Clinical Problem-Solving

Simple and Complex

Siyang Leng, M.D., Brahmajee K. Nallamothu, M.D., M.P.H., Sanjay Saint, M.D., M.P.H., Leonard J. Appleman, M.D., Ph.D., and Gregory M. Bump, M.D.

In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

A 44-year-old man presented to the emergency department with chest pain that had started 1 hour earlier and had awakened him from sleep. The pain was severe, substernal, burning, radiating to the left arm, and accompanied by nausea and nonbilious, nonbloody vomiting. For the past month he had experienced intermittent chest pain of a similar character but less intense. The pain was not related to exertion and lasted for hours to days at a time. Antacids and omeprazole had provided temporary relief. He reported no dyspnea, lower-extremity edema, immobility, fever, cough, or trauma.

Conditions that should be ruled out first are the lethal causes of chest pain: acute coronary syndromes, pulmonary embolism, aortic dissection, pneumothorax, pericardial tamponade, and mediastinitis. Of these conditions, an acute coronary syndrome is the most likely, based on the chest pain as described and the presence of similar but less intense episodes over the previous month. Nausea and vomiting may occur with acute coronary syndromes but are nonspecific. Other causes of chest pain such as gastroesophageal reflux or musculoskeletal disorders are also possible.

The patient’s medical history was unremarkable, but he had not seen a physician for years. Medications included omeprazole and antacids as needed. He reported that he did not use tobacco, alcohol, or illicit drugs. He was employed as a physician. There was no family history of premature coronary artery disease. On physical examination, he was afebrile; the blood pressure was 133/83 mm Hg (approximately the same in both arms), the heart rate 61 beats per minute, and the oxygen saturation 97% while he was breathing ambient air. He appeared to be in considerable distress, clutching his chest. He was thin. The trachea was midline. Cardiac examination revealed a regular rhythm without extra heart sounds, no jugular venous distention, and no lower-extremity edema. Breath sounds were normal in both lungs. Chest palpation did not produce pain. The abdomen was soft and nontender, with normal bowel sounds. There was no organomegaly or lymphadenopathy. Examination of the skin was unremarkable.

The patient has no known atherosclerotic risk factors but apparently has not undergone screening for diabetes or hyperlipidemia. He reports that he does not use recreational drugs, which might confer a predisposition to coronary ischemia, although such reporting is not necessarily reliable. His vital signs are stable — a somewhat reassuring finding.
The troponin level was 0.08 ng per milliliter (normal value, <0.10). The white-cell count was 22,000 per cubic millimeter, with 74% neutrophils, 18% band forms, 2% lymphocytes, 4% monocytes, 1% eosinophils, and 1% basophils. The platelet count was 771,000 per cubic millimeter. The hemoglobin level was 17.5 g per deciliter. The prothrombin time was 14.9 seconds (normal range, 11.7 to 15.3), international normalized ratio 1.2, and partial-thromboplastin time 27.6 seconds (normal range, 22.7 to 35.6). The fasting serum glucose level was 192 mg per deciliter (10.7 mmol per liter). The results of other blood chemical and liver-function tests were unremarkable. A chest radiograph showed a normal mediastinum without pulmonary edema, cardiomegaly, or air-space disease. A 12-lead electrocardiogram obtained 2 hours after the onset of the chest pain revealed a normal sinus rhythm; ST-segment elevations in leads V2 to V6, I, and aVL; and ST-segment depression in lead III (Fig. 1).

The electrocardiogram shows an acute injury pattern in the anterolateral wall of the heart that is consistent with ST-segment elevation myocardial infarction (STEMI) in the territory of the left anterior descending coronary artery. Given that the patient presented early after the onset of chest pain, the normal troponin level does not rule out STEMI. Other conditions that may mimic STEMI, such as pericarditis, should also be considered; however, the localized changes on the electrocardiogram and the character of the pain argue against this diagnosis. The patient should undergo emergency coronary angiography with planned percutaneous coronary intervention if the facilities are rapidly available. The administration of aspirin, intravenous heparin, and a thienopyridine is reasonable, along with oxygen and morphine. I would be cautious about prescribing beta-blockers, given that the heart rate is relatively low for an anterolateral STEMI.

