A Rare Etiology of Severe Thrombocytopenia in Patient with Chronic Liver Disease

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Abstract

Thrombocytopenia is a common complication in patients with chronic liver disease and is multi-factorial. It complicates the management and worsens the prognosis. Treatment options are costly and include platelet transfusion, splenectomy, splenic artery embolization, TIPPS and thrombopoietin (TPO) agonists.

Here we are presenting a patient with decompensated liver disease with known chronic alcoholism and profound thrombocytopenia despite multiple platelet transfusions. On further work up we found a coexistent autoimmune etiology. Thrombocytopenia promptly responded to steroids, a cost effective option.

Introduction

Thrombocytopenia, a common complication in patients with chronic liver disease, is seen in nearly 75% of cirrhotic patients.[1] The pathogenesis of thrombocytopenia in chronic liver disease is multi-factorial.[1] Initially it was thought that thrombocytopenia in CLD is only due to portal hypertension where there will be an enlargement of spleen which causes destruction of platelets. So initially treatment for thrombocytopenia was aimed at reversing portal hypertension. But persistently decreased platelets were noted even in patients without splenomegaly.[2] So other factors like intrasplenic production of autoantibodies and plasma expansion resulting in hemodilution also contribute to thrombocytopenia. Suppression of platelet production in bone marrow is also another factor which is seen in HCV infection and alcohol related chronic liver disease. Antiviral therapy like interferon alfa also induces thrombocytopenia.[3] In some patients of CLD there is an evidence based autoantibodies related destruction of platelets and it is mostly observed in HCV related cases.[4] Here autoantibodies are directed against platelet surface antigens and enhance the removal of platelets by splenic and hepatic reticuloendothelial systems there by triggering rapid destruction as seen in chronic ITP. TPO is a potent cytokine produced by liver, bone marrow and kidney which regulates megkaryocytes and platelet production.[5] In cirrhotic patients with thrombocytopenia, low circulating levels of TPO is seen compared to cirrhotic patient with normal platelet count.[6] The treatment options available for severe thrombocytopenia are platelet transfusion, splenic artery embolization, splenectomy and TIPS. Platelet transfusion is indicated in patients with less than 10,000-20,000/µl platelets in uncomplicated patients and less than 50,000/µl in patients undergoing procedures.[7] Newly derived options include recombinant interleukin-11, eltrombopag and recombinant TPO.

Case Summary

A, 50 year old male patient with ethanol related chronic liver disease and no other comorbidities, came to EMD with the complaints of melaena, gum bleed and haematuria for 10 days, fever with chills, abdominal pain and distention for 3 days.

On examination, patient was pale and febrile with stable vital parameters. He had minimal ascites and epigastric tenderness.

Serial CBC, LFT and RFT are summarized in Table.1. Upper GI endoscopy showed esophageal varices and portal gastropathy and EVL done immediately. Ultrasound abdomen Showed features of CLD and portal hypertension with medical renal disease. Ascitic fluid analysis had no evidence of peritonitis. Urine culture showed significant bacteria (E.coli) and managed accordingly. He had severe thrombocytopenia which was managed with platelet transfusions. Bone marrow aspiration and biopsy showed dimorphic anemia with thrombocytopenia, megaloblastic erythroid hyperplasia and mild megakaryocytic hyperplasia. His serum B12 and folate level were within normal range. Hepatis B, C, HIV, Dengue virus, *Helicobacter pylori*, scrub typhus, leptospirosis infection and Coomb's test were negative. Renal failure was stabilized with hemodialysis.

As his thrombocytopenia persisted despite multiple platelet transfusions (total 19 units) and other common causes of thrombocytopenia being ruled out, we suspected of some uncommon etiology including an autoimmune condition. ANA tested was positive with fine granular++, cytoplasmic+ pattern. He was positive for smooth muscle antibody and negative for anti-ds DNA Ab and hence he was diagnosed to have autoimmune hepatitis type-1 with associated ITP. We started steroids (Inj. methylprednisolone 125 mg IV OD for 3 days followed by oral prednisolone 60mg OD). His platelet count started improving from 2nd day of IV steroid.

On follow-up visits, his platelet count was in safe range (> 1 lakh / cu.mm3) with low dose oral steroid and is currently being managed as ITP.

