Thrombocytopenia and Alcoholism

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SUMMARY **Eight patients with acute and chronic alcoholism and liver disease, who suffered one or more episodes of acute thrombocytopenic purpura after heavy alcoholic intake, are described. Recovery was rapid after withdrawal from alcohol, and the use of corticosteroids did not appear to alter their course. Folic acid deficiency, splenic pooling of platelets, and massive hemorrhage do not appear to be causal factors. The possible role of excessive coagulation and a direct effect of alcohol on the bone marrow or circulating platelet are discussed.**

THROMBOCYTOPENIA ACCOMPANYING advanced hepatic cirrhosis is well-known. It is usually associated with leukopenia and anemia and is attributed to hypersplenism. Improvement in the blood picture occurs after splenectomy or relief of the portal hypertension by a shunting procedure. Transient hemolytic anemia (1) and decreased granulocytic reserve (2) have been described in patients who are consuming large amounts of alcohol, but it is not generally recognized that a transient thrombocytopenic syndrome with purpura and other hemorrhagic manifestations may also occur. Palpable splenomegaly, anemia, and leukopenia are not consistently found, and recovery is spontaneous after hospitalization and withdrawal of alcohol. This paper describes a group of patients with this entity and discusses the etiology in relation to known causes of thrombocytopenia and a possible direct effect of alcohol on the bone marrow or the circulating platelet.

MATERIALS AND METHODS

Eight patients with acute thrombocytopenic purpura, a history of chronic alcoholism, and very heavy alcohol intake just before admission to Boston City Hospital are included in this study. Six patients were men and two, women. The age range was 24 to 52 years.

Platelet counts were done by phase contrast microscopy (3). Platelet survival studies were done with autologous ^{51}Cr-labeled platelets (4). Normal recovery of labeled platelets 2 hr after infusion is 60 to 80%. Normal survival is 9 to 11 days. Fibrinogen was measured by Dr. H. S. Sise, Coagulation Laboratory, Boston City Hospital, and serum folate and vitamin B_{12} were measured by Dr. R. R. Strieff, Thorndike Memorial Laboratory, Boston City Hospital, by previously described methods (5–7).

RESULTS

The clinical and admission hematological data of the entire group of patients are summarized in Table 1. Complete hematological data of Patient 6 (V. P.) are shown in Figure 1. The hematological course of the eighth thrombocytopenic episode documented in Patient 7 (F. K.) is shown in Figure 2. Hepatomegaly was present in all patients, and three patients had palpable spleens. None of the patients had a past history of gastrointestinal surgery or a hemorrhagic disorder, and no history of exposure to myelotoxic agents other than alcohol or to drugs that may produce thrombocytopenia could be obtained. Twenty episodes of thrombocytopenia were observed in this group. Platelet counts were

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TABLE 1. Clinical and Admission Hematological Data in Eight Patients with Thrombocytopenia

Patient	Age Sex	Physical Findings	Thrombocytopenic Episodes	Hematocrit	Leukocyte Count	Platelet Count	Bone Marrow	Specific Therapy	Resolution Time
	yr		*no.*	%		*/mm³*			*days*
1. R. P.	47 M	Hepatomegaly, purpura, fracture of forearm, delirium tremens	2	34 28	5,500 6,000	14,000 22,000	Normoblastic, many megakaryocytes (both episodes)	None	18 9
2. G. M.	37 M	Hepatomegaly, splenomegaly, epistaxis, purpura	1	42	5,240	62,000	Normoblastic, normal megakaryocytes	Prednisone	6
3. C. L.	40 F	Hepatomegaly, purpura, melena, delirium tremens	3	40 41 35	4,800 7,550 6,800	32,000 40,000 on smear	Normoblastic, many megakaryocytes (2 episodes)	Prednisone None None	7 5 6
4. M. H.	44 F	Hepatomegaly, purpura	1	38	4,250	49,000	———	None	7
5. M. P.	52 M	Hepatomegaly, purpura, hematoma of tongue, delirium tremens	1	44	9,800	50,000	Normoblastic, normal megakaryocytes	Prednisone	10
6. V. P.	47 M	Hepatomegaly, splenomegaly, purpura, melena	2	27 28	5,000 3,700	42,000 9,000	Normoblastic, many megakaryocytes (both episodes)	Folic acid None	6 10
7. F. K.	51 M	Hepatomegaly, purpura, delirium tremens	8	40–45	4,950–6,200	10,000–38,000	Normoblastic, many megakaryocytes (4 episodes)	Prednisone (2 episodes)	5–20
8. W. N.	24 M	Hepatomegaly, splenomegaly, purpura, melena, delirium tremens	2	40 27	7,500 5,700	58,000 20,000	Normoblastic, many megakaryocytes, occasional vacuoles, red cell precursors (2nd admission)	None None	7 12