Immediate management must be the priority, but it is also important to consider whether anything in the presentation suggests an underlying predisposing condition. The patient’s high fasting glucose level raises concern about possible diabetes, although documentation of a fasting glucose level of 126 mg per deciliter (7.0 mmol per liter) or higher on repeat measurement (or a glycated hemoglobin level of 6.5% or higher) is needed to make this diagnosis. I am also struck by the abnormal results on the complete blood count. Findings of leukocytosis with a left shift are not unusual in patients with STEMI, but the possibility of a myeloproliferative neoplasm (with
an associated hypercoagulable state) should be considered, given the higher-than-expected cell counts. After coronary angiography has been performed, I would recheck the glucose level and blood count and examine the peripheral-blood smear.

The patient was given aspirin (325 mg orally), atorvastatin (80 mg orally), clopidogrel (300 mg orally), and a 5000-U bolus of intravenous heparin. Continuous infusions of heparin and nitroglycerin were initiated, and he was transferred to a university hospital. There he underwent left-sided cardiac catheterization, which showed 100% occlusion of the left anterior descending artery (Fig. 2A). The left main, left circumflex, and right coronary arteries did not have clinically significant disease. Percutaneous coronary intervention of the left anterior descending artery with thrombosuction was performed, and two drug-eluting stents were placed, with subsequent restoration of normal flow (TIMI grade 3, according to the classification system of the Thrombolysis in Myocardial Infarction trial) (Fig. 2B). Transthoracic echocardiography showed an ejection fraction of 40%, with hypokinesis of the apex, the middle and distal anterior wall, and the middle and distal anterior septum (see videos, available with the full text of this article at NEJM.org). After the procedure, treatment with metoprolol was initiated.

Coronary angiography has confirmed the diagnosis of STEMI, and the percutaneous intervention appears to have been successful. The use of drug-eluting stents does not affect mortality among patients with STEMI but does reduce the need for subsequent procedures. I am hopeful that the patient’s left ventricular wall function and ejection fraction, which may be depressed owing to stunning of the myocardium early after STEMI, will recover. I remain concerned about the complete blood count.

The peak troponin level was 127 ng per milliliter. The level of low-density lipoprotein (LDL) cholesterol was 104 mg per deciliter (2.7 mmol per liter), high-density lipoprotein cholesterol 36 mg per deciliter (0.9 mmol per liter), and triglycerides 48 mg per deciliter (0.5 mmol per liter). On repeat measurement, the fasting serum glucose level was 109 mg per deciliter (6.0 mmol per liter), and subsequent levels remained below 110 mg per deciliter (6.1 mmol per liter). The glycated hemoglobin level was 5.7%. Levels of protein C and protein S were normal. Antithrombin III activity was 78% of the normal range, which is 85 to 140%. A test for the prothrombin-gene mutation was negative. Levels of anticardiolipin and anti–β₂-glycoprotein antibodies were normal. A hexagonal-phase phospholipid neutralization assay to test for lupus anticoagulant was positive.

The elevated troponin level confirms myocardial injury. Initiating treatment with a statin is rea-
reason able, given the recognized coronary disease and the elevated LDL cholesterol level. Dietary and lifestyle counseling should be recommended, since the patient's lipid profile and his fasting glucose and glycated hemoglobin levels suggest an increased risk of diabetes. Several tests were conducted to detect hypercoagulability, most of which showed unremarkable results. There was a slight decline in antithrombin activity, but this can occur transiently after an acute thrombotic event (as a result of antithrombin consumption) or with heparin use, and the value is not low enough to be typical of antithrombin deficiency. The presence of a lupus anticoagulant is difficult to interpret, since it may occur in normal persons or may be a false positive finding in patients taking heparin. A diagnosis of the antiphospholipid antibody syndrome requires confirmation of the positive test for lupus anticoagulant at least 12 weeks later. Evaluation for the above hypercoagulable disorders is not routinely performed in this clinical setting and generally yields little information. The yield is likely to be higher in relatively young patients, such as this one, than in older patients, but I would not perform tests for hypercoagulable disorders until more likely causes of myocardial infarction have been ruled out, unless there is a personal or family history of thrombosis. If testing is done, it should ideally be performed when the patient is not receiving anticoagulants and when there is no indication of acute thrombosis.

