

Cardiovascular Manifestations of Myeloproliferative Disorders: A Review of the Literature

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Myeloproliferative disorders (MPDs) are defined as neoplastic diseases that involve a proliferation of the myeloid stem cell or its derivatives. MPDs include chronic myeloid leukemia (CML), polycythemia rubra vera (PV), essential thrombocythemia (ET), and agnogenic myeloid metaplasia/myelofibrosis (AMM/MF). Bleeding and thrombosis are the primary causes of morbidity and mortality in patients with chronic MPDs. Thrombosis occurs in approximately one third of cases, contributing to a mortality of 15% to 40%.¹ Thrombosis may involve arteries or veins and, in some cases, involves unusual sites such as hepatic, mesenteric, or portal systems. The cardiovascular system is involved in 4% to 21% of cases of MPDs,^{2,3} and acute ischemic coronary artery disease is the presenting symptom in these cases.⁴⁻⁹ Other cardiovascular complications in patients with MPDs are valvular heart involvement, pericardial involvement, aortitis, thrombosis of major vessels (eg, inferior vena cava), pulmonary embolism, and systemic and pulmonary hypertension.

This article reviews case reports to document the different cardiovascular manifestations of MPDs and to highlight this association, particularly in younger patients who present with cardiac insult but who have no known risk factors including family history. In these cases, hematologic and oncologic causes should be sought, especially when pertinent history and clinical evaluation raise a high degree of suspicion. Indications for treatment modalities such as antiplatelet or anti-mitotic agents should be recognized. This article also emphasizes the need for further studies to evaluate cardiovascular manifestations of MPDs. Results of the literature search are listed in **Table 1**.

CLASSIFICATION OF MYELOPROLIFERATIVE DISORDERS

MPDs are chronic clonal disorders of the hemopoietic stem cell and are classified as CML, PV, ET, or AMM/MF. A degree of overlap exists between these

various disorders in clinical presentation as well as in apparent laboratory manifestations.

Chronic Myeloid Leukemia

CML is a neoplastic disorder of more differentiated myeloid cell lines and is a less aggressive disease than acute myeloid leukemia. The leukocyte count is elevated with a predominance of mature neutrophils. Chromosome analysis demonstrates the Philadelphia chromosome (a translocation of the long arm of chromosome 22 to another site, usually chromosome 9) in 90% of cases. Hydroxyurea, busulfan, or interferon- α are used for treatment. The disease inevitably progresses to an acute leukemia that has a poor prognosis.

The chronic phase of CML usually lasts 3 to 5 years. Approximately 15% of patients enter an accelerated phase, whereas 85% of patients develop acute leukemia (blast crisis) either abruptly or after 3 to 4 months of an accelerated phase. The risk of developing blast crisis is 25% each year. Blast crisis is recognized when 30% or more of myeloid cells in bone marrow are either myeloblasts or promyeloblasts. Allogenic bone marrow transplantation is the only available treatment and is offered to patients younger than age 55 years who have a human leukocyte antigen-identical allogenic sibling donor.

Polycythemia Vera

PV entails excessive production of erythrocytes despite the presence of low levels of erythropoietin. The disease often culminates in acute leukemia or myelofibrosis. **Table 2** lists the major and minor criteria used for

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Table 1. Cardiovascular Complications of Myeloproliferative Disorders: Results of a Medical Literature Search