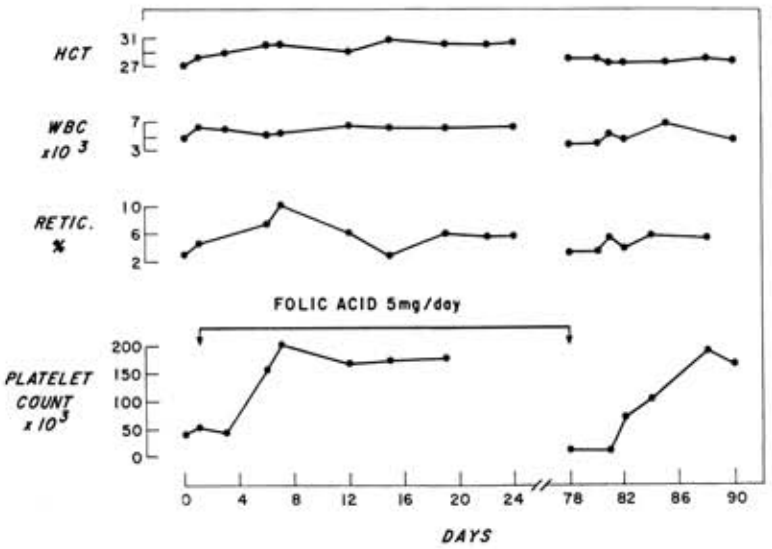

FIGURE 1. Hematological data, Patient 6 (V. P.). Folic acid therapy was continued by the patient between hospital admissions as evidenced by a high serum folate (see text). Nevertheless, he had recurrent thrombocytopenia. Hct = hematocrit; WBC = leukocyte count; retic. = reticulocytes.

usually below 50,000/mm³, and purpura was present. Three patients were anemic, and slight leukopenia was occasionally observed. Liver function tests in all patients were consistent with acute alcoholic liver disease and improved with the patients' general clinical improvement. Splenomegaly seemed to reflect the state of the patients' liver rather than the severity or the course of the thrombocytopenia. Delerium tremens was a frequent occurrence. Serum folate levels were measured in two patients (V. P. and W. M.): Patient W. M. had a normal level; V. P. had a low level on his first admission and a very high level during his second thrombocytopenic episode, which occurred while he was taking 5 mg of folic acid daily (Figure 1). Vitamin B_{12} levels were normal in both patients. Bone marrow was aspirated in all but one patient. The specimens were obtained within 24 hr of admission and showed no megaloblastic changes; megakaryocytes were normal or increased in number. In addition, no patient was included in this study if hypersegmentation of the peripheral polymorphonuclear leukocytes was noted. Lupus erythematosus preparations and antinuclear antibody tests, when done, were negative. Tests for antibodies to platelets were not done. Fibrinogen was measured in Patients V. P. and W. M. and was normal. Platelet survival studies were done on

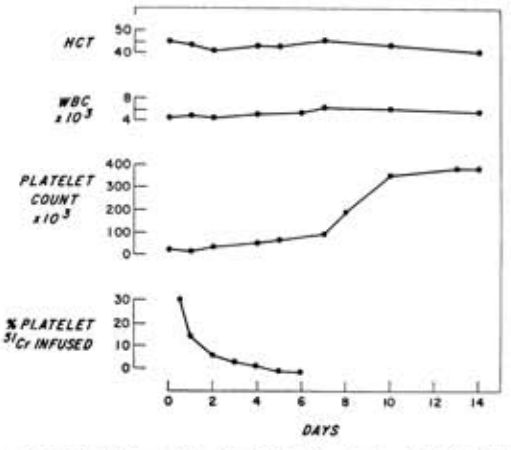

FIGURE 2. Hematological data in Patient 7 (F. K.) for his eighth thrombocytopenic episode. Platelet counts rapidly returned to normal levels. Platelet survival was initially short. Hct = hematocrit; WBC = leukocyte count.

