Severe Thrombocytopenia in Decompensated Liver Disease: An Example of Accelerated Intravascular Coagulation and Fibrinolysis

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ABSTRACT

Introduction: Advanced liver disease can present with severe thrombocytopenia that can be difficult to delineate and manage. Here we describe a unique entity of accelerated intravascular coagulation and fibrinolysis (AICF) in a patient with decompensated liver disease.

Case Presentation: A 56-year-old male with a history of alcoholic cirrhosis was admitted for weakness, nausea, metabolic derangement, and acute kidney injury determined to be secondary to decompensated liver disease. During admission, his platelet count declined to <10 000/μL requiring 8 total platelet transfusions. Laboratory and clinical evaluation supported a diagnosis of AICF, and the patient gradually improved with supportive management.

Discussion: AICF can present similarly to disseminated intravascular coagulation, and careful evaluation of specific laboratory values is required for accurate diagnosis. Appropriate management minimizes the associated increased risk of bleeding and prevents delay in procedural intervention.

Conclusions: This case highlights the importance of early clinical and laboratory correlation, multidisciplinary care, and supportive treatment in the management of AICF.

INTRODUCTION

Advanced liver disease results in an imbalance between procoagulant and anticoagulant factors that can present as a variety of hematological abnormalities, including thrombocytopenia. Thrombocytopenia in liver disease is often multifactorial, with varying degrees of platelet sequestration in the spleen, decreased liver production of thrombopoietin, and accelerated fibrinolysis.[1-3] Approximately 75% of patients with chronic liver disease have mild thrombocytopenia (100 000-150 000/μL), and approximately 13% have moderate thrombocytopenia (50 000-100 000/μL).[1] Severe thrombocytopenia (<50 000/μL) in liver disease is rare and may represent a profile of hematologic abnormalities associated with decompensated liver disease referred to as accelerated intravascular coagulation and fibrinolysis (AICF).[4]

CASE DESCRIPTION

A 58-year-old man with a history of alcoholic cirrhosis, hypertension, and type 2 diabetes presented initially to a primary care clinic for evaluation of generalized weakness, nausea, and progressive lower extremity swelling. Further review of symptoms was negative for chest pain, shortness of breath, abdominal pain, hematuria, and weight loss. Physical examination was notable for worsening ascites and lower extremity edema. Laboratory evaluation revealed elevated blood urea nitrogen, elevated creatinine, hyponatremia, hyperkalemia, low albumin, and elevated bilirubin. He was subsequently recommended for admission, upon which hepatology and nephrology were consulted. His presentation was determined to be secondary to decompensated cirrhosis complicated by acute kidney injury with both pre-renal and hepatorenal components in the setting of recent diuretic use. He underwent paracentesis on hospital day 1 and 2, which yielded 8 total liters of serous, amber-colored fluid. Subsequent fluid studies were negative for spontaneous bacterial peritonitis and malignancy (Table 1). Albumin challenge was completed, and appropriate albumin supplementation was given. Kidney function improved on hospital day 6 with supportive treatment. Persistent hypoten-

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Table 1. Peritoneal Fluid Studies From Hospital Day 1

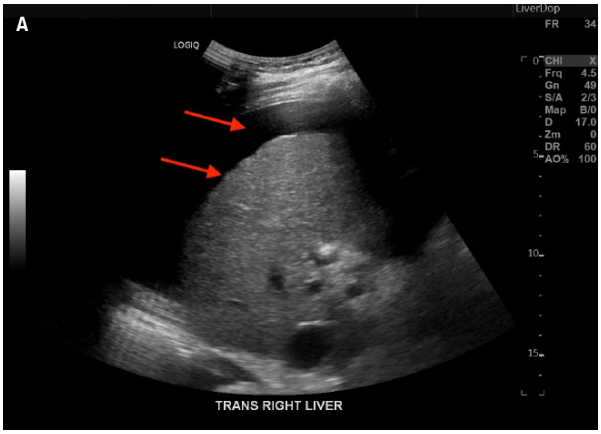
Peritoneal Fluid Studies	Hospital Day 1
Color	Yellow
Clarity	Cloudy
White blood cell count (/uL)	91
Lymphocyte (%)	71
Monocyte/macrophage (%)	29
Amylase (U/L)	7
Protein (g/dl)	1.4
Glucose (mg/dL)	223
Lactate dehydrogenase (U/L)	43
Aerobic/anaerobic culture with Gram stain	Negative 5 days

Table 2. Select Complete Blood Cell Count Results Throughout Hospital Admission

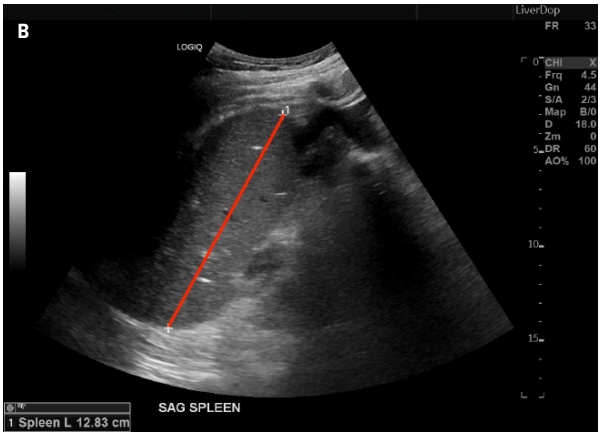
Complete Blood Cell Count	WBC Count (10e3/uL)	Hemoglobin (g/dL)	MCV (fl)	Platelet Count (10e3/uL)
Ref Ranges	**3.9 – 11.2**	**13.7 – 17.5**	**79 – 98**	**165 – 366**
Day 1	4.8	10.5	102	94
Day 2	2.8	8.2	101	60
Day 3	2.9	7.7	104	30
Day 4	3.5	8.0	106	19
Day 5	2.9	7.7	107	8
Day 6	3.1	7.8	106	10
Day 7	2.7	7.5	106	10
Day 8	2.9	7.8	108	30
Day 9	3.6	7.4	105	20
Day 10	3.5	7.4	106	10
Day 11	4.6	8.4	106	12
Day 12	3.8	8.2	105	22
Day 13	3.3	7.7	112	27
Day 14	3.2	8.6	109	13

Abbreviations: WBC, white blood cell; MCV, mean corpuscular volume; ref, reference.

