Anemia and Thrombocytopenia in a 63-Year-Old Man

Stenographic reports of weekly clinicopathologic conferences held in Barnes and Wohl Hospitals are published in each issue of the *Journal*. Members of the Departments of Internal Medicine, Radiology, and Pathology of the Washington University School of Medicine participate jointly in these conferences. Kenneth M. Ludmerer, M.D., and John M. Kissane, M.D., are the editors of this feature.

A 63-year-old white man was admitted to Barnes Hospital on March 2, 1982, for evaluation of anemia and thrombocytopenia.

The patient had enjoyed good health all his life until approximately one year before admission, when he noted easy bruisability. Six weeks before admission he began to feel progressively more fatigued, and malaise, chronic nausea, and early satiety developed. Around that time he also experienced a prolonged nosebleed that was treated with packing and a four-day course of penicillin. Four weeks before admission dyspnea on exertion, which continued to worsen, and nocturia developed. In addition, he began to experience frequent shortness of breath; these episodes were brought on by exertion and relieved by rest. Except for a weight loss of six pounds, he denied other symptoms, including melena. He had been taking no medications and did not use alcohol.

Physical examination at the time of admission revealed an obese man in no distress. The blood pressure was 110/60 mm Hg and the pulse rate 105 beats/min, without orthostasis. Except for pale conjunctivae and a II/VI systolic murmur at the left sternal border, the results of the remainder of the examination were normal. Results of examination of the stool were negative for occult blood. Results of laboratory studies included a hemoglobin level of 5.1 g/dl, a hematocrit value of 16.2 percent, a mean corpuscular volume of 54 μ^3, a white blood cell count of 5,200/mm^3, a platelet count of 17,000/mm^3, and a reticulocyte count of 4 percent. The peripheral smear showed marked hypochromia and microcytosis as well as moderate poikilocytosis and anisocytosis. Large immature platelets and occasional teardrop cells were seen. The white cell differential was normal. A screen for disseminated intravascular coagulation was negative, and the results of urinalysis were normal. Routine chemistries were unremarkable, as were the chest X-ray and electrocardiogram. A bone marrow aspirate showed marked megakaryocytic and erythroid hyperplasia and no stainable iron. The impression was probable idiopathic thrombocytopenic purpura; treatment with prednisone was begun (100 mg four times a day) and the patient was given transfusions of 4 units of packed cells.

After admission, results of additional studies included a serum iron level of 22 μg/dl, an iron binding capacity of 313 μg/dl, and negative results of collagen vascular evaluation. An upper gastrointestinal series showed prominent rugal folds in the body and antrum of the stomach, which were believed to be either a normal variant or consistent with gastritis. The upper gastrointestinal series also demonstrated esophageal reflux, which cleared rapidly, and no evidence of ulceration. A barium enema showed multiple diverticuli. Initially, the patient's platelet count increased to 89,000/mm^3 but then decreased to 30,000/mm^3. Oral iron therapy was begun, and brisk reticulocytosis ensued. After two weeks of persistent thrombocytopenia, the patient was scheduled for splenectomy.

CLINICAL DISCUSSION

Dr. Philip Majerus: This man was apparently in good health until a year before admission, when he noted easy bruisability. He had a six-pound weight loss, although he was obese. There was no history of alcohol ingestion. Important features of the admitting physical examination included the fact that there were no postural changes in his blood pressure and no petechiae. His heart and lungs were normal and his spleen was not felt. His stool was guaiac positive and negative on various examinations. A bone marrow examination performed on the day of admission showed hypercellular marrow with erythroid and megakaryocyte hyperplasia. He was thought to have idiopathic thrombocytopenic purpura and was treated with prednisone (100 mg four times a day) and 4 units of packed erythrocytes. A couple of days later, blood drawn on admission showed a serum iron level of 22 μg/dl and a total iron binding capacity of 313 μg/dl. His platelet count during prednisone therapy ranged between 89,000 and 30,000/mm^3. He had prompt reticulocytosis after the institution of iron therapy. Two weeks after admission we were told that he was "scheduled for a splenectomy."

