Hemorrhagic Thrombocythemia; Control of Postsplenectomy Thrombocytosis with Melphalan

By THOMAS A. BENSINGER, GERALD L. LOGUE AND R. WAYNE RUNDLES

Hemorrhagic thrombocythemia is a relatively well-defined myeloproliferative disease in which the major abnormality is the excessive production of megakaryocytes and platelets. In its natural evolution acute and chronic bleeding from the gastrointestinal tract, thromboembolic phenomena, gastric and esophageal varices, and infarction atrophy of the spleen are the important clinical features. Disastrous complications may follow splenectomy. Removal of the spleen by surgery, or infarction and atrophy allows masses of platelets to circulate which produce thrombi or emboli in small vessels and ultimately hemorrhage. Effective treatment requires the suppression of megakaryocyte growth and thrombopoiesis. In four patients who developed severe postsplenectomy hemorrhagic thrombocythemia, melphalan (L-phenylalanine mustard) therapy effectively controlled the abnormal thrombocytosis and clinical evidence of disease.

A VARIETY of myeloproliferative diseases in which the major abnormality is the excessive production of megakaryocytes and platelets was first defined as a clinical entity by Epstein and Goedel in 1934.1 The important features of the disease were described as extreme elevation of the platelet count, thromboembolic phenomenon, acute, chronic, and recurrent bleeding from the gastrointestinal tract, anemia and shrunken spleen.

Many case reports have been published since 1934.2-12 Two excellent reviews have emphasized the unique features of the disease, criteria for diagnosis, natural history and complications.5,13 Some benefits from irradiation therapy, 32P, nitrogen mustard compounds and bulsulfan have been reported.5,13

The purpose of the present report is 1) to emphasize the hazard of splenectomy in these patients, since a nearly uncontrollable thrombocytosis may result, and 2) report four patients in whom the extreme thrombocytosis that followed splenectomy was effectively controlled by therapy with L-phenylalanine mustard (melphalan, Alkeran, L-Sarcolysin, C. B. 3025).

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Supported in part by USPHS Grant CA-3177 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare. Generous supplies of melphalan (Alkeran) were provided by Dr. George H. Hitchings, Burroughs Wellcome & Co., Tuckahoe, N. Y.

First submitted September 9, 1969; revised November 24, 1969; accepted for publication January 28, 1970.

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CASE REPORT

P.Y.S., No. B3 9 708. This 54-year-old housewife was first referred to Duke Hospital on July 5, 1962, for diagnostic studies in reference to splenomegaly.

At age seven she had a ruptured appendix and during most of her adult life had recurrent gastrointestinal cramps and bloating. A hysterectomy was done in January 1962 for menorrhagia and during the operation an enlarged spleen was found. In subsequent months her spleen continued to enlarge and this led to her being referred for hematologic study. On physical examination, the only relevant abnormalities were a slightly enlarged liver and a spleen which filled most of the left upper quadrant of the abdomen. Her hemoglobin concentration was 12.3 Gm. per cent, white cell count 8500/cu. mm., packed red cell volume 41.5 per cent, and the platelets 490,000/cu. mm. The formed elements in the peripheral blood appeared normal except for a rare immature granulocyte and an occasional red cell which contained a Howell-Jolly body. X-ray studies of the upper gastrointestinal tract failed to show esophageal varices, but prominent gastric markings were interpreted as possible varices. Bone marrow aspirated from the sternum was very cellular and contained a large number of megakaryocytes. Splenic puncture yielded a dilute specimen with masses of platelets and a few marrow elements. The patient was considered to have an atypical, asymptomatic myeloproliferative disease. Plans were made to keep her under observation.

Examination four months later showed no definite changes in her physical status. Her hemoglobin concentration was 14.0 Gm. per cent, white cell count 14,000/cu.mm., and volume of packed red cells 46.0 per cent. The overlying platelet layer was 2 mm. and the platelet count 1,000,000.

On November 24, 1962, a massive hematemesis occurred without premonitory symptoms. She was treated with blood transfusions and esophageal tamponade. Bleeding ceased after three to four days. A percutaneous splenoportogram showed dilated splenic veins connecting with the gastric varices. She was thought to have thrombosis of the splenic vein and splenectomy was recommended.

At operation on December 10, 1962, a grossly enlarged spleen was found with collateral venous channels extending from it to the upper portion of the stomach. The splenic vein appeared to be thrombosed. The portal pressure was 270 mm. of saline. The spleen was resected and weighed 1030 Gm. Sections showed congestion, diffuse fibrosis and a moderately recent infarct.