Myeloproliferative Disorder	Cardiovascular Complication	Source
Myelofibrosis	Pulmonary hypertension	Garcia-Manero G, Schuster SJ, Patrick H, et al: Pulmonary hypertension in patients with myelofibrosis secondary to myeloproliferative diseases. <i>Am J Hematol</i> 1999;60:130–135.
Polycythemia vera	Coronary vasculopathy	Hermanns B, Handt S, Kindler J, et al: Coronary vasculopathy in polycythemia vera. <i>Pathol Oncol Res</i> 1998;4:37–39.
Essential thrombocythemia	Multivessel coronary thrombosis	Michaels AD, Whisenant B, MacGregor JS: Multivessel coronary thrombosis treated with abciximab (ReoPro) in a patient with essential thrombocythemia. <i>Clin Cardiol</i> 1998;21:134–138.
Essential thrombocythemia	Angina pectoris	Ohto T, Shihara H, Miyauchi Y, et al: A case of coronary artery bypass surgery using left internal thoracic artery and right gastroepiploic artery for a patient with essential thrombocythemia. <i>Jpn J Thorac Cardiovasc Surg</i> 1998;46:767–771.
Essential thrombocythemia	Digital gangrene	Fernando EA, Senanayake B, Sivakumaran S: Essential thrombocythemia: an uncommon cause of digital gangrene. <i>Ceylon Med J</i> 1998;43:34–35.
Essential thrombocythemia	Acute coronary occlusion, stent thrombosis	Turgut T, Harjai KJ, Edupuganti R, et al: Acute coronary occlusion and in-stent thrombosis in a patient with essential thrombocythemia. <i>Cathet Cardiovasc Diagn</i> 1998;45:428–433.
Essential thrombocytosis	Left ventricular dysfunction, large left ventricular thrombi	Calton R, Mani A, Calton N, et al: Essential thrombocytosis associated with left ventricular dysfunction and large left ventricular thrombi. <i>Indian Heart J</i> 1998;50:436–438.
Chronic myelogenous leukemia	Thrombotic thrombocytopenic purpura	Rachmani R, Avigdor A, Youkla M, et al: Thrombotic thrombocytopenic purpura complicating chronic myelogenous leukemia treated with interferon- α . A report of two successfully treated patients. <i>Acta Haematol</i> 1998;100:204–206.
Essential thrombocytosis	Portal vein thrombosis	Mossier C, Kerbl R, Wagner T, et al: Portal vein thrombosis in a 17-year-old female adolescent with essential thrombocytosis. <i>Pediatr Hematol Oncol</i> 1997;14:457–462.
Chronic myelomonocytic leukemia	Recurrent venous thromboembolic disease	Evans G, Pasi KJ, Mehta A, et al: Recurrent venous thromboembolic disease and factor XI concentrate in a patient with severe factor XI deficiency, chronic myelomonocytic leukaemia, factor V Leiden and heterozygous plasminogen deficiency. <i>Blood Coagul Fibrinolysis</i> 1997;8:437–440.
Polycythemia vera	Left ventricular and aortic valve thrombosis	Al-Saif S, Bhat RP, Hijazi A, et al: Left ventricular and aortic valve thrombosis caused by polycythemia rubra vera successfully treated with streptokinase. <i>Am Heart J</i> 1996;131:397–399.
Essential thrombocythemia	Central retinal vein occlusion and neovascular glaucoma	Yoshizumi MO, Townsend-Pico W: Essential thrombocythemia and central retinal vein occlusion with neovascular glaucoma. <i>Am J Ophthalmol</i> 1996;121:728–730.
Essential thrombocythemia	Thrombosis of the superior mesenteric artery	Adorjan T, Czeglédi Z, Szikora L, et al: Thrombosis in the small branches of the superior mesenteric artery in the early stages of essential thrombocythemia. <i>Orv Hetil</i> 1996;137:527–529.
Essential thrombocytosis	POEMS syndrome, arterial thrombosis	Zenone T, Bastion Y, Salles G, et al: POEMS syndrome, arterial thrombosis and thrombocythemia. <i>J Intern Med</i> 1996;240:107–109.
Polycythemia vera	Pulmonary hypertension	Nand S, Orfei E: Pulmonary hypertension in polycythemia vera. <i>Am J Hematol</i> 1994;47:242–244.
Myelofibrosis	Acute myocardial infarction	Ho YL, Chen WJ, Wu CC, Lee YT: Acute myocardial infarction in a case of myelofibrosis with patent coronary arteries and arteriovenous fistulae draining into the main pulmonary artery. <i>Int J Cardiol</i> 1994;46:49–51.
Polycythemia vera	Myocardial infarction	Venegoni P, Schroth G: Myocardial infarction and polycythemia vera: how should we treat it? <i>Cathet Cardiovasc Diagn</i> 1994;32:259–261.
Essential thrombocythemia	Ischemic stroke	Casto L, Camerlingo M, Finazzi G, et al: Essential thrombocythemia and ischemic stroke: report of six cases. <i>Ital J Neurol Sci</i> 1994;15:359–362.
Essential thrombocythemia	Mitral stenosis, cerebral thrombosis	Nonami Y, Sasahashi N, Satoh K, et al: A case report: mitral valve replacement for the patient with essential thrombocythemia. <i>Nippon Kyobu Geka Gakkai Zasshi</i> 1993;41:1567–1572.
Essential thrombocytosis	Coronary vasospasm, multiple coronary thrombosis, unstable angina	Koh KK, Cho Sk, Kim SS, et al: Coronary vasospasm, multiple coronary thrombosis, unstable angina and essential thrombocytosis. <i>Int J Cardiol</i> 1993;41:168–170.

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Table 1. Cardiovascular Complications of Myeloproliferative Disorders (*continued*)