Today's discussion is going to be short. Let us begin by considering the possibility that this patient had something other than idiopathic thrombocytopenic purpura. The major, nonautoimmune causes of thrombocytopenia associated with normal megakaryocytes in the bone marrow fall into five categories. The first is infiltrative diseases of the spleen. Among these are a variety of tumors, such as hemangiomas, lymphomas, and even hamartomas of the spleen. Other infiltrations, such as Gaucher's disease, also fit into this category. The mechanism by which these disorders cause thrombocytopenia is not well understood, but apparently involves pooling of platelets within the substance of the spleen. It is not really clear that the platelets are phagocytized or are destroyed in the manner in which erythrocytes are destroyed in hypersplenism. The second category includes a variety of causes of hypersplenism, the most common of which would be cryptogenic cirrhosis. Any disorder that results in portal hypertension can lead to secondary splenomegaly and consequent pooling of platelets within the spleen. A variety of chronic infections and inflammatory disorders can produce splenomegaly and thrombocytopenia on a similar basis. The third category of nonimmunologic causes include deficiencies of a number of vitamins that are required for normal thrombocytopoiesis, such as vitamin B_{12}, folic acid, and iron. Although vitamin B_{12} and folic acid deficiency are commonly associated with thrombocytopenia, in today's case they cannot be seriously considered in the differential diagnosis since the patient had normal B_{12} and folate levels. Iron deficiency is considered a cause of thrombocytopenia, although I have never seen thrombocytopenia develop in a patient with simple iron deficiency on that account. In fact, most patients with iron deficiency have thrombocytosis for reasons that are not apparent. The fourth diagnostic category is microangiopathic hemolytic anemia. This condition can be caused by a variety of processes that destroy the formed elements in the blood by turbulent flow or because of some foreign material in the circulation or fibrin strands exposed to blood. These stimuli all lead to platelet activation and accelerated platelet destruction. There really is no evidence for microangiopathic changes in this case. The fifth category includes disorders such as thrombotic thrombocytopenic purpura that are characterized by thrombocytopenia, hemolytic anemia, fever, renal failure, neurologic symptoms, and signs of microangiopathic hemolytic anemia. This patient had none of these signs or symptoms. I will return to this list in a moment.

In trying to sort out any difficult clinical problem, the most important thing to do at the outset is to decide what feature of the case is the most unusual and therefore the most important single finding. If you can figure that out, the rest is relatively easy. In this patient's record, the feature that strikes me as the most important is the mean corpuscular volume of 54 μ^3. This patient had evidence of what appears to be severe microcytic, hypochromic anemia. There are basically only two causes of microcytosis of that degree. One is iron-deficiency anemia and the other is thalassemia. These two possibilities are easily distinguished on the basis of other information that we have in this case. This patient had a very low serum iron level of 22 μg/dl and only 7 percent saturation of his iron binding capacity, findings that are essentially diagnostic of iron-deficiency anemia. Additionally, his bone marrow showed no stainable iron, which is also consistent with that diag-

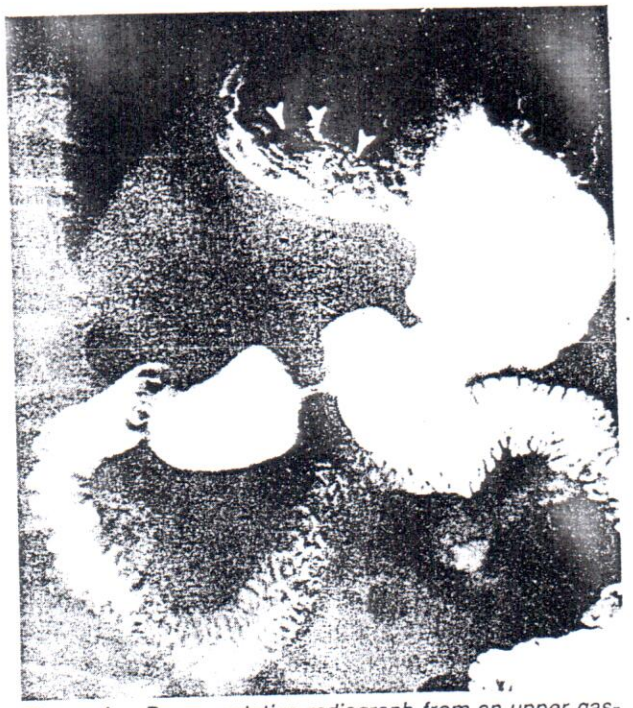

Figure 1. Representative radiograph from an upper gastrointestinal series demonstrates a smooth mass (arrowheads) indenting the gastric lumen along the lesser curvature extending inferiorly from the cardia.

nosis. The final proof was that the patient responded briskly to iron therapy, leaving no question that he had severe iron-deficiency anemia.