Figure. Image From Ultrasound of Liver and Spleen



A. Arrows highligh nodular liver edge as evidence of cirrhosis, as well as surrounding ascites.



B. Line highlights spleen length of 12.83cm, indicative of minimal splenomegaly.

sion throughout admission required titration of midodrine up to 15 mg 3 times daily.

Platelet levels gradually declined from 94 000/µL on admission to 8000/µL on hospital day 5 (Table 2). Hematology was consulted and recommended platelet transfusion for platelet counts less than 10 000/µL. Thrombocytopenia persisted despite the transfusion of 8 total units of platelets from hospital day 5 to day 10. Thrombocytopenia initially was attributed to a combination of decreased liver production of thrombopoietin and possible splenic sequestration, both secondary to decompensated liver failure. Ultrasound of the liver and spleen was negative for thrombus and revealed minimal splenomegaly (Figure). On hospital day 8, physical exam was notable for scattered petechiae, oozing from an intravenous line site, and increasing ascites. Laboratory evaluation revealed increased prothrombin time (PT) (18.2 seconds) and partial thromboplastin time (pTT) (44.3 seconds), decreased fibrinogen (101 mg/dL), and elevated D-dimer (4.35 mg/L fibrinogen equivalent units), prompting concern for disseminated intravascular coagulation (DIC). Additional laboratory evaluation revealed factor VIII activity of 175%, within the normal reference range of 64% to 189%, which lessened suspicion for DIC and pointed towards hyperfibrinolysis secondary to decompensated liver disease. The patient did not meet the criteria for liver transplantation; thus, supportive care was favored by hematology and hepatology. Platelet levels remained low but gradually stabilized without any further evidence of bleeding. The patient was subsequently discharged on hospital day 10 with close outpatient follow-up.

DISCUSSION

AICF and DIC have similar clinical presentations that may include oozing of blood from venipuncture sites, thrombocytopenia, prolonged PT and pTT, decreased fibrinogen, and elevated D-dimer.[5] The exact cause of AICF is unknown, but elevated levels of tissue

plasminogen activator resulting from decreased hepatic clearance, as well as decreased levels of antifibrinolytic factors, have been hypothesized as potential contributors.[4,6] There is additional evidence that ascitic fluid has fibrinolytic properties, and its absorption through the thoracic duct also can contribute to the systemic accelerated fibrinolysis seen in advanced liver disease.[2]

While AICF can present similarly to DIC, they can be differentiated by evaluation of specific clotting factor activity levels. In DIC, the levels and, thus, activity of all clotting factors decrease due to their rapid systemic consumption. However, in AICF, low clotting factor activity is due to decreased clotting factor production in the liver; thus, only those factors produced in the liver will have low activity. Since clotting factor VIII is produced by endothelial cells systemically, its activity will be normal or slightly increased in AICF, allowing for the differentiation between AICF and DIC.[7] Additionally, increased level of factor VIII has been associated with cirrhosis, further aiding in the differentiation between AICF and DIC.[3,7]

The distinction between DIC and AICF is important as it directs the management of thrombocytopenia in advanced liver disease. The gold standard for management of DIC is treatment of the underlying condition.[7] While treatment of other causes of thrombocytopenia in advanced liver disease focuses on the correction of splenic sequestration and decreased thrombopoietin, the exact cause of AICF remains unknown and treatment is mainly supportive.[1] Antihyperfibrinolytic therapy including ε–aminocaproic acid and tranexamic acid have been used to combat hyperfibrinolysis in advanced liver disease, specifically to prevent blood loss during liver transplantation, but evidence of their efficacy is limited.[1] As with all hematologic abnormalities associated with advanced liver disease, the definitive treatment is liver transplantation.[8]

AICF and other hematological abnormalities associated with advanced liver disease often complicate clinical courses and delay procedural interventions due to increased risk of bleeding.[1,4] While the associated increased risk of bleeding is generally accepted, the extent to which thrombocytopenia and hyperfibrinolysis contribute to it is relatively unclear.[6] The use of conventional coagulation tests with evaluation of factor VIII activity are useful in the diagnosis of AICF but offer little insight on the risk of bleeding as they only evaluate procoagulant factors.[6,9] Accurate assessment of bleeding risk in patients with AICF may be accomplished with the use of thromboelastography, which offers a better assessment of the interactions between procoagulant and anticoagulant factors as well as platelets.[9] However, current use of thromboelastography is limited by availability and lack of standardization among test protocols.[9] Regardless, the early and precise management of AICF is important to minimize the risk of bleeding, specifically in patients with decompensated liver disease for whom recurrent paracenteses may be indicated.

CONCLUSIONS

This case highlights several significant considerations for clinicians, primarily the importance of clinical and laboratory correlation to determine the most appropriate cause of thrombocytopenia in patients with advanced liver disease. In this particular case, the distinction between DIC and AICF was made through normal clotting factor VIII levels. Further, multidisciplinary management leads to swifter diagnosis and implementation of an appropriate plan of care. This minimizes bleeding risk and prevents delay in procedural intervention. Lastly, given that AICF is a complication of advanced and irreversible liver disease, treatment is largely supportive unless clinically indicated for transplantation.

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