Myeloproliferative Disorder	Cardiovascular Complication	Source
Chronic myelogenous leukemia	Pulmonary arteritis with pulmonary arterial thrombosis, recurrent endopulmonary embolization	Wagner U, Bittinger A, von Wichert P, et al: Pulmonary arteritis with pulmonary arterial thrombosis and recurrent endopulmonary embolization. <i>Clin Investig</i> 1993;71:559–563.
Postsplenectomy thrombocytosis	Inferior wall myocardial infarction	Tai YT, Yu YL, Lau CP, Fong PC: Myocardial infarction complicating postsplenectomy thrombocytosis, with early left ventricular mural thrombus formation and cerebral embolism: a case report. <i>Angiology</i> 1993;44:73–77.
Thrombocytosis with myeloid metaplasia	Pulmonary hypertension	Marvin KS, Spellberg RD: Pulmonary hypertension secondary to thrombocytosis in a patient with myeloid metaplasia. <i>Chest</i> 1993;103:642–644.
Essential thrombocythemia	Myocardial infarction	Momiyama T, Hiranaka T, Nomura F, et al: Coronary artery bypass grafting for left main trunk coronary artery lesion associated with essential thrombocythemia. <i>Clin Cardiol</i> 1993;16:691–693.
Essential thrombocythemia	Coronary heart disease	Arnar DO, Petursson MK, Jonmundsson E, Bjornsdottir J: Renovascular hypertension and coronary heart disease complicating essential thrombocythemia. <i>Eur Heart J</i> 1993;14:576–578.
Essential thrombocythemia	Coronary vasospasm and multiple coronary thrombosis	Koh KK, Cho SK, Kim SS, et al: Coronary vasospasm, multiple coronary thrombosis, unstable angina, and essential thrombocytosis. <i>Int J Cardiol</i> 1993;41:168–170.
Essential thrombocythemia	Coronary heart disease	Host NB, Saunamaki KI: Coronary heart disease in young age associated with essential thrombocythemia. <i>Am Heart J</i> 1992;124:219–221.
Essential thrombocythemia	Myocardial ischemic syndrome	Adlakha A, Bechard DL, Geer MR: Primary thrombocytosis and myocardial ischemic syndrome in a young woman. <i>Am Heart J</i> 1992;123:786–790.
Myelofibrosis	Splenic thrombosis, presence of antiphospholipid antibodies	Bregani ER, Corneo G, Pogliani EM: Antiphospholipid antibodies and splenic thrombosis in a patient with idiopathic myelofibrosis (antiphospholipid antibodies and thrombosis). <i>Haematologica</i> 1992;77:516–517.
Chronic myelogenous leukemia	Superior sagittal sinus thrombosis	Yonekura S, Nagao T, Arimori S: Superior sagittal sinus thrombosis in blastic crisis of chronic myelogenous leukemia: a case report of a complete recovery. <i>Jpn J Med</i> 1991;30:175–178.
Thrombocytosis	Pulmonary hypertension	Rostagno C, Prisco D, Abbate R, Poggesi L: Pulmonary hypertension associated with long-standing thrombocytosis. <i>Chest</i> 1991;99:1303–1305.
Polycythemia vera	Coronary thrombosis	Gosalakkal JA, Neligan MC: Coronary artery bypass grafting for coronary thrombosis complicating polycythemia rubra vera: case report. <i>Scand J Thorac Cardiovasc Surg</i> 1991;25:159–160.
Polycythemia vera	Right atrial mass in the presence of a permanent pacemaker electrode	Hendler A, Krakover R, Stryjer D, Schlesinger Z: A right atrial mass in the presence of a permanent pacemaker electrode in a patient with polycythemia vera. <i>Pacing Clin Electrophysiol</i> 1991;14:2083–2085.
Primary thrombocytosis	Multiple, relapsing thrombosis (includes myocardial infarction and pulmonary embolism)	Randi ML, Fabris F, Stocco F, et al: Multiple, relapsing thrombosis in a young man with primary thrombocytosis. <i>Blood Coagul Fibrinolysis</i> 1990;1:331–332.
Essential thrombocythemia	Recurrent cerebrovascular accidents	Abe K, Ohta S, Komiya T, et al: Fibromuscular dysplasia complicated by primary thrombocythemia presenting recurrent ischemic cerebrovascular accidents: a case report. <i>Jpn J Med</i> 1990;29:548–554.
Chronic neutrophilic leukemia	Cerebral thrombosis, left atrial thrombi	Sekino Y, Suzuki Y, Sato N, et al: Open-heart surgery in a patient with chronic leukemia. <i>Nippon Geka Gakkai Zasshi</i> 1989;90:450–453.
Myelofibrosis	Left ventricular thrombus	Stoddard MF, Pearson AC, Kanter KR, Labovitz AJ: Left ventricular thrombus with normal left ventricular wall motion in a patient with myelofibrosis. <i>Am Heart J</i> 1989;117:966–968.
Thrombocytosis	Multiple coronary thrombosis	Hamada Y, Matsuda Y, Fujii B, et al: Multiple coronary thrombosis in a patient with thrombocytosis. <i>Clin Cardiol</i> 1989;12:723–724.
Myeloproliferative disorder	Membranous obstruction of inferior vena cava	Sevenet F, Deramond H, Hadengue A, et al: Membranous obstruction of the inferior vena cava associated with a myeloproliferative disorder: a clue to membrane formation? <i>Gastroenterology</i> 1989;97:1019–1021.
Essential thrombocythemia	Hypertension (systemic)	Bruch JS, Stein RS, Oates JA: Hypertension complicating essential thrombocythemia. <i>Am J Med Sci</i> 1988;295:466–468.
Polycythemia vera	Acute total aortic occlusion during cardiac catheterization	Zinn P, Applegate RJ, Walsh RA: Acute total aortic occlusion during cardiac catheterization associated with polycythemia vera. <i>Cathet Cardiovasc Diagn</i> 1988;14:108–110.

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Table 1. Cardiovascular Complications of Myeloproliferative Disorders (*continued*)

