Spleno-renal Shunt, Cholecystectomy, and Appendectomy in a Patient with Hemophilia A, an Abnormal Fibrinogen, and Thrombocytopenia

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MAJOR operative surgery has recently become feasible for hemophilic patients through the availability of satisfactory factor VIII (AHF) concentrates.[2] Splenectomy and spleno-renal shunt for portal hypertension have been reported in only two hemophilic patients, of whom one survived.[3, 4] This paper reports splenectomy, spleno-renal shunt, cholecystectomy, and appendectomy in a patient with hemophilia A and an abnormal fibrinogen in whom operation was complicated by moderately severe thrombocytopenia. This patient, reported previously in abstract,[5] represents the only known association of hemophilia A and abnormal fibrinogen. Details of the hematologic and genetic studies will be reported elsewhere.

Case Report

A 55-year-old man with known hemophilia A was admitted to the Jewish Hospital in April, 1968 because of splenomegaly and recurrent gastrointestinal hemorrhage. He had become jaundiced in October, 1966 and was assumed to have homologous serum hepatitis until his wife became icteric shortly thereafter without prior transfusion or injection. In October and December of 1967 and March, 1968 he had three admissions to another hospital for melena and hematemesis. During these admissions, splenomegaly and thrombocytopenia were observed and x-ray examination revealed a hiatal hernia, cholelithiasis, and colonic diverticulosis. On admission to Jewish Hospital in April, 1968 these observations were confirmed, and he was found to be leukopenic (1,500–3,000/mm.^{3}), and thrombocytopenic (96,000/mm.^{3}). Differential white blood cell count was normal, hematocrit was 42%, erythrocyte sedimentation rate was 42 mm./hr., Coombs test and LE test were negative, and antinuclear antibody (both latex and fluorescent ANA) was absent. Urinalysis was normal. Liver function tests were indicative of hepatocellular dysfunction (SGOT 133 units, BSP 13% retention, total bilirubin 0.8 mg./100 ml., albumin 3.6 Gm./100 ml., globulin 5.0 Gm./100 ml.). A bone marrow examination showed only erythroid hyperplasia, and marrow cultures were negative. Lymphangiogram showed normal abdominal lymph nodes. Coagulation studies revealed thrombocytopenia but normal platelet function (platelet factor 3, clot retraction), a plasma factor VIII (AHF) level 8% of normal, and an abnormal fibrinogen which was subsequently distinguished from other known fibrinogen variants except fibrinogen *Zurich*.[5, 6] Family studies identified two brothers and four nephews with hemophilia A of comparable severity, none of whom had the fibrinogen variant. Seven relatives (four females, three males) were found to have the fibrinogen variant without hemophilia A. All were hemostatically normal. It was concluded that the patient had hemophilia A which was mild by AHF assay (8% of normal), but clinically moderately severe (one to two spontaneous hemarthroses annually), an asymptomatic fibrinogen variant, chronic active hepatitis with macronodular cirrhosis, portal hypertension, secondary hypersplenism with thrombocytopenia and leukopenia, together with hiatal hernia, cholelithiasis, and colonic diverticulosis. He was readmitted in August, 1968 for massive gastrointestinal hemorrhage for which initial treat-

