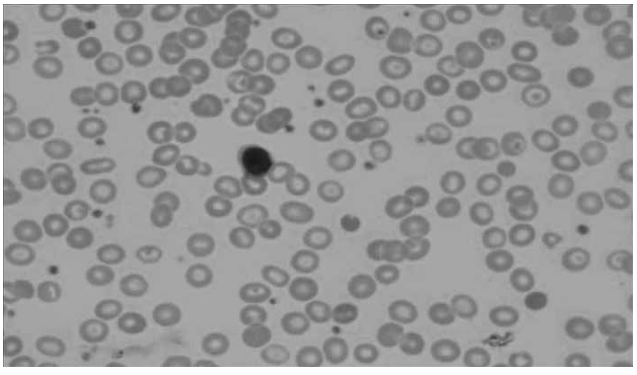

Figure 2. Peripheral smear showing target cells and nucleated RBCs.

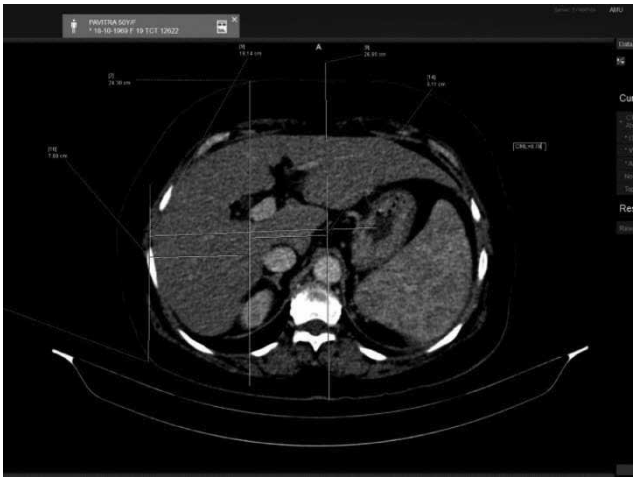

Figure 3. Endoscopy showing esophageal varices.

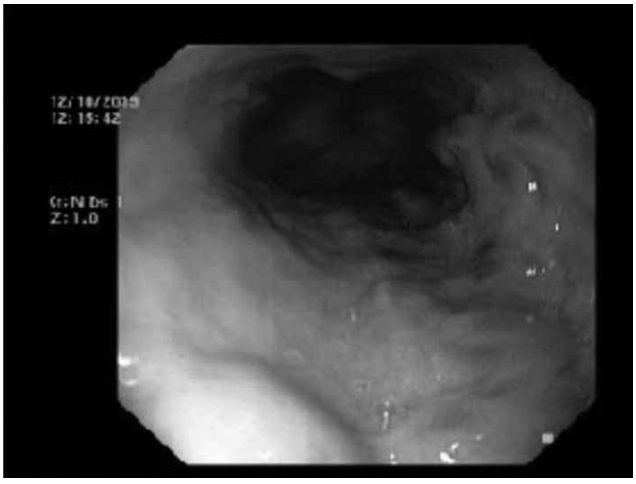

Figure 4. CECT showing caudate–right lobe ratio (C:RL ratio) of 0.78.

Since, the liver span was normal on clinical examination as well as on ultrasonography and there was no evidence of chronic liver disease or a dilated portal vein, a contrast-enhanced CT (CECT) scan of the abdomen was planned. While going for CECT, extrahepatic portal vein obstruction (EHPVO) or noncirrhotic portal fibrosis (NCPF) were suspected.

The CECT was suggestive of multiple gallbladder calculi (cholelithiasis); the caudate-right lobe ratio (C:RL ratio) was 0.78 with normal portal vein diameter (13 mm) and borderline increased splenic vein (~10.7 mm) and there were early esophageal varices noted, which confirmed the endoscopy findings (Fig. 4).

The C:RL ratio being >0.65 suggested cirrhosis of liver. To further confirm cirrhosis, transient elastography (fibroscan) was done which revealed a median stiffness of 23.11 KPa, confirming cirrhosis of liver. Thus, a final diagnosis of AIHA with cirrhosis of liver was made.

The next step in this patient was to find out the cause of cirrhosis of liver. Hepatitis B surface antigen (HBsAg) and anti-HCV (hepatitis C virus) were negative, ruling out viral hepatitis as the cause of cirrhosis. Serum ceruloplasmin, serum ferritin were normal. Total IgG was raised and antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA) and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) were positive. Anti-liver/kidney microsomal antibodies type 1 (anti-LKM-1) was negative.