What is the prospect of iron-deficiency anemia developing as a result of idiopathic thrombocytopenic purpura? Patients with autoimmune thrombocytopenia have platelets that are completely normal; in fact, some investigators have suggested that platelets in these patients are better than average in that they are young and robust. Our patient's platelet count was never lower than 17,000/mm^3. I think that it is exceedingly unlikely that a patient with a platelet count of 17,000/mm^3 or greater would have spontaneous gastrointestinal bleeding, that is, bleeding from the gastrointestinal tract without some intrinsic lesion. Furthermore, this was an elderly man who had symptoms of bruisability but no other symptoms that could be ascribable to thrombocytopenia in the distant past. When he was admitted to the hospital his hemoglobin level was 5 g/dl. The fact that he was a man in his 60s with no postural changes in blood pressure and relatively asymptomatic with that degree of anemia suggests that this was a process of very long standing. We may be certain that he had been iron deficient and anemic for a considerable length of time. Putting these features together—a patient with insufficient thrombocytopenia to account for a degree of gastrointestinal blood loss that could lead to this severe chronic anemia and the long duration of that condition—leads one to conclude that the patient almost certainly had a gastrointestinal lesion accounting for blood loss. When I went to see Dr. Sagel to go over the X-rays, I burst into his office and said, "The answer to this clinicopathologic discussion is in the gastrointestinal tract. Where is it?" And he told me.

Dr. Stuart S. Sagel: Reanalysis of the upper gastrointestinal series disclosed a definite mass involving the stomach (**Figure 1**). The lesion, seen on multiple projections, extended from the cardia along the lesser curvature and represented more than simply prominent rugal folds. The most likely cause would have been either a lymphoma or a primary adenocarcinoma of the stomach. Conceivably, the mass was secondary to a leiomyosarcoma or an extrinsic lesion pushing upon the stomach.

A radionuclide liver-spleen study demonstrated mild splenomegaly. The liver appeared normal and there was no abnormal bone marrow uptake; therefore, hepatic disease with portal hypertension was unlikely.

Dr. Majerus: So this patient had a mass lesion in the stomach and yet, when he was treated with corticosteroids, his platelet count increased from 17,000/mm^3 to 90,000/mm^3, which provides evidence of an immunologic basis for his thrombocytopenia. Therefore, we must consider the possibility of an autoimmune cause of thrombocytopenia in this patient. I have asked Dr. Varki to review for us the differential diagnosis of autoimmune thrombocytopenia.

Dr. Ajit Varki: Most cases of immune thrombocytopenia (idiopathic thrombocytopenic purpura) are idiopathic; drug-induced cases are probably second in frequency. However, I will confine my remarks to the reports of idiopathic thrombocytopenic purpura associated with other systemic diseases. Before actually going through a list of such disorders, let us first define the best criteria for identifying the existence of such associations. There should be accelerated platelet destruction in the absence of any obvious cause and an appropriate marrow response. A response to corticosteroids and/or splenectomy would provide evidence suggesting an immune basis for the thrombocytopenia. A close temporal relationship between the onset of the associated disorder and the idiopathic thrombocytopenic purpura would further strengthen the case, as would alleviation of the idiopathic thrombocytopenic purpura with successful treatment of the underlying condition. If possible, more direct evidence of an immune basis for the thrombocytopenia would be preferable, such as the demonstration of increased levels of platelet surface IgG. Ideally, of course, one would like to see a direct demonstration of the molecular basis of the association—for example, a shared antigen or a

common mechanism causing both disorders. In actual fact, most reports in the literature deal only with the temporal association between the clinical syndrome of idiopathic thrombocytopenic purpura and some other disease. Most attempts to analyze response to therapy are confounded by the fact that successful treatment of the other disease (for example, cytotoxic therapy for a lymphoma) could have a direct effect on the course of the idiopathic thrombocytopenic purpura.