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ment was received at another hospital. His bleeding stopped after transfusion with whole blood and cryoprecipitated AHF concentrate. During this admission, large esophageal varices were visualized radiologically. Liver function tests were unchanged compared to values on his initial admission in April, 1968. In September, 1968 the patient became deeply jaundiced, the total bilirubin rose to 28 mg./100 ml. and the SGOT to 1,700 units. The alkaline phosphatase was 80 International units. He improved spontaneously and was discharged without steroid therapy. The total bilirubin decreased to 1.4 mg./100 ml. by February, 1969. The patient was readmitted in February, 1969 and again in April, 1969 for gastrointestinal hemorrhages. His stools remained guaiac positive throughout April, 1969, although transfusion was not required during the latter half of the month. Liver function tests at this time included an SGOT of 51.1 units. A total protein of 9.8 Gm./100 ml. with an albumin of 3.3 Gm./100 ml., and a bilirubin of 1.5 mg./100 ml. It was concluded that portal decompression was required. The patient was readmitted (on 4–27–69) and on 4–28–69 esophagoscopy and gastroscopy were performed uneventfully while the patient received 1,000 units of glycine precipitated AHF (Method 4, Hyland). The patient's plasma AHF level was 8% of normal before the procedure and 15% of normal 10 minutes after receiving the AHF concentrate. Esophageal varices and antral gastritis were seen, but esophagitis was absent. The antral gastritis was assumed to be the immediate source of the bleeding. The hiatal hernia was small, and, in the absence of esophagitis, it was decided to make an anterior abdominal approach and avoid repairing the hernia. An operation was performed on 4–29–69 (Fig. 1) using Method 4 AHF concentrate to maintain the plasma AHF level between 60 and 90% of normal. A bilateral subcostal incision was used. Splenectomy was performed (spleen weight, 1,115 Gm.), followed by an end-to-side spleno-renal shunt. Portal pressure before the shunt was 28 cm. of water. This was reduced to 12 cm. after the shunt was formed. A gallbladder filled with stones was then removed, followed by incidental appendectomy. The operation lasted 8 hours, in good part due to insistence on complete hemostasis before the incision was closed. Platelet counts ranged from 50,000 to 80,000/mm³. during the operation. Hemostasis was normal during the first half of the operation, but increased oozing was encountered subsequently. The platelet level did not increase immediately after splenectomy, and during the second half of the operation, the patient received 10 platelet packs. One hour after the operation was

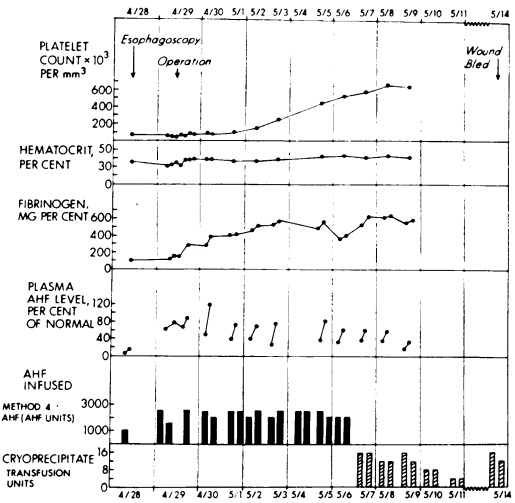

FIG. 1. Hospital course of a hemophilic patient for whom splenectomy, spleno-renal shunt, cholecystectomy, and appendectomy were performed. Plasma AHF levels represent values before and 15 minutes after injection of AHF concentrate. From 4/30/69–5/11/69 only levels before and after the morning AHF injection are shown. During 4/30–5/11/69, patient received an AHF injection every 12 hours. Plasma AHF was assayed by a kaolin-partial thromboplastin time (PTT) system using hemophilia A substrate plasma.

concluded, the platelet count was 97,000/mm³. Total operative transfusion replacement included 5 liters of bank blood, 1 liter of fresh blood, 6,250 units (content of one ml. fresh normal plasma = 1.0 unit AHF) of Method 4 AHF concentrate. After the operation was concluded, no further transfusion of blood was required, and recovery was uneventful. Thereafter, the patient received Method 4 AHF and cryoprecipitated AHF in the amounts shown (Fig. 1). Platelets and white blood cells returned to normal levels by the third postoperative day. Drains had been brought out from the splenic fossa and gallbladder bed through the lateral aspects of the wound. These were removed uneventfully on the 5th and 6th postoperative days. AHF concentrate was stopped on 5–12–69, the 12th postoperative day. On 5–14–69 bleeding from the incisional wound began. The patient was taken to the operating room where, with local anesthesia, bleeding was found to originate from one small localized area of granulation tissue. Bleeding stopped with local pressure and the placement of several additional sutures. During that day only, he received 28 transfusion units of cryoprecipitated AHF, and bleeding did not recur. The patient was discharged on 5–19–69. During June and July, 1969 he had five admissions for joint and soft tissue hemorrhages, all