On the third postoperative day her white cell count was found to be 36,000/cu. mm. The packed red cell volume was 52.0 per cent and the overlying platelet and white cell layer had risen to 5 mm. There were no major postoperative complications, however, and she returned home after 12 days in the hospital.

One month after the splenectomy she developed abdominal cramps and began to pass gross blood in her stools. On January 10, 1963, the hemoglobin concentration was 12.3 Gm. per cent, volume of packed red cells 44.0 per cent, and the white cell count 22,200/cu. mm. The packed layer of white cells and platelets in the hematocrit tube was 7 mm. In the blood film there was an enormous number of platelets and many erythrocytes contained Howell-Jolly bodies. In view of the gastrointestinal bleeding and thrombocytosis, melphalan therapy was begun (Fig. 1).

The gastrointestinal bleeding stopped, and during the following four months she was substantially well. Her hemoglobin concentration and hematocrit remained normal. The white cell count fell to around 6,500/cu. mm. The layer of packed platelets decreased to less than 1 mm. and the platelet count to 320,000/cu. mm. In September 1963 her home physician considered her well and suspended melphalan therapy.

The patient moved to New York City and was not seen by us again for more than three years. During this time she began to have episodes of gastrointestinal bleeding again, at least once or twice a year, and was hospitalized several times. In addition she developed recurrent pruritic, slightly elevated erythematous plaques lasting for a few days at a time over the posterior aspects of her legs. Diagnostic efforts at various times included repeated gastrointestinal X-ray examinations, elaborate studies of her clotting mechanism and catheriza-
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Fig. 1.—Control of postsplenectomy leukocytosis and thrombocytosis in P.Y.S. with melphalan.

tion of the celiac artery, all of which failed to identify the primary abnormality. Another surgical exploration was advised.

She returned to Duke Hospital in May 1966. The only relevant physical abnormalities were hepatomegaly and erythematous plaques on the posterior aspects of her thighs. The hemoglobin concentration was 10.3 Gm. per cent, the volume of packed red cells 36.0 per cent, and white cell count 31,900/cu. mm. The packed layer of white cells and platelets was 5 mm. Melphalan therapy was reinstituted (Fig. 1).

During the next three years she had no further gastrointestinal bleeding or skin abnormalities. Her hematologic status has been virtually normal.

S.N.D., H5 2 744. This 67-year-old widow was referred to Duke Hospital in January 1969 for diagnostic studies in reference to severe anemia and gastrointestinal bleeding which developed one to two months after splenectomy.

In 1963 she began to have episodes of confusion, headaches and amblyopia. She was found to have fluctuating arterial hypertension and hemorrhoids. After the latter were removed she developed thrombophlebitis and bilateral varicose veins. In 1964 a cholecystectomy was performed. Stones were not present and postoperatively she had acute thrombophlebitis again and pulmonary emboli. She continued to be chronically ill and, in August 1968, extreme malaise, fatigue and abdominal swelling led to further diagnostic studies at her community hospital.

On physical examination the major abnormality was an enlarged spleen. Her hemoglobin concentration was 15.3 Gm. per cent, volume of packed red cells 51.0 per cent and white cell count 15,500/cu. mm. The formed elements in the peripheral film appeared to be normal. Aspirated bone marrow was normally cellular and contained an enormous number of megakaryocytes.

Splenectomy was performed on October 28, 1969, mainly to establish a diagnosis. The
spleen weighed 850 Gm. and sections showed chronic congestion with many megakaryocytes. The patient recovered from the splenectomy without difficulty. Within one to two days, though, she developed a leukocytosis of over 50,000 and thrombocytosis. After returning home she began to have dark stools and symptoms of anemia. Ten weeks after splenectomy, when she was found to have a hemoglobin concentration of 4.4 Gm. per cent, she was referred to Duke Hospital for hematologic consultation.

On examination she appeared chronically ill, pale, and undernourished. Except for moderate hepatomegaly and varicose veins, there were no relevant physical abnormalities. Soon after admission to the hospital she was transfused with four units of packed red cells. Her hemoglobin concentration then was 9.0 Gm. per cent, volume of packed red cells 34.5 per cent and the white cell count 93,400/cu.mm. The packed white cell and platelet layer was 5.5 mm. The platelet count was over 3.0 million. In the peripheral blood film, many of the platelets were large, poorly stained and clumped. There was an occasional immature granulocyte and many nucleated red cells. Bone marrow aspirated from the sternum again was very cellular. In the films there was a great increase in number of megakaryocytes with an abundance of adherent platelets. No stainable iron was present.