On recheck the day after the cardiac catheterization, the white-cell count was 13,800 per cubic millimeter (91% neutrophils, 4% lymphocytes, and 5% monocytes), the hemoglobin level was 15.6 g per deciliter, and the platelet count was 610,000 per cubic millimeter. The patient recalled being informed about a high platelet count — approximately 600,000 per cubic millimeter — when he donated platelets 12 years earlier, but this finding was not investigated further at that time. He reported no bleeding or other thrombotic events and did not have burning pain in his hands or feet, headache, dizziness, or other neurologic symptoms. He reported intermittent, generalized pruritus after taking hot showers. A peripheral-blood smear showed an increased number of platelets and occasional giant platelets. There were no circulating nucleated red cells, dacryocytes, or immature myeloid cells. The patient had had an elevated platelet count years earlier. At this point, it is important to determine whether this thrombocytosis is primary or secondary. Primary thrombocytosis results from a clonal hematologic disorder, whereas secondary thrombocytosis is a reactive process commonly due to conditions such as infection, inflammation, cancer, drug reaction, or iron deficiency. The patient's clinical presentation does not suggest secondary thrombocytosis. The intense inflammatory response from STEMI can cause transient elevations in platelet levels, but his elevated platelet count 12 years ago suggests a more long-standing underlying condition. Pruritus with exposure to warm water, as this patient reports, is a classic, although nonspecific, finding associated with myeloproliferative neoplasms. Since primary thrombocytosis confers a predisposition to both bleeding and thrombosis, it is important to make a definitive diagnosis in order to reduce the risk of complications in the future.

Testing of peripheral blood for the Janus kinase 2 (JAK2) V617F mutation was positive. The serum lactate dehydrogenase level was 445 U per liter (normal value, <171). Bone marrow biopsy revealed approximately 70% cellularity, with trilineage hematopoiesis and a slightly increased myeloid-to-erythroid ratio. The number of blasts was not increased. Megakaryocytes were markedly increased in number, showed prominent clustering, and included large, atypical forms. Reticulin, but not collagenous, fibrosis was noted (Fig. 3). The histologic features confirmed a myeloproliferative neoplasm, which was consistent with either myelofibrosis or essential thrombocytethemia. The trilineage marrow hypercellularity and peripheral-blood leukocytosis favored a diagnosis of primary myelofibrosis. Results of karyotypic analysis were normal.

The finding of a myeloproliferative neoplasm explains this patient's presentation. I suspect that the positive result on the lupus anticoagulant test noted earlier is a false positive result; it is unlikely that the patient has an additional hypercoagulable disorder, and in any case, this would not change the immediate management of his condition. The lactate dehydrogenase level is often increased in myelofibrosis, but since it can also be increased after a recent myocardial infarction, it is not a diagnostically useful finding.
in this case. The absence of splenomegaly, which occurs as a result of extramedullary hematopoiesis, suggests that the patient is in the proliferative, prefibrotic phase of myelofibrosis.

The myeloproliferative neoplasms are associated with arterial and venous thrombosis but also with bleeding. This complicates decision making with regard to long-term dual antiplatelet therapy, which is typically recommended for at least 12 months after drug-eluting stents are placed. At this point, I would continue low-dose aspirin and clopidogrel therapy, although this regimen may need to be revisited, depending on the patient’s clinical course. I would also continue the atorvastatin and metoprolol and add an angiotensin-converting–enzyme inhibitor to reduce the risk of recurrent events.

Treatment with hydroxyurea, at a dose of 500 mg given twice daily, was initiated, and the patient was discharged home. At the 6-month follow-up visit, he had no further angina or bleeding. His platelet, red-cell, and white-cell counts had normalized, and a repeat echocardiogram showed an ejection fraction of 50%.

COMMENTS

When a myocardial infarction occurs in a patient who does not have traditional risk factors for coronary artery disease, alternative causes should be sought. Important causes include hypercoagulable states, coronary vasospasm (e.g., from cocaine use), coronary inflammation, anomalous coronary arteries, coronary dissection, and embolization. As our discussant notes, the patient’s thrombocytosis suggested the presence of a myeloproliferative neoplasm, particularly because the elevated platelet count appeared to be of long standing. This group of myeloproliferative disorders, consisting primarily of polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myelogenous leukemia, is associated with hypercoagulability.

The incidence of thrombosis in patients with myeloproliferative neoplasms remains unclear but is significantly elevated, as compared with the incidence in a general population. Arterial thromboses are more common than venous thromboses; strokes are most frequent, followed by myocardial infarction and peripheral arterial occlusion. Paradoxically, patients with myeloproliferative neoplasms are also prone to bleeding, which is typically mucocutaneous and is less frequent and severe than thrombosis. Multiple mechanisms may account for these blood diatheses: hyperviscosity, platelet-aggregation ab-
normalities, leukocytosis leading to increased activation of the coagulation system, and various downstream effects of the JAK2 mutation.\textsuperscript{3,4}