Patient F. K. on two occasions. The first study, done while the platelet count was rising, was 9 days. The second study (Figure 2) was begun 12 hr after the patient's most recent admission. The platelet count remained low (15,000 to 25,000/mm^3) for 3 days and then began to rise. Survival during this period was 5 days, with a 2-hr recovery of 30%. To determine the effect of alcohol on circulating platelets, two patients were infused with 2,000 ml of a 5% ethanol solution at a rate of approximately 11 ml/min, and serial platelet counts were done. As previously reported (8), on three separate occasions Patient C. L. had a fall in platelet count to 10, 25, and 40% 4 to 6 hr after the infusion was begun. These studies were undertaken after the patient's platelet count had remained normal for 3 days. The platelet count remained normal during the periods between ethanol infusions which were separated by 5 to 7 days, and significant variation in platelet count could not be demonstrated on one day when ethanol was not administered. On one occasion autologous platelets were labeled with ^{51}Cr and reinfused before the administration of ethanol. The fall in platelet radioactivity paralleled the fall in platelet count. Most of the platelet radioactivity returned in 24 hr when the platelet count returned to normal, indicating that temporary platelet sequestration had occurred rather than indicating permanent destruction. Scanning did not show significant change in hepatic or splenic radioactivity. This indicated that these organs were not the site of platelet sequestration. The second patient, F. K., had no change in platelet count in response to similar quantities of ethanol.

Corticosteroid therapy was administered to four patients on five different occasions. The recovery rate did not differ from that seen in those who were not treated with steroids (Table 2). The resolution time, which refers to the time from admission to the day when a normal platelet count was obtained (150,000 platelets/mm^3), was rapid (5 to 20 days) with or without specific therapy, and there were no serious sequels. No patients had progression of hemorrhagic manifestations during their hospital course.

TABLE 2. Comparison of Patients Treated with Corticosteroids and Untreated Patients

	Treated Patients	Untreated Patients
Number of episodes	5	15
Resolution time, *days*	5–13	5–20
Complications	None	None

DISCUSSION

A group of patients has been described with acute and chronic alcoholism, hepatomegaly, abnormal liver function tests, and acute transient thrombocytopenic purpura. The acute nature of the thrombocytopenia in these patients and the rapid remission after hospitalization are in sharp contrast to the chronic thrombocytopenia seen in patients with advanced liver disease. At present a number of specific factors are known to cause thrombocytopenia in patients with alcoholism. These include folic acid deficiency (9), splenic pooling of platelets (10), massive hemorrhage (11), and intravascular coagulation (12).

A deficiency of folic acid cannot be excluded fully as a cause for this syndrome. However, only patients without megaloblastic changes in bone marrow specimens that were obtained shortly after admission and only those with no hypersegmentation of the peripheral polymorphonuclear cells were included in this study. It is theoretically possible that hospital diet brought about complete reversal of megaloblastic changes in the marrow before aspiration was performed; however, while megaloblastic bone marrow may revert to normal within hours after administration of folic acid either by medication or by normal diet, some morphologic evidence usually

