

# Subacute Stent Thrombosis in a Patient with Polycythemia Vera

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**P**atients presenting with ST-elevated myocardial infarction (MI) require immediate reperfusion of the myocardium, which is typically achieved by placement of an intracoronary stent. Following coronary stenting, patients are at increased risk of thrombosis due to endothelial disruption that occurs during the procedure. Postoperatively treating patients with a combination of clopidogrel and aspirin greatly reduces this risk.<sup>1,2</sup> However, managing the risk for stent thrombosis in patients who have concomitant polycythemia vera is complicated due to blood abnormalities that predispose these patients to thromboembolic events. In addition, there are no established guidelines addressing stent thrombosis prevention in patients with polycythemia vera. This article presents the case of failed standard postprocedural antiplatelet therapy in a patient with polycythemia vera who subsequently underwent immediate coronary intervention.

## CASE PRESENTATION

### Initial Presentation and History

A 78-year-old man presented to the emergency department with acute chest discomfort. The patient reported substernal pressure radiating to his jaw, associated with weakness, shortness of breath, pallor, and profuse sweating not relieved with rest. He denied experiencing these symptoms previously. Prior to presentation, the patient took aspirin (325 mg). Past medical history was significant for polycythemia vera treated with hydroxyurea 15 mg/kg daily; hypertension controlled with metoprolol 25 mg twice daily, hydrochlorothiazide 12.5 mg/day, and ramipril 5 mg/day; previous tobacco use (60 pack-years); and prior transient ischemic attacks for which he was noncompliant with aspirin therapy (325 mg/day).

### Physical Examination

On examination, the patient's vital signs were: temperature of 97.5°F, blood pressure of 143/89 mm Hg, heart rate of 70 bpm, respiratory rate of 16 breaths/min, and oxygen saturation of 98% on 2 L oxygen via nasal

cannula. The patient was alert, oriented, and in no acute distress. No jugular venous distension was noted. Cardiovascular examination identified a regular rate and rhythm with no murmurs. Respiratory examination was normal. The rest of the physical examination was unremarkable.

### Diagnosis and Treatment

On 12-lead electrocardiography, there was a 3-mm ST-T elevation in leads II, III, and aVF (**Figure 1**). Complete blood count revealed a hemoglobin level of 14.3 g/dL (normal, 14.0–17.5 g/dL), red blood cell (RBC) count of 4,700,000 cells/ $\mu$ L (normal, 43,000,000–57,000,000 cells/ $\mu$ L), and platelet count of 479,000 cells/ $\mu$ L (normal, 150,000–350,000 cells/ $\mu$ L). Assays for cardiac enzymes revealed a troponin T level of 0.46 ng/mL (normal, 0.0–0.1 ng/mL). Chest radiograph was unremarkable. The patient was admitted to the hospital and immediately underwent coronary angiography, which identified a 75% stenosis of the left anterior descending artery and 100% stenosis of the right coronary artery (RCA). Significant thrombosis was noted in the RCA, and multiple attempts at balloon angioplasty failed to open the obstructed vessel. Percutaneous transluminal coronary angioplasty allowed the placement of 3 bare metal stents in the RCA.

A postintervention transthoracic echocardiogram showed mild hypokinesis of the basal inferior wall, grade I diastolic dysfunction, and an ejection fraction of 61%. The patient's hospital course proceeded without complication, and he was discharged on hospital day 4 with a medication regimen that included metoprolol 50 mg twice daily, atorvastatin 40 mg at bedtime,