She was given two additional blood transfusions, intramuscular iron injections and melphalan chemotherapy. The initial dose was 6 to 10 mg. daily and after a month 2 mg. daily. During the first few days of therapy the packed layer of platelets ranged up to 10 mm. She continued to have brisk gastrointestinal bleeding and on many days she complained that central vision was very blurred. Repeated funduscopic examinations showed no striking abnormalities. After three weeks in the hospital her gastrointestinal bleeding had almost stopped and she was able to return home. Her hemoglobin concentration was 10.7 Gm. per cent, and white cell count 11,600/cu.mm. The packed layer of platelets had fallen to 1.5 mm. at this time and the platelet count to 90,000/cu.mm. The patient regained her strength rapidly and during the following eight months felt well. She had no further visual trouble or headaches. Her hemoglobin level and hematocrit rose to normal. The white cell count was held around 5-6,000/cu.mm. The packed platelet layer fell to less than 1 mm. with the platelet count ranging around 230-270,000/cu.mm.

C.R., G3 8 685. This 41-year-old housewife was admitted to Duke Hospital on June 1, 1969, to consider establishing a venacava shunt for the treatment of portal hypertension associated with recurrent gastrointestinal bleeding.

Her previous medical history was most remarkable. In late 1962, her family surgeon discovered a mass in her left abdomen. A few weeks later at laparotomy, an enlarged spleen was found and removed. The pathologist's interpretation was “congestion,” but a later review showed the presence of numerous megakaryocytes and normoblasts. Three months after the splenectomy she began to have recurrent episodes of acute and chronic gastrointestinal bleeding. These continued for seven years.

In 1964 an abdominal exploration was performed in an attempt to find a bleeding site. None was discovered. The portal vein could not be identified at operation. The inferior mesenteric vein was anastamosed to the renal vein. Melena continued after the operation and in the fall of 1965 she vomited bright red blood. Esophageal varices were demonstrated by X-ray studies and esophagoscopy following which a partial esophagectomy was done. In the summer of 1968 celiac and superior mesenteric angiography was done during an episode of gastrointestinal hemorrhage. Bleeding into the antrum of the stomach was demonstrated. In February 1969 angiographic studies again showed brisk bleeding into the stomach, thereupon partial gastrectomy was carried out. After the operation she continued to have impaired health, weight loss and black tarry stools. During the seven years of her illness she had been given more than 80 blood transfusions.

On physical examination the relevant findings were multiple abdominal scars and a moderately enlarged liver. Stools contained occult blood. Her hemoglobin concentration was 9.9 Gm. per cent, white cell 19,000/cu.mm., and volume of packed red cells 29.0 per cent with a 4.5 mm. overlying layer of platelets and white cells.

In the aspirated bone marrow there were large clumps of platelets and megakaryocytes. Other marrow elements were scarce. There was no stainable iron. Sections of bone marrow
obtained from the posterior iliac spine showed a hypercellular marrow, some fibrosis and a greatly increased number of megakaryocytes.

Melphalan therapy was begun with a dose of 6 to 10 mg. daily for three weeks and then 2 mg. daily. During four weeks of hospitalization she developed thrombophlebitis at the left ankle for the first time and symptoms of pulmonary embolism. She was given heparin for seven days without complication and during this time the gastrointestinal bleeding ceased. At the time of discharge the hemoglobin concentration was 9.4 Gm. per cent, white cell count 9,260/cu.mm. and the platelet layer was 1.5 mm.

During the next two months at home she gained six pounds in weight. She had no further gastrointestinal bleeding. Her hemoglobin concentration returned to normal and the platelet count was 510,000/cu.mm.

W.B.E., G4 0 974. This 48-year-old carpenter was first seen at Duke Hospital in January 1965 for studies in reference to postsplenectomy anemia, a high platelet count and gastrointestinal bleeding. Early in life he had good health. Bleeding hemorrhoids developed in his late 30's and were removed in February 1962. He was well then until November 1963 when he developed severe pain in his left upper abdomen and was found to have an enlarged spleen. His hemoglobin concentration was 17.2 Gm. per cent, volume of packed red cells 48.0 per cent and white cell count 7900/cu.mm. Lymphoma was suspected and splenectomy undertaken. The spleen weighed 1000 Gm., but sections showed no diagnostic features. His postoperative convalescence was prolonged by the development of a subdiaphragmatic abscess, which drained intermittently for nine months. An incisional hernia developed.

