Case Reports

Off-Pump Myocardial Revascularization

in a High-Risk Patient with Essential Thrombocythemia

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Essential thrombocythemia is a rare type of myeloproliferative disorder. Cerebral, myocardial, and peripheral thrombosis are all frequent complications of the disease.

A 71-year-old man presented with severe coronary artery disease, associated with cerebral vascular ischemic changes and erythromelalgia. His platelet count was 1,486 ×10³/μL. The patient underwent successful myocardial revascularization by means of an off-pump technique after his platelet count had been reduced by hydroxycarbamide administration.

We conclude that the use of off-pump cardiopulmonary bypass in high-risk patients with essential thrombocythemia is safe. Reducing platelet count via the administration of hydroxycarbamide and the careful balancing of antiplatelets and anticoagulants is crucial in determining the outcome of surgery. ***(Tex Heart Inst J 2014;41(5):537-42)***

Essential thrombocythemia is a chronic myeloproliferative disease characterized by persistent elevation of platelet count.[1,2] Patients might remain asymptomatic; however, most have a tendency toward thrombosis and to a lesser extent toward hemorrhage affecting the cerebral, coronary, and peripheral vessels.

Cardiovascular sequelae among these patients vary from 4% to 21%.[1] The incidence of coronary artery disease can reach 9.4%, and this is accompanied by a high incidence of acute myocardial infarction.[2]

We present the case of an elderly man with manifestations of essential thrombocythemia. Both medical and surgical management are discussed.

Key words: *Blood platelets/metabolism; coronary artery bypass, off-pump; graft survival; hydroxycarbamide; Janus kinase 2; megakaryocytes; platelet count; plateletpheresis; thrombocythemia, essential/blood/drug therapy; treatment outcome; vascular patency*

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Case Report

In September 2012, a 71-year-old heavy smoker presented at another hospital for evaluation of dyspnea and dizziness. During the preceding 2 months, this man had been admitted to various hospitals with dyspnea, wheezy chest, and peripheral edema. He was told that all his symptoms were related to smoking, and he was treated for emphysema.

During routine laboratory investigations, a high platelet count of 1,486 ×10³/μL was found, with a hemoglobin level of 14 g/dL, a hematocrit of 37.9%, a mean corpuscular volume of 82 fL, and a white blood count of 8.4 K/μL. Results of other blood tests were normal.

The diagnosis of essential thrombocythemia was confirmed by bone marrow aspirate, which showed an increased number of megakaryocytes; other hemopoietic elements were normal (Fig. 1). Reverse transcription polymerase chain reaction analysis for the Philadelphia chromosome was negative. The patient was given hydroxycarbamide (2 g/d), aspirin (100 mg/d), clopidogrel (75 mg/d), a diuretic, and a bronchodilator. During the course of treatment, he had a syncopal attack, which lasted for a few minutes.

The patient was referred to our hospital after a carotid artery duplex scan yielded normal results and a brain magnetic resonance image showed signs of senile atrophic changes, together with bilateral small vascular ischemic changes (Fig. 2).

On admission, the patient was slightly tachypneic. His blood pressure was normal, and he had a regular pulse of 78 beats/min. His oxygen saturation on room air was 88%.

Chest examination showed a bilateral decrease in air entry. Scattered wheezes were heard all over the chest, together with fine crepitations along the lung bases. Cardiac examination revealed a soft pansystolic murmur over the mitral area, extending to the axilla. There was mild bilateral peripheral edema and painful light-blue coloration

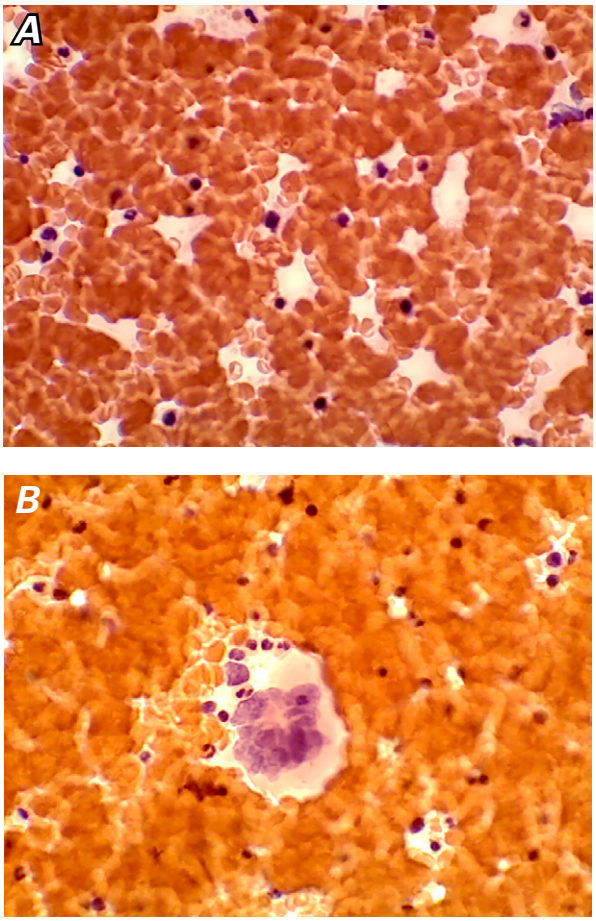

Fig. 1 *Photomicrographs of bone marrow aspirate show **A**) an increased number of megakaryocytes, in addition to normal erythroid and granulocytic cells and **B**) large megakaryocytes with hyperlobulated nuclei (H & E, orig. ×60).*