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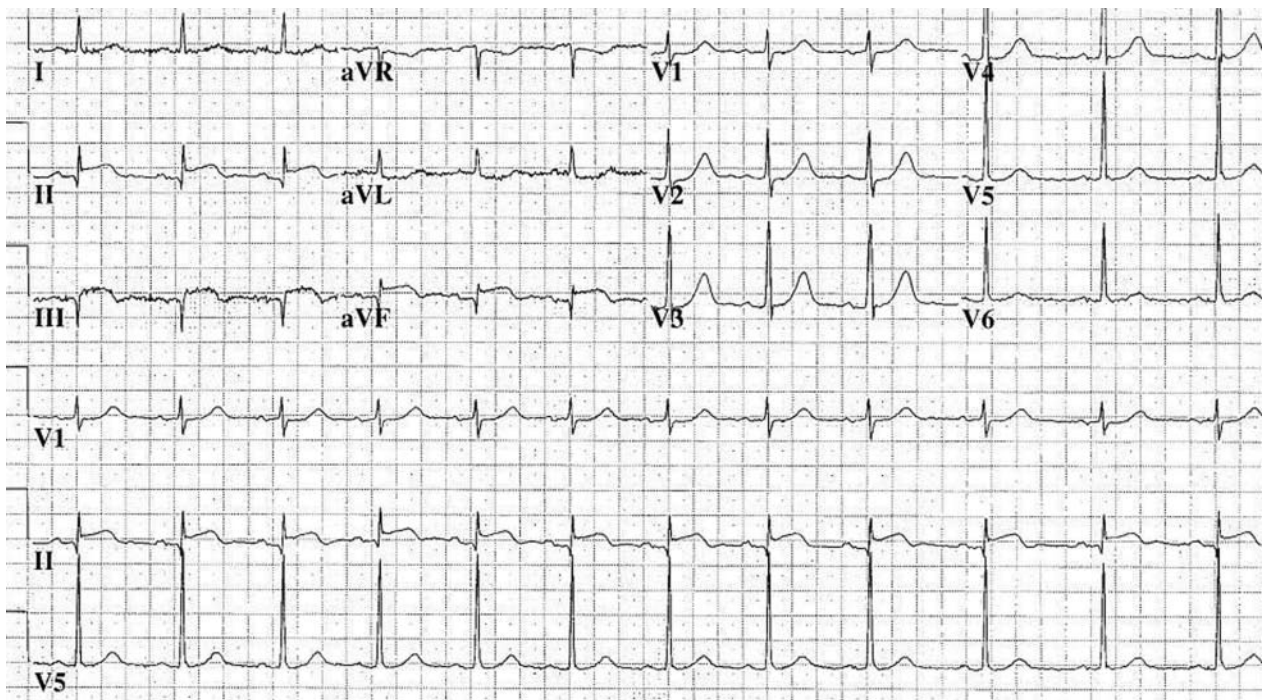


Figure 1. An electrocardiogram taken at admission of the case patient demonstrating ST-T elevation in leads II, III, and aVF.

ramipril 10 mg/day, hydrochlorothiazide 25 mg/day, aspirin 325 mg/day, and clopidogrel 75 mg/day. The patient was instructed to resume his previous medications.