spontaneous. Such frequency was unusual for this patient who previously had approximately one spontaneous hemathrosis annually. During these bleeding episodes, no circulating anticoagulant was detected and the patient's response to AHF transfusion was unchanged. After July, 1969 these joint and tissue hemorrhages stopped. In September, 1969 he suffered a recurrence of hepatitis with bilirubin reaching 31.5 mg./100 ml. and the SGOT 1,700 units. The patient improved spontaneously. Since operation, all stools have been guaiac tested by the patient aind found negative for blood. Platelets and white blood cells remain at normal levels. Following return of platelets to normal levels, platelet function studies were repeated and revealed normal results for the following tests: modified Ivy bleeding time, platelet count, clot retraction, platelet factor 3 release, platelet adhesiveness to glass, and platelet aggregation in response to adenosine diphosphate (ADP), thrombin, epinephrine, and collagen.

Discussion

This patient is a good example of the fact that the most major operative surgery may be successfully performed on hemophiliacs provided they have no circulating anticoagulant, adequate stores of AHF concentrate are available, and laboratory facilities for reliable AHF assays are present.

The essentially normal hemostatic response in the presence of an abnormal fibrinogen was anticipated, since other family members with the fibrinogen variant, but no hemophilia, had tolerated major trauma. The fact that the patient was no more severely afflicted than his two hemophilic brothers who have normal fibrinogen molecules suggested the same conclusion prior to identifying other family members with the fibrinogen variant. The rise in plasma fibrinogen levels shown in Figure 1 was expected because of the contamination of both Method 4 and cryoprecipitated AHF concentrates with fibrinogen.

Except for increased oozing during the second half of the operation, the patient did well despite moderately severe thrombocytopenia (50,000 to 80,000/mm^3.). This point deserves emphasis, since thrombocytopenia of this degree, *per se,* probably should not preclude a necessary operation in such patients provided the platelet function is normal, as it was in this case.

Overt hepatitis with jaundice is uncommon in hemophiliacs despite their frequent transfusions. Why this patient has chronic hepatitis with acute exacerbations is unknown.

The hemophiliacs in this family have all been afflicted more severely than one would anticipate from plasma AHF levels of 5 to 8%. None has circulating anticoagulants, and the disparity between clinical symptoms and plasma AHF levels is unexplained.

The identification of this patient as having hemophilia A rather than von Willebrand's disease to account for low plasma factor VIII (AHF) level is supported by the following evidence: a typical hemophiliac response to the infusion of AHF concentrates (Fig. 1); membership in a kindred in which only males have the clinical manifestations of factor VIII deficiency (the patient's daughter is asymptomatic but has a plasma AHF level of 21%, and is presumably a carrier); a normal bleeding time and normal platelet function including platelet adhesiveness to glass.

Two other hemophiliacs have received spleno-renal shunts. One died postoperatively in association with the appearance of a circulating inhibitor to AHF (4). The second patient survived (3), but postoperatively developed an increased incidence of joint and muscle hemorrhages.[1] A similarly increased incidence of joint and muscle hemorrhage occurred in our patient postoperatively, but this later subsided with improvement in muscle tone and strength. At no time did an inhibitor appear, nor did the endogenous plasma AHF level decline. Plasma AHF levels on 10/29/69 and 11/7/69 were 13% and 8% of normal, respectively (no transfusions had been received for over a month). With extensive operation in any patient, a pe-

riod of considerable catabolism and muscle weakness may occur. Resumption of normal activity after such an insult could be related to the increased incidence of spontaneous hemorrhage observed in hemophiliacs.

Summary

A patient with hemophilia A and an abnormal fibrinogen developed hepatitis followed by macro-nodular cirrhosis, portal hypertension, esophageal varices, splenomegaly, leukopenia, and thrombocytopenia. Recurrent gastrointestinal hemorrhage was treated successfully by splenectomy and spleno-renal shunt performed during infusions of AHF concentrates (Method 4 glycine precipitated AHF and cryoprecipitated AHF). Cholecystectomy (for cholelithiasis) and incidental appendectomy were also performed. After the operation, the patient experienced an unusual but transient series of joint and muscle hemorrhages.

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