Myeloproliferative Disorder	Cardiovascular Complication	Source
Myeloproliferative disorder	Left ventricular thrombus	Toto AS, Parameswaran R, Kotler MN, Parry W: Rapid development of left ventricular thrombus in a patient with myeloproliferative disorder. <i>Am Heart J</i> 1987;114:436–437.
Agnogenic myeloid metaplasia	Left ventricular thrombus	Daley P, Ptacin M, Horwitz M, et al: Left ventricular thrombus in agnogenic myeloid metaplasia. <i>Cardiology</i> 1987;74:53–57.
Myelofibrosis	Pulmonary emboli, renal vein thrombosis	Myelofibrosis, renal vein thrombosis, and pulmonary emboli. <i>NY State J Med</i> 1987;87:599–605.
Myelofibrosis	Portal venous thrombotic occlusion, cavernous transformation around the biliary tree	Ogawa S, Doishita K, Yamazaki Y, et al: Primary myelofibrosis associated with portal venous thrombotic occlusion and cavernous transformation around the biliary tree. <i>J Clin Gastroenterol</i> 1987;9:115–116.
Essential thrombocytosis	Hypertension, renal artery stenosis	Laguerre G, Antelin C, Kabaker M: Essential thrombocythemia and hypertension as a result of stenosis of the renal artery. <i>Arch Mal Coeur Vaiss</i> 1986;79:792–795.
Essential thrombocytosis	Lateral sinus thrombosis, intracranial hypertension	Mitchell D, Fisher J, Irving D, et al: Lateral sinus thrombosis and intracranial hypertension in essential thrombocythaemia. <i>J Neurol Neurosurg Psychiatry</i> 1986;49:218–219.
Agnogenic myeloid metaplasia	Postsplenectomy pericardial effusion	Nagler A, Brenner B, Argov S, Tatarsky I: Postsplenectomy pericardial effusion in two patients with myeloid metaplasia. <i>Arch Intern Med</i> 1986;146:600–601.
Agnogenic myeloid metaplasia	Massive pericardial effusion caused by extramedullary hematopoiesis	Vilaseca J, Arnau JM, Tallada N, et al: Agnogenic myeloid metaplasia presenting as massive pericardial effusion due to extramedullary hematopoiesis. <i>Acta Haematol</i> 1985;73:239–240.
Polycythemia vera	Coronary artery thrombosis	Pezzella AT, Esente P: Coronary artery thrombosis complicating polycythemia vera: an unusual indication for myocardial revascularization. <i>Mil Med</i> 1985;150:614–616.
Myelofibrosis	Pericardial hematopoiesis with tamponade	Haedersdal C, Hasselbalch H, Devantier A, Saunamaki K: Pericardial haematopoiesis with tamponade in myelofibrosis. <i>Scand J Haematol</i> 1985;34:270–273.
Myelofibrosis	Portal hypertension	Jacobs P, Maze S, Tayob F, et al: Myelofibrosis, splenomegaly, and portal hypertension. <i>Acta Haematol</i> 1985;74:45–48.
Aclarubicin for leukemia	QTc prolongation (corrected QT interval for heart rate)	Iwata N, Karasawa M, Omine M, et al: Aclarubicin-associated QTc prolongation and ventricular fibrillation. <i>Cancer Treat Rep</i> 1984;68:527–529.
Essential thrombocythemia	Recurrent myocardial infarction	Douste-Blazy P, Taudou MJ, Delay M, et al: Essential thrombocythaemia and recurrent myocardial infarction. <i>Lancet</i> 1984;2:992.
Essential thrombocythemia	Acute myocardial infarction	Pick RA, Glover MU, Nanfro JJ, et al: Acute myocardial infarction with essential thrombocythemia in a young man. <i>Am Heart J</i> 1983;106:406–407.
Essential thrombocythemia	Superior sagittal sinus thrombosis	Murphy MF, Clarke CR, Brearley RL: Superior sagittal sinus thrombosis and essential thrombocythemia. <i>Br Med J (Clin Res Ed)</i> 1983;287:1344.
Thrombocytosis	Fatal coronary heart disease	Saffitz JE, Phillips ER, Temeszy-Armos PN, Roberts WC: Thrombocytosis and fatal coronary heart disease. <i>Am J Cardiol</i> 1983;52:651–652.
Agnogenic myeloid metaplasia	Pericardial tamponade	Bubley G, Come P, MacDougall D, et al: Pericardial tamponade associated with myeloid metaplasia. <i>Am J Hematol</i> 1983;14:185–188.
Thrombocytosis and agnogenic myeloid metaplasia	Left ventricular mural thrombus	Baker KM, Hess CE, Ayers CR, et al: Left ventricular mural thrombus in a patient with thrombocytosis and agnogenic myeloid metaplasia. <i>Arch Intern Med</i> 1981;141:1527–1529.
Essential thrombocythemia and polycythemia vera	Pulmonary embolism	Bjorkholm M, Mellstedt H, Sawe U: Essential thrombocythaemia and polycythaemia vera presenting with pulmonary embolism mimicking pneumonia: case reports. <i>Haematologica</i> 1981;66:667–672.
Primary thrombocythemia	Myocardial infarction	Okayasu N, Murata M, Ueda A, et al: Primary thrombocythemia and myocardial infarction in a 26-year-old woman with normal coronary arteriogram. <i>Jpn Heart J</i> 1981;22:439–445.
Myelofibrosis	Portal vein thrombosis (pylithrombosis)	Aufschneider M, Salzer GM: Pylethrombosis following splenectomy. <i>MMW Munch Med Wochenschr</i> 1981;123:1503–1505.
Essential thrombocythemia	Bilateral posterior cerebral artery occlusion	Shio H, Ueki J: A case of essential thrombocythemia associated with cortical blindness due to bilateral posterior cerebral artery occlusion. <i>Nippon Naika Gakkai Zasshi</i> 1980;69:745–750.

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Table 1. Cardiovascular Complications of Myeloproliferative Disorders (*continued*)

Myeloproliferative Disorder	Cardiovascular Complication	Source
Polycythemia vera	Intraventricular thrombosis; a case of intractable cardiac failure	Ali M, Fayemi AO, Malcolm D, Braun EV: Intraventricular thrombosis in polycythemia vera: a cause of intractable cardiac failure. <i>Am Heart J</i> 1980;100:520–522.
Thrombocytosis	Coronary thrombosis and acute myocardial infarction	Virmani R, Popovsky MA, Roberts WC: Thrombocytosis, coronary thrombosis, and acute myocardial infarction. <i>Am J Med</i> 1979;67:498–506.
Agnogenic myeloid metaplasia	Cardiac tamponade caused by pericardial extramedullary hematopoiesis	Pipoly GM, Rogers J: Cardiac tamponade resulting from pericardial extramedullary hematopoiesis: a case report and review of the literature. <i>Cancer</i> 1979;44:1504–1506.
Polycythemia vera	Recurrent superior vena cava thrombosis and pulmonary emboli	Lesser L, Walter PF, Hardison JE: Ligation for the superior vena cava for recurrent pulmonary emboli. <i>South Med J</i> 1979;72:940–941.
Leukemia	Reversible heart block	Maguire LC, Sharlip ID, Spaulding JT, Tewfik HH: Reversible heart block in acute leukemia. <i>JAMA</i> 1978;240:668–669.
Essential thrombocythemia	Pericarditis	Averback P, Moinuddin M: Pericarditis as a manifestation of essential thrombocythemia. <i>Can Med Assoc J</i> 1977;117:154–156.
Agnogenic myeloid metaplasia	Pericarditis	Ashman SG, Kahn S, Williams AC: Pericarditis secondary to tooth extraction in a patient with myeloid metaplasia: report of case. <i>J Oral Surg</i> 1973;31:881–884.
Polycythemia vera	Idiopathic aortitis and arteritis	Belobradek Z, Steiner I: Idiopathic aortitis and arteritis in a woman with polycythaemia vera. <i>Sb Ved Lek Fak Karlovy Univerzity Hradci Kralove</i> 1972;15:583–588.
Polycythemia vera	Aortic stenosis	A case of polycythaemia with aortic stenosis demonstrated at the Royal Postgraduate Medical School. <i>BMJ</i> 1967;3:848–852.

POEMS = Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

the diagnosis of PV. Thromboembolism is a devastating complication that occurs in 15% to 60% of patients with PV and is the single most common cause of death in this disorder, accounting for 10% to 40% of the mortality in patients with PV. Thromboembolism may occur despite good hematologic control with phlebotomy, radioactive phosphorus, alkylating agents, or hydroxyurea. In all patients, the hematocrit should initially be maintained at less than 46% by phlebotomy. Newer agents, such as interferon- α and anagrelide, have also shown some promise in the management of polycythemia vera. Bleeding occurs in 15% to 35% of patients and causes death in 6% to 30% of cases, fewer than the number of deaths caused by thromboembolism. The risk of bleeding correlates with bleeding time, but not with platelet aggregation abnormalities.⁹ The use of antiplatelet agents increases the risk of hemorrhage.