### Readmission

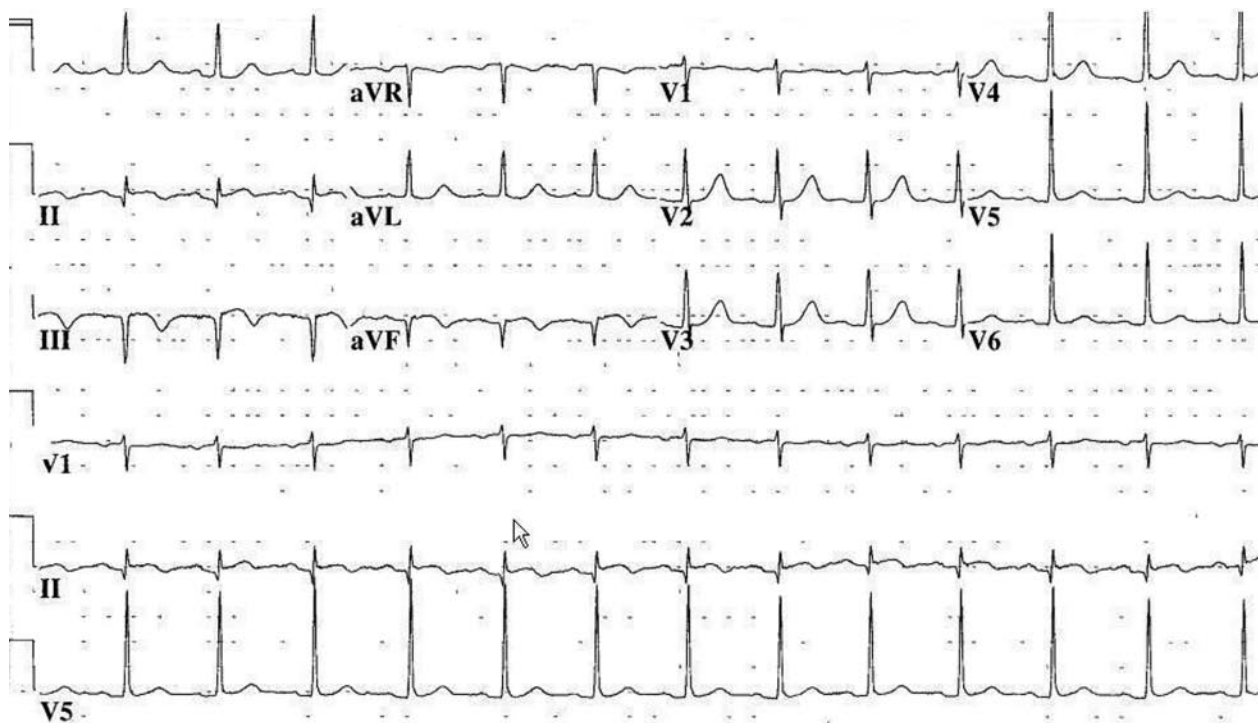
Two days after discharge, the patient noted recurrent substernal chest pain of 5 minutes' duration. He proceeded to the emergency department and was administered nitroglycerin, which relieved his chest pain. Repeat electrocardiography showed Q waves and 2-mm ST-T elevations with T-wave inversions in leads II, III, and aVF (Figure 2). New-onset ST depression was noted in leads V<sub>2</sub> and V<sub>3</sub>. Repeat complete blood count showed a hemoglobin of 12.8 g/dL and platelet count of 675,000 cells/ $\mu$ L. The patient was readmitted to the hospital and immediately underwent coronary angiography. The procedure noted reocclusion of his RCA stents requiring the placement of 2 additional bare metal stents.

Recommendation at discharge on hospital day 5 was to increase the dosage of hydroxyurea to 20 mg/kg daily due to his recent coronary thrombosis and increased risk of recurrent thrombosis due to concomitant polycythemia vera. The patient was also prescribed warfarin 5 mg/daily with a target international normal ratio of 2 to 3. Hematology consultation recommended adding warfarin to the patient's current antiplatelet regimen with aspirin and clopidogrel because it was

thought that the platelets in polycythemia vera do not respond well to traditional antiplatelet medications and that the addition of clotting factor inhibitors may provide further protection. Cardiothoracic surgeons did not consider the patient to be a good candidate for coronary artery bypass grafting (CABG) because concomitant polycythemia vera placed him at a high risk for a fatal perioperative thrombotic event.

### ACUTE MI IN POLYCYTHEMIA VERA

Polycythemia vera is a myeloproliferative disorder that is characterized by an increase in phenotypically normal RBCs with an associated increase in red cell mass as well as a possible increase in granulocytes and platelets in the absence of a recognizable physiologic stimulus (Table).<sup>3</sup> Clinical features include headache, pruritus, dyspnea, blurred vision, facial plethora, splenomegaly, and thromboembolic events. These signs and symptoms are caused by hyperviscosity, hypervolemia, and hypermetabolism that occur in polycythemia vera.<sup>3</sup> Thromboembolic events are the most significant and life-threatening complication of this disorder, resulting in reduced life expectancy as compared with the general population.<sup>4</sup> Recently, there has been a dramatic reduction in the number of thrombotic complications in patients with polycythemia vera due to the use of phlebotomy and/or chemotherapy<sup>5</sup> along with antiplatelet therapy.<sup>6</sup> These



**Figure 2.** An electrocardiogram taken at the case patient's second admission demonstrating Q waves and 2-mm ST-T elevations with T-wave inversions in leads II, III, and aVF.

treatments lower blood hyperviscosity and lead to improved survival.<sup>6</sup> However, recent evidence has shown that the pathophysiology of thromboembolic events in polycythemia vera and essential thrombocythemia is not yet completely understood, as reduction of platelet count alone often is not sufficient to protect against thrombotic complications, indicating that other factors contribute to thrombosis.<sup>7,8</sup> Furthermore, much remains to be learned regarding the optimal management of acute MI and stent thrombosis prevention in patients with polycythemia vera. The following section summarizes the various prophylactic and treatment approaches available for managing acute MI in patients with concomitant polycythemia vera.