One year later, when he was admitted to his community hospital for repair of the hernia, he was found to be anemic. The hemoglobin concentration was 8.0 Gm. per cent, volume of packed red cells 29.0 per cent and white cell count 16,250/cu.mm. The platelet count was increased to 1.9–2.7 million/cu.mm. He was given four blood transfusions and the hernia repair postponed pending further hematologic studies.

On his first visit to Duke Hospital there were no relevant physical abnormalities other than a palpable liver and a large incisional hernia. His hemoglobin concentration was 11.1 Gm. per cent, white cell count was 17,130/cu.mm., and volume of packed red cells 40.0 per cent with a 5.5 mm. layer of overlying platelets. In the blood film masses of platelets were adherent to megakaryocyte nuclei. Aspirated sternal marrow was cellular and contained a greatly increased number of young and mature megakaryocytes. There was no stainable iron.

Melphalan therapy was instituted with a dose of 4 mg. daily for two months which was then reduced to 2 mg. daily. Two months later he was entirely well and working 12–14 hours per day. His hemoglobin concentration was 14.9 Gm. per cent, white cell count 4,175/cu.mm., volume of packed red cells 51.0 per cent and packed platelet layer 1 mm. The platelet count was 615,000/cu.mm.

He was then lost to our followup for over two years. The incisional hernia was repaired in September 1965 uneventfully and in July 1966 his gall bladder was removed. During this time melphalan therapy was suspended. In October 1966 he began to have recurrent gastrointestinal bleeding and during the next eight months was hospitalized on six occasions. He was given blood transfusions each time and had another surgical exploration in attempt to identify a site of bleeding.

On the occasion of his seventh episode of gastrointestinal bleeding, on May 20, 1967, he returned to Duke Hospital. His hemoglobin concentration was 9.5 Gm. per cent, volume of packed red cells 34.0 per cent and white cell count 13,300/cu.mm. The layer of packed white cells and platelets was 6 mm. and the platelet count was 1,810,000/cu.mm.

X-ray studies of the gastrointestinal tract and sigmoidoscopic examination showed no evidence of localized disease.

Melphalan therapy was resumed and oral iron administration begun. During an eleven day stay in the hospital the bleeding stopped. His hematologic status improved and became normal in a matter of three to four months. The platelet count continued to range around 400,000/cu.mm. During the next one-and-one-half years, with maintained chemo-
therapy, there has been no further evidence of gastrointestinal bleeding. He has continued to work full time.

**DISCUSSION**

The diagnosis of hemorrhagic thrombocythemia is usually not made very early in the course of the disease, often not until after splenectomy, and even may be overlooked after major thromboembolic or bleeding abnormalities have developed. Bleeding is usually the first symptom and enlargement of the spleen the first physical sign. Splenomegaly may be discovered at a time when the peripheral blood is normal, except for minimal thrombocytosis, perhaps, or neutrophilic leukocytosis with a small percentage of immature granulocytes. The distinctive finding, an increased number of megakaryocytes in the bone marrow is difficult to quantitate and the apparent number of platelets produced may be modified by splenic activity. Splenectomy in individuals with a normal bone marrow produces some thrombocytosis but in this myeloproliferative disease it produces a thrombocytosis five to 10 times as great. There is no absolute hard and fast line of diagnostic demarkation between hemorrhagic thrombocythemia and instances of mild polycythemia vera with conspicuous thrombocytosis. Some overlapping of manifestations is characteristic in the myeloproliferative diseases and the consequences of splenectomy would be substantially the same in patients with comparable degrees of excessive megakaryocyte activity as illustrated by the fatal case cited by Gilbert.14

As the natural history of hemorrhagic thrombocythemia unfolds, acute, chronic or recurrent gastrointestinal bleeding, without identifiable local lesions frequently becomes the major problem. Occasionally the appearance of esophageal or gastric varices complicates the diagnostic problem. Infarction atrophy of the spleen, a unique feature of this myeloproliferative disease, probably occurs more frequently than heretofore recognized.15 As this occurs a large spleen is reduced to a nubbin. As spleen function becomes compromised, thrombocytosis and granulocytosis become more pronounced. The presence of target cells and Howell–Jolly bodies in the red cells may indicate the development of "hyposplenism."16,17 Marsh and colleagues have shown in such patients that the removal of Cr-labeled heat damaged red cells from the circulating blood by splenic sequestration is impaired.15