Essential Thrombocythemia

ET is defined as a disorder with a platelet count greater than 600,000/mm³ and marked proliferation of bone marrow megakaryocytes.⁸ Thrombocytosis can be primary or secondary (reactive). Autonomous thrombocytosis can occur in MPD as PV or in isolated cases as primary or essential thrombocytosis. Thrombosis and bleeding are the major complications of ET

and the main causes of morbidity and mortality in patients with this disorder. Digital vessels, mesenteric and hepatic vessels, veins of the penis, and arteries and veins in unusual sites are the vascular sites involved. Cardiovascular complication rates in patients with ET range from 4% to 21%.^{2,3}

Acute ischemic coronary artery disease may be a presenting symptom of ET.^{4,5} Asymptomatic patients should not be treated unless they develop an occlusive vascular disease. Symptomatic patients should be treated with hydroxyurea or busulfan to maintain a platelet count lower than 600,000/mm³ without lowering the granulocyte count to less than 1500/mm³. Select patients with only thrombotic events can be managed with antiplatelet agents such as aspirin, which has led to improvement in many patients. The use of myelosuppressive agents should be considered in patients who fail therapy with antiplatelet agents or in patients who are symptomatic and have vascular occlusive disease.

Agnogenic Myeloid Metaplasia and Myelofibrosis

Diagnostic criteria for AMM/MF include: 1) splenomegaly, 2) leukoerythroblastic blood smear, 3) marrow fibrosis, and 4) extramedullary hematopoiesis. Extramedullary hematopoiesis in unusual sites such as pericardium has been reported to lead to

Table 2. Major and Minor Criteria for Diagnosis of Polycythemia Vera *

Major criteria (A)

A1: Erythrocyte mass greater than 36 mL/kg in men or greater than 32 mL/kg in women or packed cell volume > 0.51 in men and > 0.48 in women

A2: Splenomegaly

A3: Oxygen saturation greater than 92%

Minor criteria (B)

B1: Platelet count higher than 400,000/mm³

B2: Leukocyte count higher than 12,000/mm³ (no fever or infection)

B3: Leukocyte alkaline phosphatase score higher than 100

B4: Vitamin B₁₂ level higher than 900 pg/mL or unsaturated vitamin B₁₂-binding capacity higher than 2200 pg/mL

*Diagnosis requires the presence of all three major criteria or two major criteria (excluding splenomegaly) and two minor criteria; for example, A1 + A2 + A3 or A1 + A3 + any two B.

cardiovascular presentations. Management measures include transfusion, steroids for thrombocytopenia, and, possibly, splenectomy. Radiotherapy may be used for bone pain or for hypersplenism. Death usually results from acute leukemia or bone marrow failure.

CARDIOVASCULAR MANIFESTATIONS OF MYELOPROLIFERATIVE DISORDERS
Myocardial Disease

Coronary artery disease. MPDs, particularly PV and ET, have long been recognized to predispose to thrombosis. The most common sites include the cerebral, digital, mesenteric, portal, and retinal circulations; the coronary circulation may be infrequently involved. Acute myocardial ischemia in patients younger than age 30 years is a rare event and, when detected, suggests underlying coronary atherosclerosis, which is often caused by a predisposing factor such as diabetes mellitus, hypertension, or hypercholesterolemia.¹⁰ In other cases, unusual medical conditions may underlie coronary ischemia in young patients, and one such condition is an MPD. Signs of ischemic heart disease can be the sole clinical manifestation of such disorders.⁴⁻⁷

A review of case reports revealed that cardiovascular complications are most commonly associated with ET, followed by PV. Furthermore, of the spectrum of cardiac complications, coronary artery disease is the most common presentation and may be the first manifesta-

tion as reported in cases of PV^{6,7} and ET.^{4,5} Also, a case of recurrent myocardial infarction in a patient with ET was reported.¹¹ Absolute thrombocytosis has been recognized as a major risk factor for thrombotic complications in ET, but patient age, duration of thrombocytosis, and a history of previous thrombotic events may also help identify patients at risk for complications.¹²⁻¹⁵ Other risk factors for vascular disease, such as smoking, hypertension, diabetes mellitus, and hyperlipidemia, have received little attention in ET, which is primarily a disease of the elderly population, a group already at increased risk for stroke, heart attack, and atherosclerotic peripheral vascular disease.¹⁶ Several reports stress that cigarette smoking causes coronary vasoconstriction or carbon monoxide damage to endothelium and increases platelet aggregation.⁴ Possible causes of cardiac ischemic events include coronary thrombosis, coronary vasospasm, and possibly an arteritis associated with such disorders. Both acute and recurrent episodes of myocardial infarction have been reported in patients with ET.

Coronary vasculopathy. Thrombosis secondary to hyperviscosity and high platelet count is primarily discussed as the origin of infarction in patients with MPDs such as PV. However, Hermanns et al¹⁷ reported vasculopathy in coronary vessels in a patient with PV; on necroscopy, marked intimal proliferation and unchanged media and adventitia of coronary vessels were noted. Proliferation was found to cause multiple occlusions and was interpreted as an alternate mechanism for vascular occlusion in PV.

Mural thrombus. Intracardiac thrombus has been reported, particularly in the left ventricle and right atrium. A case of intractable cardiac failure secondary to intraventricular thrombus was also found.