### Management

**Aspirin prophylaxis and treatment.** Use of aspirin in all acute coronary events (unless specific contraindications exist) is currently recommended by the American College of Chest Physicians.<sup>9</sup> The prophylactic use of aspirin in polycythemia vera patients has previously been studied. Landolfi et al<sup>6</sup> conducted a double-blind, placebo-controlled randomized trial in 518 patients with polycythemia vera that demonstrated prophylaxis with aspirin 100 mg reduced the risk of nonfatal MI, nonfatal stroke, pulmonary embolism, major venous thrombosis, or

**Table.** Hematologic Characteristics of Polycythemia Vera

	Female	Male
Hemoglobin (g/dL) or	> 16.5	> 18.5
Hematocrit (%)	> 50	> 56
Red cell mass (mL/kg)	> 32	> 36
White blood cell count (cells/ $\mu$ L)	> 12,000	
Platelets (cells/ $\mu$ L)	> 400,000	

Data from Cao M, Olsen RJ, Zu Y. Polycythemia vera: new clinicopathological perspectives. *Arch Pathol Lab Med* 2006;130:1126-32.

death from cardiovascular causes (relative risk, 0.40 [95% confidence interval, 0.18-0.91];  $P = 0.03$ ) as compared with placebo; however, overall mortality and cardiovascular mortality were not significantly reduced. In addition, the incidence of bleeding was not significantly increased in the aspirin group.<sup>6</sup> In an article that reviewed data from 86 studies, Willoughby et al<sup>10</sup> found that prophylactic aspirin use in patients with polycythemia vera reduced the occurrence of major vascular events by 22% and nonfatal MI by 30%. Willoughby et al<sup>10</sup> also reviewed data showing that long-term use of higher doses ( $\geq 300$  mg/day) of prophylactic aspirin in polycythemia vera patients was associated with an increased incidence of bleeding. Based on these data, it can be inferred

that initiating therapy with aspirin up to a maximum dose of 300 mg in polycythemia vera patients who present with an acute coronary syndrome and then quickly reducing the dose to 100 mg by discharge for long-term prophylactic use would provide the greatest benefit in mortality reduction with a minimal risk for bleeding.

**Cytoreduction prophylaxis and treatment.** The purpose of prophylactic cytoreduction in managing patients with polycythemia vera is to reduce the risk of thrombosis, which accounts for the morbidity and mortality associated with the disease. Phlebotomy and myelosuppression are the treatment options most often utilized, either alone or in combination. The aim of phlebotomy is to reduce hyperviscosity by maintaining a hematocrit level less than 45% in white men and 42% in blacks and women.<sup>11</sup> Use of myelosuppressive agents such as hydroxyurea also reduces hyperviscosity, although there may be some increased risk for developing leukemia, and patients often will require supplemental phlebotomy.<sup>11</sup> Hydroxyurea is usually reserved for polycythemia vera patients older than age 70 years, who have a history of thrombosis, or who develop a platelet count greater than 400,000 cells/ $\mu$ L.<sup>3</sup>

Cytoreduction also has been used as an adjuvant treatment modality for acute MI in patients with polycythemia vera. Typically, cytoreduction is not used in patients without polycythemia vera who present with an acute coronary syndrome because the coronary thrombosis is primarily caused by platelet aggregation alone (usually around ruptured coronary plaques). It is debated whether coronary thrombosis in patients with polycythemia vera is due solely to platelet aggregation, RBC aggregation caused by hyperviscosity associated with polycythemia vera, or a combination of both factors.<sup>12</sup> The use of cytoreduction in polycythemia vera is supported by a case report in which phlebotomy was performed prior to coronary reperfusion and was successful in preventing stent restenosis; aspirin was also administered (dose not reported).<sup>12</sup> Venegoni et al<sup>13</sup> concludes that combining coronary reperfusion with exchange phlebotomy may be the most appropriate course of treatment as it avoids the increased risk of bleeding associated with other antiplatelet agents. Future studies are needed to determine whether a true benefit exists with the use of a combination of aspirin and phlebotomy as preprocedural treatment in polycythemia vera patients who present with acute coronary syndromes.

