Platelet Abnormalities in Hepatobiliary Diseases*

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ABSTRACT

Platelet abnormalities associated with hepatobiliary diseases include increased (thrombocytosis) and decreased (thrombocytopenia) numbers of platelets as well as abnormalities in function (thrombocytopenia or thrombasthenia). Hepatic diseases that are accompanied by platelet abnormalities include hepatitis, cirrhosis, portal hypertension, and neoplastic disorders both benign and malignant. The objective of this work is to examine the platelet abnormalities that occur with a variety of hepatobiliary disorders. Thrombocytosis is seen as a reactive entity following splenectomy. Thrombocytopenia is associated with hypersplenism, dysproteinemias and liver disease related disseminated intravascular coagulation (DIC). Qualitative platelet abnormalities are found in hepatic failure, liver diseases associated with high or low levels of lipid, and with medications given for a variety of hepatocellular diseases. Clinically common and significant platelet abnormalities associated with liver disease are thrombocytopenia secondary to portal hypertension and the thrombasthenias following metabolic changes and/or therapeutic interventions of liver disease.

Introduction

The entire range of platelet abnormalities can be found in association with hepatobiliary diseases (HBD). Thrombocytopenia can occur rarely with primary or secondary liver tumors. Thrombocytopenia occurs in association with portal hypertension and hypersplenism. Thrombasthenias are noted in association with advanced hepatic failure. Some HBD are associated with a combination of more than one platelet abnormality.

The most common hepatic diseases associated with platelet abnormalities include hepatitis, cirrhosis, portal hypertension, hypersplenism, vascular and other tumors of the liver. The platelet abnormalities related to hepatocellular disease may occur with or without other clinical manifestations of hepatic disease such as jaundice, cutaneous changes, portal hypertension, hepatic coma and precoma, impaired hepatic detoxification, or altered lipid and immunoglobulin metabolism.

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The relationship of thrombocytopenia, thrombocytopenia, thrombasthenia, and combinations of platelet abnormalities that are seen in a variety of HBD will be examined.

Methods

Thrombocytopenia, thrombocytosis, and thrombasthenia occur in association with HBD (table I). Thrombocytopenias will be examined in light of consumption, sequestration, and immune phenomena.

Thrombocytosis will be reviewed related to status postsplenectomy and malignant hepatic neoplasms.

Thrombasthenias are assessed in light of hepatic failure, lipid abnormalities, and medications taken by patients with hepatobiliary disease.

Results

Thrombocytopenias may be secondary to decreased production or increased consumption (or sequestration), and may be separated into immune and non-immune types in association with HBD. Hepatobiliary diseases associated with thrombocytopenia include the aplastic anemia which sometimes follows hepatitis, viral infections of the liver, therapeutic agents taken in conjunction with liver diseases, and vitamin deficiencies associated with nutritional abnormalities of the liver. Alcohol is associated with severe thrombocytopenia in some individuals. The contributing factors of folate and other nutritional deficiencies and hypersplenism that may be present in patients who are ethanol abusers do not have to be present for the thrombocytopenia to occur. In those instances where the thrombocytopenia is directly related to alcohol and there are no other underlying problems, platelet counts may recover within one week after the cessation of alcohol and the provision of proper nutrients and vitamins.

Thrombocytopenia associated with increased peripheral destruction and/or sequestration of platelets with or without a nutritional component is common in liver disease. Cirrhosis, particularly if associated with portal hypertension and hypersplenism, is a well recognized cause of thrombocytopenia. Other hepatic disorders, such as hemangiomas and hemangioblastomas, may sequester and destroy platelets as well. Hepatic disease with alterations of immunoglobulins, other proteins and lipids can result in decreased platelet counts either through changes of platelet membrane binding sites, aggregation and clumping of platelets with subsequent removal, or sequestration and destruction.

Thrombocytosis is most often encountered as a secondary or reactive phenomenon. The platelet count rarely exceeds \(1,000 \times 10^9\) per L (one million platelets per millimeter\(^3\)). The spleen is the major site for removal of platelets. At any moment, approximately one-third of the total number of circulating platelets may be within the geographic confines of the spleen. Splenectomy results in a prompt 48 hour to one week increase in the platelet count. Thrombocytosis following splenectomy is usually self-correcting with platelet counts returning to normal over six to 12 weeks. Platelet morphology in reactive thrombocytosis is usually normal as are platelet function tests.

| Platelet Abnormalities in Hepatobiliary Diseases | 
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| **Thrombocytopenia:** | Decreased production | Increased consumption | Combination |
| **Thrombocytosis:** | Reactive | Malignancy associated |
| **Thrombasthenia:** | Secondary to medications | Toxic-metabolic effects |
Thrombocytosis associated with hepatocellular tumors is unusual. Malignancies of hepatocellular and canalicular cellular types have been reported to be associated with thrombocytosis. A distinction is made of thrombocytopenia from thrombocytosis. Thrombocytosis is defined as a marked and persistent elevation in the platelet count as a result of a myeloproliferative disorder. In those instances where the thrombocytosis is secondary to hepatocellular malignancy, the condition may have a natural history which is consistent with an unremitting rise in the platelet count.

Thrombocytopenias or qualitative platelet abnormalities occur associated with hepatic failure or secondary to medications given for the underlying hepatobiliary disease. The causes of thrombasthenias in hepatic failure are thought to be related to abnormalities of platelet metabolism secondary to excess lipids or toxic metabolic end product accumulations seen in severe hepatic decompensation.

Medications taken by people with hepatic disease can result in qualitative and/or qualitative platelet abnormalities. These medications include aspirin, other nonsteroidal anti-inflammatory agents, heparin, high doses of penicillin, and chemically related antibiotics, clofibrate, propranolol, hydroxychloroquine, and alcohol. Many other medications which may be taken by patients with liver disease have been reported to interfere with platelet function.

Discussion

Hepatobiliary diseases of many types are associated with platelet abnormalities. These include thrombocytopenia, thrombasthenia or thrombocytopathy, and thrombocytosis. A common clinical disorder associated with mild to moderate thrombocytopenia is viral associated hepatitis. Clinically significant thrombocytopenia is found associated with hepatic cirrhosis, portal hypertension, and hypersplenism. Thrombocytopathies are most often associated with the medications given to people with liver disease. Aspirin is the most common offender. Hepatic failure and abnormal lipids and/or proteins have also been implicated in thrombocytopathies.

Thrombocytosis is an infrequent accompaniment of liver disease. It is seen in its reactive form after the removal of the spleen or secondary to regenerative responses following some liver disease associated anemias. Post splenectomy thrombocytosis occurs within 48 hours to one week. Usually, the platelet count returns to normal by the end of two months. Rarely, tumors involving the liver are associated with thrombocytosis probably through the mechanism of the production of a megakaryocyte growth stimulating factor elaborated by the tumor.

Conclusion

Hepatobiliary diseases are associated with a myriad of quantitative and qualitative platelet abnormalities. Advanced liver disease associated with portal hypertension results in thrombocytopenia and thrombocytopathy. Although thrombocytopenia is clinically the entity most often associated with hepatobiliary disease, thrombocytopathies and thrombocytosis do occur.

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References