Hypertension

Systemic hypertension. A review of case reports also revealed a case in which the blood pressure of a patient with systemic hypertension that had been refractory to antihypertensive therapy returned to normal after a modest antihypertensive regimen following percutaneous transluminal renal angioplasty and reduction of the platelet count. Similarly, Bruch et al¹⁸ reported reduction of blood pressure in a patient with ET when treatment of ET with cytoreductive therapy was maintained. Possible mechanisms may include vascular occlusion and the effect of prolonged PV on normal vascular distensibility. A case of renal artery stenosis resulting in hypertension was also encountered.¹⁹

Pulmonary hypertension. Pulmonary hypertension has been reported in patients with PV and has been

postulated to develop secondary to pulmonary vascular occlusion.²⁰⁻²² Development of pulmonary hypertension in patients with myelofibrosis is attributable to hematopoietic infiltration of the pulmonary parenchyma, portal hypertension, thrombocytosis, hypercoagulability, and left ventricular failure, as examined by Garcia-Manero et al²³ in a series of patients. These researchers suggested that patients with myelofibrosis and dyspnea should undergo Doppler echocardiography to evaluate pulmonary artery pressures.

Valvular Disease

Cardiac valve abnormalities. Various cardiac valve abnormalities have been reported in patients with MPDs. Reisner et al²⁴ reported that some patients with a history of an MPD have clinically significant valvular disease, particularly when the history is complicated by a thromboembolic event. Valvular abnormalities encountered in these studies included mitral valve regurgitation, aortic valve thickening, mitral annulus calcification, mitral valve thickening, and aortic valve regurgitation.

Pericardial Disease

A spectrum of pericardial abnormalities have been found in patients with MPDs, including pericardial effusion, pericardial tamponade, and pericarditis. Possible causes of pericardial disease secondary to MPDs include pericardial extramedullary hematopoiesis and, possibly, infarction secondary to ischemia associated with MPDs.

Major Vessel Disease

Changes in major blood vessels such as membranous obstruction of inferior vena cava, aortitis, arteritis, and superior vena cava thrombosis have been reported secondary to hypercoagulability associated with MPDs.

Abdominal vessels. Different abdominal vessels have been found to have thrombotic occlusion in MPDs. According to the literature, common vessels affected include the hepatic vein (Budd-Chiari syndrome; hepatic vein thrombosis), the portal vein, and the branches of the superior mesenteric artery.

Budd-Chiari syndrome. In Western countries, the chronic MPDs are considered the main etiology of Budd-Chiari syndrome.²⁵⁻²⁷ Therapeutic options for this syndrome include anticoagulation with heparin, fibrinolysis followed by oral anticoagulation, and appropriate treatment of the underlying MPD with alkylating agents.²⁵⁻²⁷ If these treatments fail, angioplasty, stenting, venous decompression with portal-systemic shunts, or liver transplantation are considered.

Renal vascular system. Three cases of stenosis of a renal artery have been reported in patients with ET.¹⁹ In all three cases, neither vascular risk factors nor hereditary vascular disease were present. Researchers postulated that high levels of platelets in ET may be responsible for early atherosclerosis, causing stenosis of a renal artery. Resultant hypertension was also seen in these cases. Also reported in the literature was a case of renal vein thrombosis in a patient with MF.²⁸

Other Manifestations

Pulmonary embolism. The hypercoagulability of myeloproliferative disorders is also associated with pulmonary embolism in patients with ET, PV, MF, and CML. In one case report, complete thrombotic occlusion of the pulmonary arterial system accompanied with pulmonary arteritis was found upon necropsy in a patient with CML.²⁹

Thrombotic thrombocytopenic purpura. Rachmani et al³⁰ reported two patients with CML who developed thrombotic thrombocytopenic purpura after treatment with interferon- α . In one patient, a lymphoblastic transformation was recognized concomitantly.³⁰

Arterial thrombosis resulting in digital gangrene. Cases of ET complicated by digital gangrene have been reported. In one small study of 10 patients with this manifestation, marked clinical improvement and reduction and normalization of the platelet count were reported with the use of busulfan.³¹

Cerebrovascular disease. Cerebrovascular accidents (CVAs) are frequent in patients with MPDs, even in young patients and particularly in patients with atherosclerotic risk factors (eg, tobacco use, hypertension). Different affected vascular areas have been reported in these patients:

- 1) Superior sagittal sinus thrombosis in a blastic crisis of CML as well as in a case of ET^{32,33}
- 2) Cortical blindness caused by bilateral posterior cerebral artery occlusion in a case of ET³⁴
- 3) Lateral sinus thrombosis and intracranial hypertension in ET³⁵
- 4) Recurrent CVAs in ET in a case of fibromuscular dysplasia³⁶
- 5) Acute ischemic strokes in ET secondary to obstruction of large intracranial and extracranial vessels³⁷
- 6) Central retinal vein occlusion with neovascular glaucoma³⁸

Early diagnosis, recognition of these complications, and appropriate treatment with antiplatelet agents are crucial in ameliorating these problems.

Table 3. Pathogenesis of Hypercoagulability Secondary to Polycythemia Vera

Increased hematocrit and hyperviscosity
Erythrocyte effect on platelet interaction with the vessel wall
Iron deficiency
Platelet abnormalities (quantitative and qualitative)
Coagulation system abnormalities

POEMS syndrome and essential thrombocythemia.

POEMS is an acronym for **P**olyneuropathy, **O**rgano-megaly, **E**ndocrinopathy, **M**onoclonal gammopathy, and **S**kin changes. Zenone et al³⁹ reported a case of POEMS syndrome in a patient with ET who had no evidence of solitary plasmacytoma, multiple myeloma, or Castleman's disease. This patient also had arterial thrombotic complications.³⁹

Essential thrombocythemia and pregnancy. ET in pregnancy is associated with adverse perinatal outcomes, including abortion, intrauterine fetal death, abruptio placentae, intrauterine growth retardation, and premature delivery.⁴⁰ The possible underlying mechanism is thrombosis of uteroplacental circulation; histologic examination of the placenta in one of the cases showed an ischemic lesion.⁴¹ Treatments used during pregnancy include acetylsalicylic acid, dipyridamole, heparin, and plateletpheresis. Milano et al⁴² reported a case of successful treatment of ET in a pregnant patient with recombinant interferon- α -2a.