Cytoreduction, either by phlebotomy or medical myelosuppression, may also be helpful in the postprocedural state. Although there are no data from studies that directly examine this issue, De Stefano et al<sup>14</sup> performed a retrospective multicenter cohort study of 235 polycy-

themia vera patients with previous venous or arterial thrombosis that showed cytoreduction was effective in reducing rethrombosis by 70% in patients with recent acute coronary syndrome who were treated medically. Turakhia et al<sup>15</sup> provide evidence that suggests the possible pathophysiology behind this finding. In this retrospective study of 3787 patients from the general population who presented with acute coronary syndrome and underwent treatment with fibrinolytic therapy, an increased platelet count remained independently associated with residual thrombus in the coronary artery as seen on coronary angiography, even after adjustment for multiple variables. From these data, it can be inferred that actively reducing the platelet count would decrease the amount of residual coronary thrombosis, thus reducing the likelihood of repeat thrombosis.

**Coronary reperfusion.** It is uncertain which type of coronary reperfusion procedure is optimal for treating acute coronary syndromes in patients with polycythemia vera. Percutaneous coronary intervention (PCI) with or without stent placement is a well-recognized treatment option in the general population,<sup>1,2,12,13,15,16</sup> but as was seen in this case report, coronary rethrombosis remains a serious complication in patients with polycythemia vera. Fibrinolytic therapy and CABG are acceptable and sometimes necessary alternatives to PCI. Unfortunately, the effectiveness of fibrinolytic therapy as the sole treatment of an acute coronary syndrome in patients with polycythemia vera is unknown. As was observed by Turakhia et al,<sup>15</sup> effective fibrinolytic therapy may be undermined by residual coronary thrombus, which potentially may be seen in polycythemia vera patients who have high platelet counts. In regards to treatment with CABG, patients with polycythemia vera are predisposed to postoperative thrombosis. However, Wasserman et al<sup>17</sup> demonstrated that controlling blood counts in polycythemia vera patients undergoing CABG reduced but did not eliminate the risk for postoperative thrombosis and hemorrhage. Future studies are needed to determine which intervention is the most appropriate in patients with polycythemia vera.

**Anticoagulation with other agents.** The role of warfarin in the postcoronary stent treatment plan for patients with polycythemia vera has not been determined, and the use of warfarin cannot be recommended at this time. Zavalloni et al<sup>16</sup> report a polycythemia vera patient who failed conventional antiplatelet therapy after coronary stent placement. This patient was restented and then successfully treated with warfarin therapy in addition to his antiplatelet therapy. An additional episode of stent thrombosis occurred after his

warfarin was discontinued. Although this case suggests warfarin may serve as a key treatment in the postprocedural state, multiple randomized trials have since shown that, in the general population, warfarin provides little benefit over aspirin alone on early outcomes in patients undergoing stent implantation and is not recommended for use in this setting.<sup>9</sup> Anticoagulation with single-agent heparin has been investigated in patients with polycythemia vera but has not been shown to be effective.<sup>13,18</sup> Combination therapy with heparin has not been studied.

## SUMMARY

There are no current guidelines that address stent restenosis risk reduction or treatment of acute MI in patients with polycythemia vera. However, the available literature suggests that in addition to standard antiplatelet therapy, cytoreduction, either through medication or phlebotomy, may reduce stent restenosis risk in the polycythemia vera population.<sup>11-13</sup> PCI remains a viable treatment option for acute MI, with fibrinolytic therapy and CABG as alternatives in medically optimized patients. Although 1 case report suggests that the addition of warfarin to standard antiplatelet therapy may provide added protection from stent restenosis in patients with polycythemia vera,<sup>16</sup> most trials recommend against the routine use of warfarin after PCI.<sup>10</sup> More research is needed in order to determine whether any or all of the treatment modalities discussed here can result in improved survival rates. **HP**

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