Postsplenectomy reactive thrombocytosis

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Thrombocytosis is frequently encountered as an incidental laboratory finding. The most common etiology is reactive (secondary) thrombocytosis due to infections, trauma, surgery, or occult malignancy. Even though thrombocytosis is benign and self-limiting in most cases, it can result in hemorrhage or thrombosis. The hypercoagulable state is characterized by episodes of thrombosis and can be due to inherited or acquired conditions. Extreme thrombocytosis may result in thrombotic events such as acute myocardial infarction, mesenteric vein thrombosis, and pulmonary embolism. It is important for physicians to be familiar with the complications associated with thrombocytosis. Postsplenectomy reactive thrombocytosis has an incidence of about 75% to 82%. Thrombosis in association with elevated platelet count after splenectomy is well recognized, with an incidence of approximately 5%. This case report describes a 61-year-old patient who underwent emergent splenectomy and presented 1 week later with acute ST segment elevation myocardial infarction. Severe thrombocytosis, which was not present prior to splenectomy, was noted, and a diagnosis of reactive thrombocytosis was initially made. Involvement of the right coronary artery led to emergent percutaneous transluminal coronary angioplasty. Essential thrombocytosis was considered when treatment with hydroxyurea failed to lower the platelet count. A review of arterial and venous thrombosis in patients with severe thrombocytosis is presented, and the approach to the management of such patients is discussed.

The normal platelet count in adults ranges from 150 to 450 K/μL. The definition of thrombocytosis varies among authors (1, 2) but is most commonly defined as a platelet count >500 K/μL (3). Platelet counts >1000 K/μL are not unusual in a general hospital population (1); however, such extreme numbers are encountered more commonly in myeloproliferative disorders or after splenectomy (4). In one study, 75% of individuals without myeloproliferative disorders developed thrombocytosis after splenectomy (5). Platelet counts after splenectomy have been reported to increase 30% to 100%, with a peak reached at 7 to 20 days postoperatively (3). Common complications of thrombocytosis include thrombosis and hemorrhage. Postsplenectomy venous thrombosis is usually associated with platelet counts >600 to 800 K/μL (6, 7) and occurs in approximately 5% of patients (8). Less commonly, postsplenectomy thrombocytosis results in arterial thrombosis that leads to stroke or myocardial infarction (9, 10).

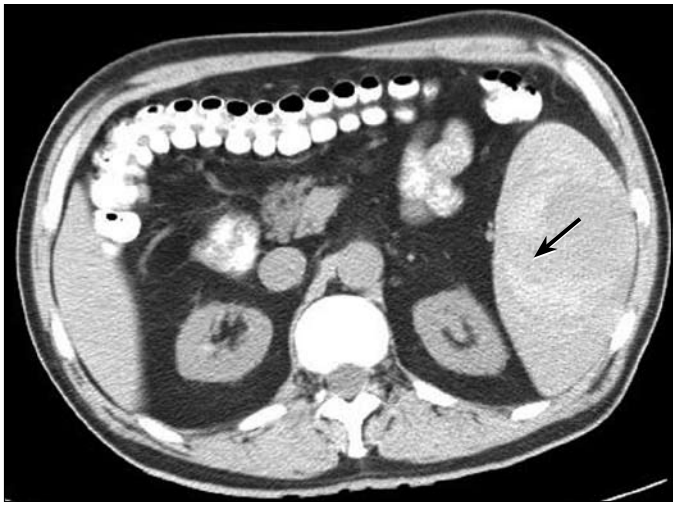

Figure 1. Computed tomography scan without contrast at initial presentation. Note the hematoma (arrow).

Regardless of the cause, thrombocytosis leads to platelet hyperaggregation; therefore, the first line of therapy is the administration of platelet-antiaggregating medication such as aspirin. For extreme thrombocytosis with evidence of arterial or venous thrombosis, patients may need cytoreductive agents such as hydroxyurea or anagrelide with close monitoring of platelet counts (11, 12).

CASE REPORT

A 61-year-old white man with previous systemic hypertension and hypothyroidism presented at the outpatient clinic with a 1-day history of left upper quadrant abdominal pain. The pain was described as constant, severe, and nonradiating.

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Examination showed tenderness to palpation in the left upper quadrant and a possible mass measuring 5 to 7 cm. An ultrasound of the abdomen showed a mass in the spleen. The patient was hospitalized.