PATHOGENESIS

Chronic Myeloid Leukemia

Increased thrombogenesis in CML may be explained by Virchow's triad, which consists of the following three abnormalities: 1) changes in the vessel wall, 2) changes in blood flow, and 3) changes in blood constituents. Changes in the vessel wall are secondary to an increased number of leukocytes, which causes platelets to come in contact with the wall or affects the distensibility of the wall. Changes in blood flow occur secondary to elevated leukocyte counts, which may affect blood flow, particularly when leukocytosis is extreme (more than 300,000/mm³). Changes in blood constituents consist of coagulation system abnormalities, thrombocytosis, and myelofibrosis.

Polycythemia Vera

As mentioned previously, thromboembolism occurs in approximately 15% to 60% of cases of PV and is the cause of mortality in 10% to 40% of cases. Thromboses in PV are mainly venous and are associated with pul-

monary embolism. However, arterial thromboembolism and intra-abdominal venous thromboses also occur in PV. The pathophysiology of thromboembolism is not clear, but multiple factors are thought to be implicated in the hypercoagulability associated with PV. These factors include: 1) increased hematocrit and hyperviscosity, 2) erythrocyte effect on platelet interaction with the vessel wall, 3) iron deficiency, 4) platelet dysfunction, and 5) coagulation system abnormalities (**Table 3**).

Increased hematocrit and hyperviscosity. Increased hematocrit and blood viscosity correlate well with the incidence of thrombosis. Hematocrit levels higher than 60% are associated with a 38-fold increase in the incidence of thrombosis compared with hematocrit levels of 40% to 44%.⁴³ Two mechanisms may account for this increase: 1) axial migration of erythrocytes causing more platelets to have contact with the vessel wall, thus promoting thrombogenesis, and 2) the effect of chronic PV on normal vascular distensibility that causes increased thrombogenesis.

Erythrocyte effect on platelet interaction with the vessel wall. Axial migration of erythrocytes may result in more platelets coming in contact with the vessel wall, thereby enhancing thrombogenesis.

Iron deficiency. Iron deficiency results from phlebotomy, hemorrhage, and the disease itself. Iron deficiency increases membrane stiffness, which decreases erythrocyte deformability and leads to hyperviscosity.

Platelet dysfunction. Platelet abnormalities may be qualitative or quantitative. A significantly increased platelet count in excess of 500,000/mm³ to 650,000/mm³ increases the predisposition to develop thrombosis of the cerebral or coronary circulation.^{1,3,44} Qualitative abnormalities include: hypoaggregability or hyperaggregability, abnormal bleeding time, acquired storage pool disease, membrane abnormalities, and decreased aggregation with epinephrine, collagen, and adenosine diphosphate.

Coagulation system abnormalities. Several mechanisms may account for coagulation system abnormalities in PV, including: 1) release of intravascular thromboplastins and proteases from erythrocytes and platelets, which may activate the intrinsic coagulation cascade; 2) increased levels of antithrombin III; 3) decreased fibrinogen survival, with chronic intravascular coagulation;⁴⁴ 4) deficiency of protein C, protein S, and plasminogen; and 5) decreased fibrinolytic activity caused by higher plasmatic plasminogen activator inhibitor (PAI)-1 activity and platelet PAI-1.⁴⁵

Essential Thrombocythemia

Several mechanisms have been postulated to contribute to the thrombosis associated with thrombocytosis,

including: 1) platelet activation as the result of endothelial injury; 2) platelet release of thromboxane A₂, which induces coronary spasm and subsequent thrombosis; 3) selective lipoxigenase deficiency; 4) altered platelet granule glycoprotein; 5) increased activity of fibrinolysis inhibitors (eg, PAI-1), so that a hypofibrinolysis state could be an additional factor contributing to thrombogenesis;⁴⁵ 6) probable contributing factors such as smoking (carbon monoxide);^{4,11} 7) reduction of antithrombin III, protein C, and protein S,⁴⁴ and 8) abnormalities of von Willebrand's factor.⁴⁶

Agnogenic Myeloid Metaplasia

Possible mechanisms to explain the association of AMM and thrombogenesis include thrombocytosis, extramedullary hematopoiesis, coagulation profile abnormalities, and postsplenectomy status. Antiphospholipid antibodies have also been reported in these patients (Table 1). Abnormalities of megakaryocytopoiesis and thrombocytes, including thrombocytes with giant forms with either hypertrophy of open canalicular system or abundance of dense granules, and β-glycogen accumulation have been reported.⁴⁷ Pylethrombosis following splenectomy has also been reported.⁴⁷

MANAGEMENT

Watchful Waiting Approach

In an asymptomatic patient, a watchful waiting approach may be warranted, although it is difficult for the physician to withhold treatment until a potentially serious thrombotic event occurs. Review of the medical literature shows that most patients with ET who have a major thrombotic complication either have the complication at the time of diagnosis or after preceding, less severe, thrombotic symptoms. Based on this generalization from the literature, it is reasonable to omit myelosuppressive therapy in asymptomatic patients with ET. Similarly, young patients with PV who have no thrombotic manifestations can be managed with phlebotomy alone. No evidence-based data show that myelosuppressive therapy should be instituted secondary to high platelet count or an effort to prevent myeloid metaplasia. However, in patients with PV or ET who have a history of previous thrombotic manifestations, the risk-benefit ratio favors myelosuppressive therapy.⁴⁸

Phlebotomy

Clinical data have indicated that thrombotic complications can be prevented by maintaining the hematocrit below 45% with phlebotomy alone initially.⁴³ In younger patients with normal cardiovascular status, a 450-mL phlebotomy can be performed every other day until the

Table 4. Guidelines for the Management of Polycythemia Vera

Age	Individualized Therapy
< 50 years	Phlebotomy only when possible
50 to 70 years	Phlebotomy with or without hydroxyurea
> 70 years	Radioactive phosphorus (³² P) or hydroxyurea and phlebotomy

hematocrit is less than 45%. In older patients or patients with a history of cardiovascular disease, smaller phlebotomies (200 to 300 mL) should be performed twice weekly until the hematocrit is less than 45%.