Discussion

The causes of thrombocytopenia in chronic liver disease may be due to sequestrating function of spleen, presence of antiplatelet antibodies and impaired thrombopoietin production in cirrhotic patients.[6] It is very important to differentiate ITP from common cause of thrombocytopenia in CLD as the management differs. Hypersplenism in liver disease due to portal hypertension

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Table 1: Blood investigation (CBC, LFT, RFT) reports

	Normal	Day1	Day3	Day5	Day7	Day10
Hb (g/dl)	13-17	7.1	6.4	6.0	7.8	9.6
PCV (%)	40-50	21.3				
WBC count/µl	4-10X10^3	5.4X10	5.0X10^3			76X10^3
MCV (fl)	80-100	96.6				
Neutrophils (%)	40-80	70.7				
Lymphocytes (%)	20-40	17.6				
Monocytes (%)	2-10	10.8				
Eosinophils (%)	1-6	0.9				
Basophils (%)	0-2	0.0				
Platelet count/µl	150-400X10^3	6X10^3	3X10^3	4X10^3	36X10^3	125X10^3
ESR (AEFH)	3-10	106	98	78	78	45
Serum Protein (g/dl)	6.4-8.3	6.5		6.8		6.9
Serum Albumin (g/dl)	3.4-4.8	2.3		2.6		2.9
Serum globulin (g/dl)	1.8-3.6	4.2		4.2		4.0
Total bilirubin (mg/dl)	0.2-1.0	1.2				1.1
Direct/indirect	0-0.2/0.2-0.8	0.8/0.4				
SGOT (u/l)	5-38	62				54
SGPT (u/l)	5-41	15				14
ALP (u/l)	40-129	205				154
GGT (u/l)	10-66	409				126
Serum creatinine (mg/dl)	0.8-1.25	2.3	4.43	3.95	3.4	2.1

causes increased sequestration of platelets within spleen leaving less in circulation. However it is also to be clear that thrombocytopenia can occur in liver cirrhosis without splenomegaly.[2] Thrombopoietin is a cytokine produced by the liver which plays a key role in platelet production and subsequent function may be low in cirrhosis. Thrombocytopenia in liver disease without evidence of cirrhosis, splenomegaly and interferon is recognized especially in patients with hepatitis C and auto immune hepatitis.

Based on persistent thrombocytopenia, ANA and anti SMA positivity we diagnosed him as AIH type-1 and associated ITP. The International Autoimmune Hepatitis Group proposed a scoring system to standardize the diagnosis, useful for clinical trials, but that may be inaccurate in individual cases.[8] Liver biopsy was not done for two reasons-severe thrombocytopenia and patient refusal.

Autoimmune hepatitis (AIH) is a chronic and progressive necroinflammatory and fibrotic process of the liver of unknown cause that occurs in children and adults, usually associated with the presence of autoantibodies and Hypergammaglobulinemia.[8] Affected individuals often have concurrent extrahepatic autoimmune disorder like rheumatoid arthritis, Sjogren's syndrome and auto immune thyroiditis but association with idiopathic (immune) thrombocytopenic purpura has been rarely reported.[9-13]

ITP is an autoimmune disease characterized by a low platelet count, mucocutaneous bleeding, normal bone marrow findings and the absence of other causes of thrombocytopenia in which anti-platelet autoantibodies such as PAIgG induces platelet destruction.[14] There is a case series of 5 patients with AIH type-2 where patients had at least one associated autoimmune disorder including IgE-induced IgA deficiency, ITP, and arthritis.[15] In an Indian case series of 10 patients with AIH, three had underlying rheumatic disease (SLE, Sjogren's and Rheumatoid arthritis each one), while others had primary AIH. In the same report, 2 patients were found to have autoimmune thrombocytopenia and were managed by immunosuppressant.[16] Indeed prednisolone administration is a treatment option for AIH and is also effective for ITP. Therefore ITP should be considered when liver dysfunction is accompanied by severe thrombocytopenia particularly in the autoimmune types of liver disease.

Though in our patient there was normal bilirubin, SGOT and SGPT (which is usually elevated in hepatitis) but persistent thrombocytopenia and positive ANA with SMA made us to consider it AIH type-1.

Conclusion

It is worthy to evaluate for an alternative autoimmune etiology for CLD if thrombocytopenia is severe or persisting as there are better and cost effective treatment options i.e. steroids.

Learning points

1. All CLD with history of alcohol ingestion is not purely alcohol related.
2. Thrombocytopenia in CLD should be evaluated for causes other than alcohol and hypersplenism.
3. All autoimmune hepatitis may not have gross LFT derangement.

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