With the caveat, then, that we are dealing only with guilt by association rather than with evidence of direct cause-and-effect relationships, we may now list the various disorders that have been reported to cause "secondary" idiopathic thrombocytopenic purpura [1,2]. There is little disagreement that autoimmune disorders such as systemic lupus erythematosus, Hashimoto's thyroiditis, Graves' disease, and scleroderma can be associated with idiopathic thrombocytopenic purpura. Occasional case reports also indicate a temporal relationship between idiopathic thrombocytopenic purpura and granulomatous diseases such as tuberculosis and sarcoidosis. This brings us to the malignancies. There is reasonable evidence of an association between lymphoreticular malignancies (particularly chronic lymphocytic leukemia) and idiopathic thrombocytopenic purpura. With regard to nonlymphoid tumors, however, the picture is far less clear. Before 1979 I could only find a few sporadic case reports of associations between nonlymphoid malignancies and idiopathic thrombocytopenic purpura. These consisted of three cases of bronchogenic carcinoma and one of breast cancer. In 1979, Kim and Boggs [3] reported several additional cases. I will discuss this series in greater detail because I believe it could have some bearing on the case under discussion today. The investigators reviewed the records of 52 patients with the diagnosis of idiopathic thrombocytopenic purpura seen over an eight-year period at the University of Pittsburgh. All of these patients had the typical clinical syndrome of idiopathic thrombocytopenic purpura, with no evidence of other causes of accelerated platelet destruction, such as disseminated intravascular coagulation and sepsis. There were 10 cases in which a malignancy closely preceded, closely followed, or coincided with the onset of the idiopathic thrombocytopenic purpura. Eight of these patients responded transiently to corticosteroids and seven to splenectomy; five experienced a sustained remission. Overall, almost 20 percent of the cases of idiopathic thrombocytopenic purpura reported by Kim and Boggs were associated with a malignancy. Although this rather high incidence could have resulted from a somewhat skewed population seen on a subspecialty referral service, it is of particular note that more than half the tumors were nonlymphoid; three arose from the gastrointestinal tract. Also of interest was another observation: although seven of 10 patients with tumors were over the age of 60, only seven of the remaining 42 patients were older than 60. In summary, then, 50 percent of Kim and Boggs' patients with idiopathic thrombocytopenic purpura over the age of 60 had an associated tumor, and more than half the tumors were of nonlymphoid origin. These figures obviously have some bearing on the case under discussion today.

Dr. Majerus: Let us return for a moment to the list of nonimmunologic causes of thrombocytopenia. The possibility of some disease in the spleen being discovered at the time of surgery seems rather unlikely since the patient had no evidence of splenomegaly of any magnitude, even by liver-spleen scan. Furthermore, it is difficult to see how this could account for the gastrointestinal blood loss. Before I saw the mass in his stomach it seemed to me that another reasonable possibility would be that the patient had cryptogenic cirrhosis with portal hypertension and thrombocytopenia on that basis. One could explain gastrointestinal bleeding in that situation by the fact that he might have had bleeding esophageal varices. Certainly in opposition to that diagnosis, but by no means excluding it, is the fact that chemistries and liver function test results were completely normal and that he had no history of any drinking or liver disease. The positive response to corticosteroids cannot be dismissed, and it seems much more likely that this patient did in fact have autoimmune thrombocytopenia. In the article that Dr. Varki cited [3], it appears that the response to corticosteroids or splenectomy in patients with associated malignancies was the same as in those persons who had the idiopathic autoimmune disorder. Only in the last few years have investigators begun to elucidate the antigenic stimuli and the antigens involved in immune thrombocytopenia. The picture that is emerging is somewhat different from that seen in the autoimmune hemolytic anemias, in which most of the autoantibodies are related to Rh blood group antigens. In the case of platelets, it appears that antibodies are directed against a variety of platelet cell surface antigens [4]. A few years ago Rod McEver, who was working in my laboratory, made monoclonal antibodies directed against platelets in the hope of using them as tools to elucidate various congenital bleeding disorders. He was able to produce a number of monoclonal antibodies, and in the course of so doing he found that three of six cloned antibodies showed cross-reactivity with intestinal epithelial cells. That is, there were antigens apparently shared by platelets and cells in the gastrointestinal tract. None of these three showed the same pattern of immunofluorescence with a variety of human tissues; that is, it was clear that all three were different antigens. Nor were they distinct only to the gastrointestinal tract and