Laboratory values were significant for a hemoglobin level of 15.5 g/dL (reference range, 13.5–18.0 g/dL), a hematocrit of 43.4% (reference range, 4.0%–52.0%), and a platelet count of 125 K/μL (reference range, 140–440 K/μL). The patient's vitamin B_{12} level on admission was 50 pg/mL (reference range, 180–914 pg/mL). The low platelet count upon admission was suggestive of splenomegaly, low levels of vitamin B_{12}, and hyperfunction of the spleen. An echocardiogram ruled out endocarditis. A computed tomography scan of the abdomen without contrast revealed a hemorrhagic mass measuring 10 × 7.4 × 6.7 cm *(Figure 1).*

Table 1. Characteristics of blood count in relation to hospital course

Variable	Admission	Postoperative day 0	1	3	5	7 (readmission)	8	9	10	11	14	21
Platelet count (K/μL)	125	153	226	515	813	1061	1078	1371	1524	1378	1172	623
White blood cell count (K/μL)	7.3	3.8	10.1	10.6	12.0	17.6	13.4	15.6	18.2	10.4	2.7	5.2
Hemoglobin (g/dL)	15.5	10.1	9.0	9.5	9.3	10.6	9.0	10.2	10.9	10.4	10.4	10.7
Hematocrit (%)	43.4	28.2	25.3	27.0	27.4	31.4	26.6	31.0	32.7	31.0	31.2	32.2

The patient was started on aggressive vitamin B_{12} replacement. His hemoglobin dropped on the subsequent day from 15.5 to 10.1 g/dL, and he developed hypotension with no signs of sepsis. Due to the concern of continuous bleeding into his spleen and the possibility of an underlying neoplasm, a splenectomy was performed. Histological studies of the mass showed extensive hemorrhage and fibrin deposits, which supported the diagnosis of a splenic hemorrhage and hematoma.

After the surgery, reactive thrombocytosis was observed in the patient. His platelet count was 226 K/μL immediately after splenectomy and was abnormally elevated to 813 K/μL on postoperative day 5, the day of his discharge *(Table 1).* The patient remained asymptomatic at discharge, and the recommendations for reactive thrombocytosis after splenectomy (e.g., mobilization, increased fluid intake) were discussed with him. He was started on 81 mg of aspirin per day.

The patient presented to the emergency department 3 days after discharge with chest pain. Because the electrocardiogram suggested an inferior wall acute myocardial infarction *(Figure 2),* he underwent immediate cardiac catheterization, which revealed complete blockage of the distal right coronary artery. He was treated with balloon dilation without a stent.

His platelet count was 1061 K/μL upon readmission and increased to 1524 K/μL during the 2 days after admission (Table 1). He was started on hydroxyurea, and 1 week after his readmission his platelet count began decreasing. He experienced severe nausea, vomiting, and leukopenia and was switched to 0.5 mg of anagrelide 3 times a day. On discharge, his platelet count was 623 K/μL. The patient also underwent bone marrow biopsy, which ruled out myeloproliferative disorders.

At 1-year follow-up, the patient's complete blood count remains normal. He continues his B_{12} supplement, and anagrelide has been titrated to 0.5 mg twice a day. He has been asymptomatic and working full-time with no recurrent cardiac events.

DISCUSSION

Reactive thrombocytosis is the presence of high platelet count in response to infection, trauma, or surgery (4, 13). The platelet count in reactive thrombocytosis is expected to normalize after resolution of the underlying condition (3). Secondary causes of an elevated platelet count (e.g., myeloproliferative disorders, splenectomy, and occult malignancy) must be ruled out in such patients.

Reactive thrombocytosis is a common cause of thrombocytosis (2, 4). In one study of patients with thrombocytosis, reactive thrombocytosis was diagnosed in 70% and primary thrombocytosis in only 22% (14). Similarly, in patients with extreme thrombocytosis (i.e., platelet count >1000 K/μL [15]), reactive thrombocytosis is a more common cause of thrombocytosis than is primary or essential thrombocytosis (1). In another study of 280 patients with a platelet count >1000 K/μL,

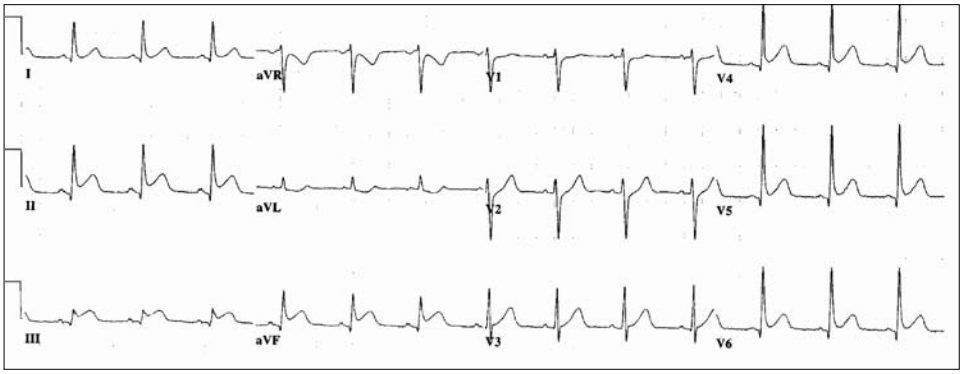

Figure 2. Electrocardiogram on readmission for acute chest pain. Acute ST segment elevation is shown in leads II, III, and aVF.

Table 2. Etiology of extreme thrombocytosis*

Causes	Percentage reported
Infection	31%
Postsplenectomy	19%
Malignancy	14%
Trauma	14%
Inflammation	9%
Blood loss	6%
Rebound thrombocytosis	3%
Uncertain etiology	4%

*Adapted from Buss DH et al, 1994 (1) with permission from Elsevier. Extreme thrombocytosis is defined as a platelet count ≥1000 K/µL (15).