It is tempting and sometimes wise clinical judgment to recommend removal of an enlarged spleen when the underlying diagnosis cannot be ascertained. Splenectomy is sometimes done, too, when splenomegaly is discovered during surgery undertaken for other reasons. In patients with occult thrombocythemia and related myeloproliferative diseases, removal of the spleen may unleash a striking leukocytosis, thrombocytosis, and rarely erythrocytosis. This response to splenectomy may be the first tangible indication that a myeloproliferative abnormality is present. The postsplenectomy thrombocytosis and leukocytosis in these patients is much greater than that which develops after splenectomy in individuals with normal bone marrow.16,18 The high counts persist indefinitely and may become progressively more severe, regardless of the presence or absence of anemia.19 The immediate risk of splenectomy in patients
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with thrombocythemia does not seem to be excessive, but after a few weeks of sustained thrombocytosis, acute or chronic gastrointestinal bleeding or thromboembolic phenomenon are likely to develop. The initiation of appropriate therapy before serious complications develop is a matter of considerable urgency. The hazard of splenectomy in these patients, converting a mild relatively benign thrombocythemia into a serious hemorrhagic thrombocythemia, has been noted by Gunz, Crosby, Wintrobe, and others.

The platelet morphology in patients with thrombocythemia is often grossly abnormal. Giant forms, pleomorphism, irregularity in staining, and clumps of platelets adhering to megakaryocyte nuclei are common. The large and variable size of the platelets and their tendency to clump together make counting inaccurate or virtually impossible. With moderate or extreme thrombocytosis, the best measure of platelet mass is the thickness of the packed platelet layer overlying the leukocytes and red cells in a macrohematocrit tube.

Abnormal platelet function appears to be a characteristic of hemorrhagic thrombocythemia. Hardisty and Wolff found that thromboplastin generation from platelets was slow and subnormal in patients with abnormal bleeding. McClure and associates found that platelets from patients with thrombocythemia, some of whom had polycythemia vera, had reduced adhesiveness, reduced 5-hydroxytryptamine content and uptake, and reduced ATP. The clotting activity of intact platelets was reduced while that of lysed platelets was normal. These findings were interpreted to mean that the platelet surface was abnormal. Spaet and colleagues found platelet aggregation diminished in response to ADP, virtually no response to epinephrine, but normal responses with collagen. Serotonin uptake was variable.

The life span of platelets in thrombocythemia, recently studied by Harker and Finch, appears to be normal in most instances. The megakaryocyte mass was increased from two to 15 times normal, in proportion to the increased number of platelets. Ineffective thrombopoiesis was found in one patient. Similar findings were present in patients with polycythemia vera.

Thrombocythemia of at least moderate degree occurs in about half of all the patients with untreated granulocytic leukemia and in many patients with polycythemia vera, myeloid metaplasia, myelofibrosis and myelosclerosis. The one striking difference between hemorrhagic thrombocythemia and other myeloproliferative disorders concerns the spleen. In nearly half of all patients reported with hemorrhagic thrombocythemia, the spleen had either been removed or was atrophic. In the surgical specimens congestion, fibrosis, and infarction have been the outstanding findings and repeated infarctions lead to splenic atrophy or autosplenectomy. When the spleen is removed, either by infarction or surgery, platelets are no longer sequestered but circulate in masses which may form thrombi or emboli in small blood vessels, and finally infarction and hemorrhage.

The therapeutic problem in hemorrhagic thrombocythemia is similar to that in other myeloproliferative diseases in which excessive thrombocytosis is a major feature and requires the judicious suppression of bone marrow function by irradiation or chemical agents. Whole body irradiation, nitrogen
mustard and derivatives, busulfan and antimetabolites have been used by various investigators. The rarity of the disease, its variation in severity and mode of evolution and the frequency of acute complications, make accurate comparison of different therapeutic agents almost impossible.

In 1960–61 a series of studies regarding the effect of nitrogen mustard compounds in various hematopoietic malignancies led us to undertake a comprehensive study of L-phenylalanine mustard (melphalan, Alkeran, L-Sarcolysin, C.B. 3025). Beneficial effects at least comparable and possibly superior to those of standard agents were observed in a number of myeloproliferative diseases, among them hemorrhagic thrombocythemia. Detailed reports of studies in other diseases will be made elsewhere.23,24

In the four patients whose case histories are summarized above, spectacular thrombocytosis followed splenectomy. Melphalan chemotherapy was effective in controlling the excessive platelet proliferation and associated clinical complications in each. Relapses followed the suspension of therapy and control reestablished by resuming treatment. As in the management of patients with polycythemia vera,24 the initial dose of melphalan was 6–10 mg. daily for approximately a week and then 4–6 mg. daily for two to four weeks. The long-term maintenance dose averaged around 2–4 mg. per week. With reasonable attention to regulating the dose of melphalan in reference to its hematologic effects, the chemical can be used safely for an indefinite period of time.

REFERENCES

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