Thus, a final diagnosis was made: AIHA with chronic liver disease (Type 1 AIH-related) Child-Pugh Class A with portal hypertension with Grade II esophageal varices with massive splenomegaly.

DISCUSSION

Our case is unusual because there were multiple contributing factors for massive splenomegaly in the same patient. Patient had AIHA which could explain all the findings on GBP and imaging and could explain splenomegaly in the patient. There was persistent thrombocytopenia which could be explained by hypersplenism (which is known to present with pancytopenia). However, the history of melena could only partially be explained by thrombocytopenia and a work-up was required. Melena itself can lead to iron deficiency which can lead to extramedullary erythropoiesis and give rise to splenomegaly. Apart from that, the presence of esophageal varices led to a search for noncirrhotic causes of portal hypertension. It is important to remember that in this patient, the ultrasound was not suggestive of chronic liver disease or portal hypertension. In a subset of patients, there may be no evidence of cirrhosis clinically and yet there may be advanced fibrosis. The ideal investigation for such situations is to go for a liver biopsy but now a large number of noninvasive tests have evolved, which include transient elastography, aspartate transaminase-to-platelet ratio index (APRI), acoustic radiation force impulse (ARFI), MR elastography, etc. It is imperative to note that in the absence of clinical or imaging evidence of cirrhosis, the patient was further taken up for evaluation of cirrhosis, otherwise an important diagnosis could have been missed as there was sufficient evidence to explain all the findings by AIHA.

Another important tool which initially suggested cirrhosis was the C:RL ratio, which is an important index in such occult cases of cirrhosis of liver. It has been reported that C:RL ratio is useful for diagnosis of liver cirrhosis by noninvasive imaging modalities such as CT and ultrasonography. The right-to-left (R/L) hepatic lobe ratio has been shown to be highly specific (100%) and very sensitive (85.7%) for cirrhosis. Except for liver biopsy and elastography, no other combination of tests has this degree of specificity and sensitivity.

Thus, in our patient, there were multiple causes leading to massive splenomegaly:

- AIHA, leading to extravascular hemolysis in spleen
- Severe anemia leading to extramedullary hematopoiesis in spleen
- Portal hypertension, secondary to AIH-related cirrhosis of liver.

Autoimmune hepatitis is a disease of unknown cause which is characterized by interface hepatitis,

lymphoplasmacytic infiltration, hypergammaglobulinemia and autoantibodies. It has a global distribution and affects all ages and both genders. Men have an earlier age of onset. Peak incidence in men is during teenage and in women, peak incidence is after menopause. It is associated with genetic predispositions, especially human leukocyte antigen (HLA)-DRB1*03 and HLA-DRB1*04.

Patients more than 60 years of age are more likely to have autoimmune thyroid disease and rheumatologic disorders. Patients younger than 30 are more likely to have ulcerative colitis and AIHA. Celiac disease may be seen in up to 2-4% patients. About 10-15% patients of APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia) have autoimmune hepatitis.

Diagnosis depends upon liver biopsy and presence of autoantibodies. Immunofluorescence and enzyme immunoassays are available for the following autoantibodies in serum, which are helpful in making a diagnosis: ANA, ASMA, anti-LKM-1, p-ANCA, IgA anti-tTG, SLA (soluble liver antigen), ASGPR (asialoglycoprotein receptor), anti-LC1 (liver cytosol type 1). The most commonly used initial treatment options are immunosuppressive therapy with either a combination of prednisone and azathioprine, a combination of budesonide and azathioprine or high-dose prednisone monotherapy. The two most studied treatment regimens are high-dose prednisone monotherapy or combination therapy of prednisone *plus* azathioprine.

CONCLUSION

We have presented here, a case of massive splenomegaly due to AIHA, which on further evaluation came out to be associated with autoimmune hepatitis. This case is interesting for many reasons. First, once the diagnosis of AIHA was confirmed, there seemed no reason to evaluate further, but once evaluated, a diagnosis as grave as cirrhosis was confirmed. This outlines the need for cautious interpretation of imaging modalities and high index of suspicion. In our case, the ultrasound was normal, and an important indicator was the C:R/L ratio on CECT abdomen, thus highlighting the role of C:R/L in such cases of borderline imaging results and no concrete initial evidence of cirrhosis.

Secondly, once cirrhosis was confirmed using transient elastography, the diagnosis of autoimmune hepatitis leading to cirrhosis was kept as a first differential because of the strong association between AIH and AIHA. Thirdly, this case is rare as there were three causes of splenomegaly and each could have masked the diagnosis of the other: hemolysis, portal hypertension and severe anemia with extramedullary hematopoiesis.

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