The JAK2 V617F mutation (an acquired somatic mutation in the gene encoding JAK2 protein) results in a mutated tyrosine kinase capable of independently activating downstream pathways in thrombopoietin and erythropoietin signaling, as well as other cell and cytokine receptors. Cells expressing the mutation have a proliferation and survival advantage and are hypersensitive to hematopoietic growth factors. This mutation is present in more than 95\% of patients with polycythemia vera and in 50\% of patients with essential thrombocythemia and myelofibrosis. Its presence is diagnostic of a myeloproliferative neoplasm but cannot be used to distinguish among the various disorders.\textsuperscript{2,8}

In evaluating thrombocytosis, it is important to distinguish between reactive (secondary) and clonal (primary) causes. Common secondary causes include infection, tissue damage, inflammation, cancer, and iron-deficiency anemia. The most common primary causes are myeloproliferative, but in rare cases, some forms of myelodysplasia underlie this finding. Patients with clonal processes may report pruritus, usually after bathing. On physical examination, splenomegaly is more common with clonal than with reactive thrombocytosis. Although the degree of thrombocytosis does not indicate the cause, giant platelets are more common in clonal thrombocytosis than in reactive thrombocytosis. Bone marrow examination is recommended when a myeloproliferative neoplasm is suspected. Findings such as giant or dysplastic megakaryocytes, trilineage hypercellularity, and reticulin or collagenous fibrosis suggest a clonal process.\textsuperscript{2,9,10} Finally, testing for the JAK2 mutation has become important for the diagnosis; the presence of this mutation or a functionally similar mutation is now a major diagnostic criterion for polycythemia vera, essential thrombocythemia, and myelofibrosis.\textsuperscript{5}

Distinguishing among the myeloproliferative neoplasms can be difficult. Thrombocytosis can be the presenting feature not only of essential thrombocythemia but also of polycythemia vera and myelofibrosis. Reticulin fibrosis can be seen in essential thrombocythemia and may be absent in early myelofibrosis. Careful application of current diagnostic criteria (Table 1) and consultation with a specialist are recommended.\textsuperscript{2,11} The management of thrombocytosis in patients with myeloproliferative neoplasms currently entails the use of antiplatelet and cytoreductive therapies. In a randomized trial, aspirin was shown to reduce the risk of thrombosis in patients with polycythemia, but it did not reduce mortality.\textsuperscript{7} There is no similar evidence to support the use of aspirin in patients with other myeloproliferative neoplasms, and its potential benefits in reducing the risk of thrombosis must be weighed against the increased risk of bleeding. Cytoreductive therapies are considered for patients with polycythemia vera and for patients with other myeloproliferative neoplasms who are considered to be at high risk for thrombosis or bleeding, including those older than 60 years of age, those with a history of major thrombosis or hemorrhage, and those with platelet counts greater than 1.5 million per cubic millimeter. Cytoreductive therapies include phlebotomy, hydroxyurea, and interferon alfa. In a recent randomized trial involving patients with polycythemia vera, Marchioli et al. compared targets for cytoreduction (i.e., a hematocrit of less than 45\%, as compared with 45 to 50\%) and found that the lower target was associated with a significantly reduced rate of death from cardiovascular causes or major thrombotic events.\textsuperscript{12}

Hydroxyurea effectively reduces elevated cell counts, spleen size, and thrombotic risk. There is concern that hydroxyurea increases the risk of leukemic transformation, but no definitive evidence has established an association.\textsuperscript{13} Interferon alfa is also cytoreductive, but data from randomized trials about its use in patients with myeloproliferative neoplasms are lacking. Neither agent has been shown to improve survival.\textsuperscript{3,5,9,13} The decision to use hydroxyurea for our patient was based on the severity of his thrombotic event and the adverse-event profile of the medication, as compared with interferon alfa.\textsuperscript{5,9} The drug ruxolitinib, an inhibitor of both JAK1 and JAK2 recently approved by the Food and Drug Administration, has shown efficacy in reducing splenomegaly and constitutional symptoms in patients with intermediate-2 or high-risk myelofibrosis.\textsuperscript{14,15} Ruxolitinib was also shown to improve survival, as compared with placebo, in one trial,\textsuperscript{14} but it has not been shown to induce histologic or molecular remission.\textsuperscript{14-16}

Myocardial infarction, a diagnosis that is routinely considered when a patient presents with chest discomfort, led our patient to seek care. Our
case illustrates that even a seemingly straightforward presentation of a common illness may involve a more complex underlying disorder, which, when recognized, changes the approach to the patient. The ability to regularly toggle between the straightforward and the complex is one of the many skills that seasoned clinicians develop.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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R E F E R E N C E S

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Table 1. Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis (WHO, 2008).*