remains in the first 24 hr. Moreover, hypersegmentation of peripheral polymorphonuclear cells is a very sensitive indication of folic acid or vitamin B_{12} deficiency (13) and persists after the bone marrow morphology has returned to normal. Serum folate was low in one patient (V. P.) with anemia. He was treated with folic acid and had a significant rise in reticulocyte count, a modest rise in hematocrit, and a return of platelet count to normal levels (Figure 1). He had a second episode of thrombocytopenia while consuming large amounts of alcohol and taking large doses of folic acid. Serum folate during the second thrombocytopenic episode was greater than 300 ng/ml (normal 7 to 15.9 ng/ml). Vitamin B_{12} deficiency is very unusual on a dietary basis even in alcoholics unless there is preexistent alteration of their gastrointestinal tract; however, it may occur in patients with prolonged alcoholism and gastritis that has resulted in gastric atrophy and intrinsic factor deficiency. Moreover, such patients present with megaloblastic anemia and hypersegmented polymorphonuclear cells. Like persons with Addisonian pernicious anemia, these patients fail to respond to oral vitamin B_{12} (14). Thus, severe thrombocytopenia would be extremely unlikely without other evidence of a megaloblastic process.

Chronic thrombocytopenia in cirrhotic patients with large spleens has been related to the accumulation of large numbers of platelets in an exchangeable splenic platelet pool with no decrease in platelet lifespan (10). Although portal venous pressure decreases with histologic improvement in patients with acute fatty liver (15), very marked changes in the splenic platelet pool would have to occur within a short period of time to account for the rapid improvement in observed platelet count. In addition, the degree of splenomegaly usually associated with excessive pooling of platelets was not present in most of our patients. Thus, it is unlikely that splenic pooling of platelets was a factor in this syndrome.

Patients with liver disease have low platelet counts during massive gastrointestinal hemorrhage and are unable to respond in platelet numbers during the posthemorrhage period as well as patients without liver disease (11). However, none of the present group of patients bled massively. One patient lost a large amount of blood in a fracture site but did not require transfusions.

Consumption of platelets by excessive coagulation has also been suggested as a cause of thrombocytopenia. Increased fibrin split products (16), decreased half-life of fibrinogen (17), increased fibrinolysin inhibitors (18), and case reports of thrombocytopenia and hypofibrinogenemia responding to the administration of heparin (17, 19) have all been reported in patients with cirrhosis. Recent studies have demonstrated decreased platelet aggregation in patients with advanced liver disease and thrombocytopenia (20). Excessive fibrinolysis that results in increased amounts of fibrin split products was suggested as being responsible for the impaired aggregation. Therefore, there is evidence to suggest that the thrombocytopenia in some patients with liver disease may be related to fibrinolysis or excessive coagulation, two processes that are often difficult to separate clinically. Data to support such a mechanism in our patients are not available. In two patients studied (W. N. and R. P.), fibrinogen levels were normal.

Suppression of hemopoiesis by alcohol has been demonstrated in animals (21) and in man (22), and abnormal vacuolization of the red cell precursors has been noted in patients with acute alcoholism (23). In addition, alcohol affects several metabolic pathways including epinephrine metabolism (24) and serotonin degradation (25) that may influence circulating platelets. The possibility of a direct effect of alcohol

on the circulating platelet is intriguing. The response of Patient C. L. to ethanol infusion suggests this possibility. Moreover, a case has been described in which a shortened platelet survival occurred with the administration of large amounts of alcohol but returned to normal when the alcohol was withdrawn (22). Slightly shortened platelet survival in one of our patients (F. K.) and in the above patient may be due to a direct effect of alcohol. Continued intake of alcohol may be necessary to show a markedly shortened survival time.

The similarity in the clinical course of this group of patients with hepatic enlargement, abnormal liver function tests, and thrombocytopenic purpura suggests a common cause. Folic acid deficiency, splenic pooling of platelets, and hemorrhage do not appear to be primary causal factors, although, as previously mentioned, a dietary deficiency cannot be excluded. Excessive coagulation may play a role, and a direct effect of alcohol on the circulating platelet is suggested by the results of alcohol infusion studies in one patient. The possibility of antibodies against platelets induced by alcohol or its contaminants was not explored. It appears possible that alcohol induces a transiently toxic environment for platelets, and it is tempting to draw an analogy to the syndrome of alcoholism, hyperlipidemia, hemolytic anemia, and liver disease in which transient abnormalities in erythrocyte lipids have been recently demonstrated (26).

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