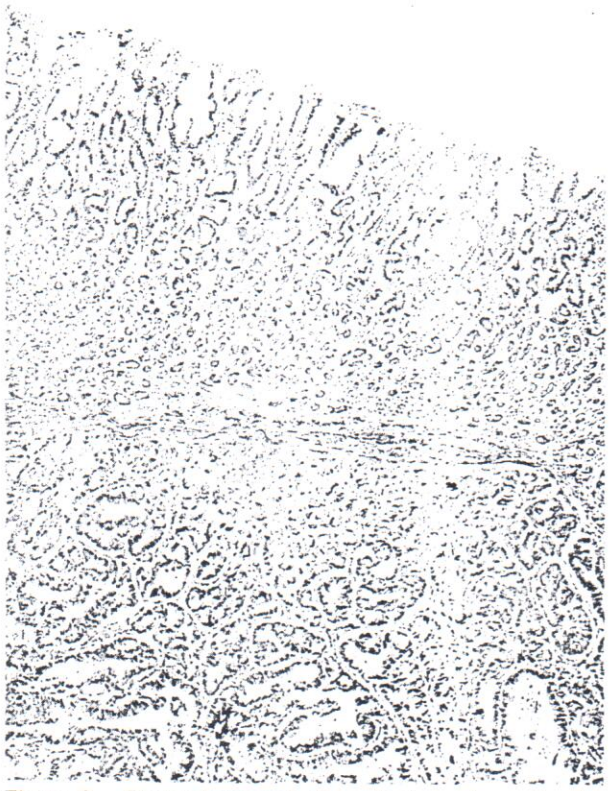

Figure 2. Photomicrograph of surgical specimen showing adenocarcinoma in the submucosa of the stomach (hematoxylin and eosin stain; magnification × 110, reduced by 7 percent).

platelets; each had reactions with some other tissues.

I mention this work to suggest the possibility that conceivably the pathogenesis of our patient's illness was that a malignant neoplasm of the gastrointestinal tract developed that led to the production of antibodies to a gastrointestinal antigen that is not normally exposed to the circulation. Just by chance, this antigen could have cross-reacted with a platelet surface antigen and in this way could have led to the destruction of his platelets. In fact, three of the patients in the report of Kim and Boggs [3] had gastrointestinal neoplasms. It is tempting to push this speculation further by suggesting that this patient had a carcinoma of the stomach and that antibodies common to his stomach cancer and to platelets led to the destruction of his platelets. Since half of the cases of autoimmune thrombocytopenia described by Kim and Boggs were lymphoid malignancies, one would have to consider the possibility that the patient had a lymphoma of the stomach. However, on statistical grounds alone, lymphoma of the stomach occurs 10 or 20 times less frequently than carcinoma of the stomach. Therefore, a carcinoma would be much more likely than a lymphoma. I believe that this patient had an adenocarcinoma of the stomach and that he had autoimmune thrombocytopenia secondary to the carcinoma.

PATHOLOGIC DISCUSSION

Dr. John Kissane: During exploration of the abdomen at laparotomy, a mass was felt in the cardia of the stomach that on frozen section proved to be an adenocarcinoma (**Figure 2**). The carcinoma consisted of a polypoid, exophytic mass, 7 by 5.5 cm, fixed to the muscularis but not involving the serosa. Of two regional lymph nodes excised, one contained metastatic carcinoma. A total gastrectomy was performed with Roux-Y interposition. A grossly normal, 225-gram spleen was also removed. Microscopically it showed only acute leukostasis.

Dr. Majerus: I would caution that my claim of a pathophysiologic association between carcinoma and autoimmune thrombocytopenia is hardly established. One can wonder how many cases of carcinoma might be found if one pulled 10 charts at random of patients in Barnes Hospital over the age of 60. It is possible that this is strictly a chance association.

Final pathologic diagnosis: Adenocarcinoma of the stomach; one of two regional lymph nodes positive for metastatic involvement; acute inflammation of the spleen.

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