Table 3. Pharmacologic agents for management of extreme thrombocytosis and associated adverse effects*

Drugs	Adverse effects
Acetyl salicylic acid	Bleeding
Hydroxyurea	Venous thrombosis, leukemic transformation
Anagrelide	Anemia, headache, tachycardia, edema
Interferon alpha	Immunosuppression
Ticlopidine	Bleeding, leukemic transformation
Enoxaparen	Bleeding, thrombocytopenia, headache
Plasmapheresis	Bleeding, infection, lung injury

*Adapted from references 11, 12, 14, 27.

reactive thrombocytosis was the cause in more than 80% and myeloproliferative disorder in only 14% (1). Splenectomy was found to be one of the main causes of extreme reactive thrombocytosis (1) *(Table 2).*

Essential thrombocytosis is the increased production of platelets in the absence of other myeloproliferative disorders. Essential thrombocytosis is characterized by persistent thrombocytosis >600 K/µL, confirmed by a bone marrow biopsy signifying megakaryocytic hyperplasia (16, 17). Essential thrombocytosis is diagnosed at a rate of 2 to 3 per 100,000 individuals every year (18). It usually affects middle-aged to elderly individuals, with an average age at diagnosis of 50 to 60 years (as in our patient), although it can affect any age population (19).

Essential thrombocytosis is not a well-recognized cause for arterial and venous thrombosis (20); however, case reports of patients with arterial and venous thrombosis requiring intervention have been reported in the literature (21, 22). Most cases of reported postsplenectomy thrombosis have been in portal, mesenteric, and splenic veins (8). Very few cases of myocardial infarction are reported with thrombocytosis, and, when it does occur, it is mainly in patients with essential thrombocytosis (10, 23, 24).

Essential thrombocytosis is a diagnosis of exclusion by ruling out known causes of reactive thrombocytosis. Even though our patient had a bone marrow biopsy that did not demonstrate megakaryocytic hyperplasia, we suspected essential thrombocytosis due to the absence of other myeloproliferative disorders and persistent thrombocytosis when the hematologist attempted to wean anagrelide. We also suspect a cumulative rebound effect from splenectomy, aggressive B_{12} treatment, and severe anemia.

Pathophysiology

Reactive thrombocytosis is thought to result from overproduction of one or more thrombopoietic factors that act on megakaryocytes or their precursors (3). Elevated levels of these growth factors are observed in various infectious, inflammatory, malignant, and traumatic processes (25). Of all the growth factors identified, interleukin (IL)-6 plays a primary role in reactive thrombocytosis (3).

Elevated IL-6 is found in some patients with iron-deficiency anemia, suggesting some other mechanism for reactive thrombocytosis in these patients. The association of iron-deficiency anemia with thrombocytosis points to an interrelationship between erythropoietic and thrombotic growth factors (3, 7). This may explain persistent thrombocytosis (as seen in our patient) in association with prolonged anemia.

The spleen plays a major role in platelet regulation, as it is the primary site of destruction of platelets, which is why thrombocytosis is seen with hyposplenism (26). Reactive thrombocytosis is a predictable finding after splenectomy, with the platelet count peaking at 1 to 3 weeks and returning to normal levels in weeks, months, and, rarely, years (3).

As pointed out above, the combination of hyposplenism, B_{12} replacement, and severe anemia could have precipitated extreme thrombocytosis in our patient.

Management

The first step in managing a patient who presents with elevated platelet count is to determine if the etiology is a primary process or a reactive response (27). The immediate risk to the patient from the increased platelet count should be assessed. Thereafter, management of the thrombocytosis and prevention of complications should be initiated. Patients with essential thrombocytosis who have had thrombotic events and cardiovascular risk factors should be treated (28). Some pharmacologic agents used for this purpose are listed in *Table 3,* along with their associated adverse effects. The anticipated reduction in risk of future thrombosis should outweigh the risk of complications from drug therapy. Hydroxyurea has been the treatment of choice (16, 17, 28) in many studies.

Anagrelide is a newer platelet-lowering agent that has been approved in patients with essential thrombocytosis. Harrison and colleagues compared hydroxyurea plus aspirin with anagrelide plus aspirin as initial therapy for essential thrombocytosis (11). The study showed that, compared with anagrelide, hydroxyurea was superior in lowering the risk of arterial thrombosis, hemorrhage, and transformation to myelofibrosis. However, it also had higher rates of venous thrombosis than anagrelide. The risk of bleeding associated with aspirin use should be kept in mind in patients with thrombocytosis. With hydroxyurea,

patients should be monitored for leukemic transformation. Long-term data on the side effects and complications of anagrelide are lacking; however, preliminary data suggest it is well tolerated, with mild to moderate anemia as a frequent side effect (12). Plasmapheresis is another option for rapid reduction of platelet count in life-saving clinical situations.

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