However, in 1986, Kaplan et al⁴⁹ reviewed the long-term management of PV and found that phlebotomy alone was paradoxically associated with an increased incidence of thromboembolism in patients who were older than age 70 years or who had a thrombotic event. To summarize, the guidelines for management of PV are shown in **Table 4**.

Cytostatic or Radioactive Agents

A literature search revealed that patients treated with mutagenic drugs such as alkylating agents or phosphorus had fewer thrombotic events but were more likely to develop acute leukemia.^{50, 51} Patients managed with phlebotomy and hydroxyurea had a decreased incidence of thrombosis and no increase in acute leukemia. Because thromboembolism as well as bleeding events are related to thrombocytosis and improve with lowering of the platelet count with immunosuppressive therapy, asymptomatic patients should not be treated unless they have an underlying vascular occlusive disease. Aspirin treatment improves the clinical course in patients with ET who develop transient cerebral and ocular ischemic events. However, most symptomatic patients should be treated with myelosuppressive agents such as hydroxyurea or busulfan, with dose adjustments to maintain the platelet count less than 600,000/mm³ without lowering the granulocyte count to less than 1500/mm³.

Antiplatelet Agents

Quantitative and qualitative platelet abnormalities are central to the pathogenesis of thrombotic complications in MPDs. Aspirin irreversibly inactivates cyclooxygenase in platelets. This effect leads to a decreased production of platelet thromboxane A₂, which has vasoconstricting and platelet-aggregating properties. In PV and ET, aspirin has been shown to benefit microvascular

thrombotic complications, especially in patients with transient cerebral or ocular ischemic events.⁵²

Treatment with acetylsalicylic acid and dipyridamole has also been attempted in splenectomized patients with MF, resulting in a decreased platelet utilization and hence increased thromboembolic episodes.⁵³

The increased risk of hemorrhage secondary to the use of aspirin and dipyridamole should be considered. Lower doses of aspirin (less than 325 mg/day) may be associated with less hemorrhagic complications and may benefit prevention of thrombotic complication; however, this hypothesis remains to be proven. The European Collaboration on Low-Dose Aspirin in PV is a randomized trial designed to assess the risk-benefit ratio of low-dose aspirin in PV and may eventually address this issue.⁵⁴

Anticoagulation

Zinn et al⁵⁵ reported the case of a patient with PV who developed acute aortic obstruction during catheterization. These authors suggested that, in acute thrombotic states, aggressive anticoagulation may be necessary and that anticoagulation should be considered in these circumstances because neither aspirin nor dipyridamole appears to be beneficial in this setting.⁵⁶

Immunotherapy

Interferon- α has shown therapeutic activity in PV and ET, evidenced in multiple small studies and single-arm trials.⁵⁷ Interferon- α may also control the chronic phase in CML and may have the advantages of inducing a Ph¹-negative status in a minority of patients. Recent reports note reversal of bone marrow fibrosis after treatment with interferon- α .⁵⁸ This data necessitates randomized controlled trials comparing interferon- α with standard therapy; the advantages of interferon- α therapy over current standard therapy include the lack of known leukemogenic and teratogenic effects as well as the potential of altering the underlying course of disease.

A recent case report notes multivessel coronary thrombosis in a patient with ET.⁵⁹ The thrombosis was treated with abciximab, resulting in thrombus resolution. Abciximab is a platelet glycoprotein IIb/IIIa, receptor-inhibiting monoclonal antibody.⁵⁹

Newer Agents

Anagrelide is a new platelet-lowering agent that interferes with megakaryocyte maturation. More than 90% of patients with ET respond to anagrelide, regardless of the presence or absence of previous therapy.

The durable responses have been obtained with a maintenance dose of 2 to 2.5 mg/day. Common side effects include headache, fluid retention, tachycardia, and arrhythmia, and are mostly secondary to the drug's direct vasodilating and positive inotropic effects.⁶⁰

Similarly, picotamide is another new antiplatelet agent that encumbers a dual antithromboxane activity: inhibition of thromboxane A₂ synthase and thromboxane A₂ receptor antagonism. In an observational, long-term trial (12 months), picotamide has been found to be safe and effective in patients with ET and thrombotic complications.⁶¹

Invasive Revascularization

Invasive procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) can be used successfully if medical treatment fails to induce sufficient symptomatic relief. Cases of post-operative thrombotic complications, including in-stent thrombosis, have been reported;⁶² this finding warrants studies to evaluate the role of antiplatelet agents in this setting. A successful case of open-heart surgery in a patient with chronic leukemia was also found.⁶³

Summary

In summary, the literature suggests that cytostatic agents or antiaggregant treatment should be reserved for symptomatic patients or patients with a positive history of thrombotic events.

COMPLICATIONS OF THERAPY

The following complications have been noted after therapy for thrombosis: 1) paradoxical thrombosis secondary to phlebotomy, 2) iron deficiency that enhances hypercoagulability, 3) induction of malignancy, which is a long-term concern in younger patients receiving myelosuppressive therapy, 4) gastrointestinal hemorrhage because antiplatelet agents are associated with increased risk of hemorrhage, especially gastrointestinal bleeding, in patients with PV, and 5) neutropenia, secondary to immunosuppressive therapy or splenectomy, resulting in infections.

CONCLUSIONS

Thrombosis is a major cause of death in patients with MPDs. The importance of a positive patient history and clinical evaluation in the assessment of thrombotic risk are stressed. Furthermore, a periodic reevaluation of the antiaggregant treatment of such patients is also necessary because treatment is associated with an increased incidence of bleeding. The review of the literature

emphasizes that clinicians should remain aware of MPDs and their association with thrombosis. After this condition is diagnosed, the need for antiplatelet or antimitotic agents should be recognized. Also, patients presenting with acute myocardial infarction and hematologic abnormalities that predispose to both bleeding and thrombosis may benefit from immediate catheterization for possible intervention or local thrombolysis. The ready availability of catheterization laboratories, medical personnel, and trained physicians provides the best chance for a good outcome in these often gravely ill patients. Finally, life-threatening thrombotic and hemorrhagic problems may be a harbinger for a silent MPD.

HP

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