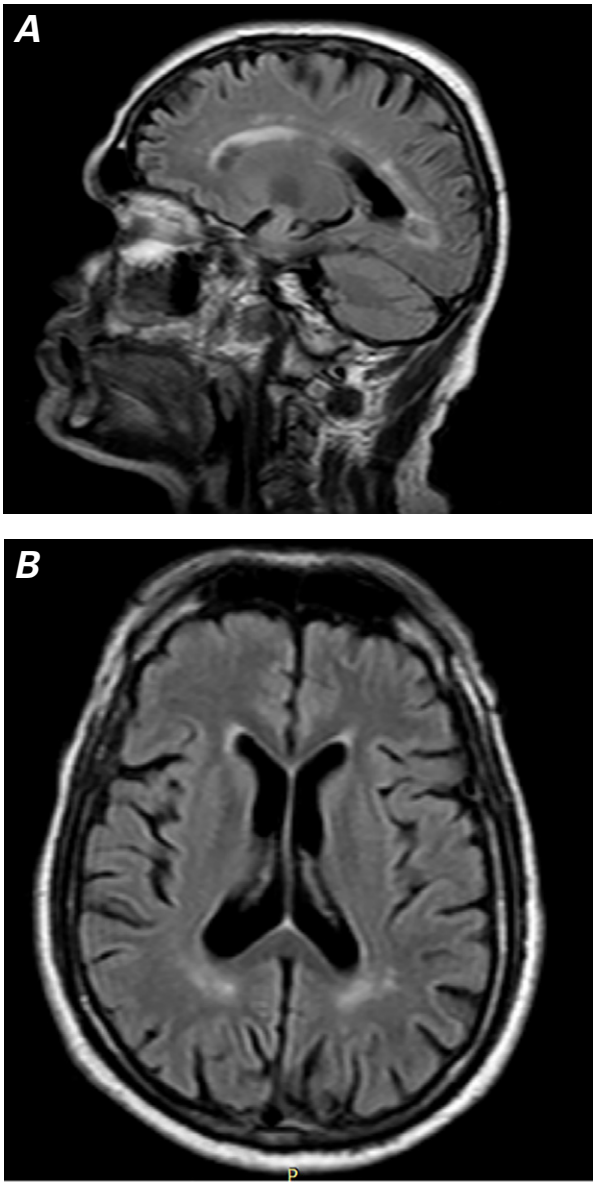

Fig. 2 *Brain magnetic resonance images (flair sequence) in **A**) sagittal and **B**) axial views show hyperintense lesions in the periventricular area.*

of the right 4th and big toes, characteristic of decreased capillary filling. Peripheral pulsations could be felt bilaterally.

No evidence of organomegaly was felt on abdominal examination. Laboratory investigations were normal except for a high platelet count of 600 $\times 10^3/\mu L$.

Chest radiography showed cardiomegaly and congested lung fields. Evidence of intraventricular conduction defects with left anterior hemiblock was seen on electrocardiography. Transthoracic echocardiography revealed a severely impaired left ventricular ejection fraction (LVEF) of 0.28, caused by anteroseptal and posterior hypokinesia in association with severe diastolic dysfunction. Coronary angiography showed complete occlusions of the right coronary artery and the left anterior descending coronary artery (LAD), both of which were associated with a mild distal lesion of the left circumflex coronary artery (Fig. 3). A thallium stress single-photon-emission computed tomographic study showed a fixed defect at the left ventricular apex, denoting scar tissue. That same study revealed minimal redistribution of the interventricular septum (denoting mild ischemia) and a small area of reversible ischemia at the anterior surface of the LV (Fig. 4).

The patient underwent myocardial revascularization via an off-pump technique, with the aid of a suction stabilizer (Medtronic, Inc.; Minneapolis, Minn). We anastomosed the left internal mammary artery to the LAD after performing endarterectomy. The right coronary and diagonal arteries were revascularized with saphenous vein graft. Recovery was uneventful, both operatively and postoperatively. The patient underwent 14 hours of ventilation, needed minimal myocardial support, and lost 450 mL of blood. During hospitalization, his platelet count varied from 302 to 571 $\times 10^3/\mu L$.

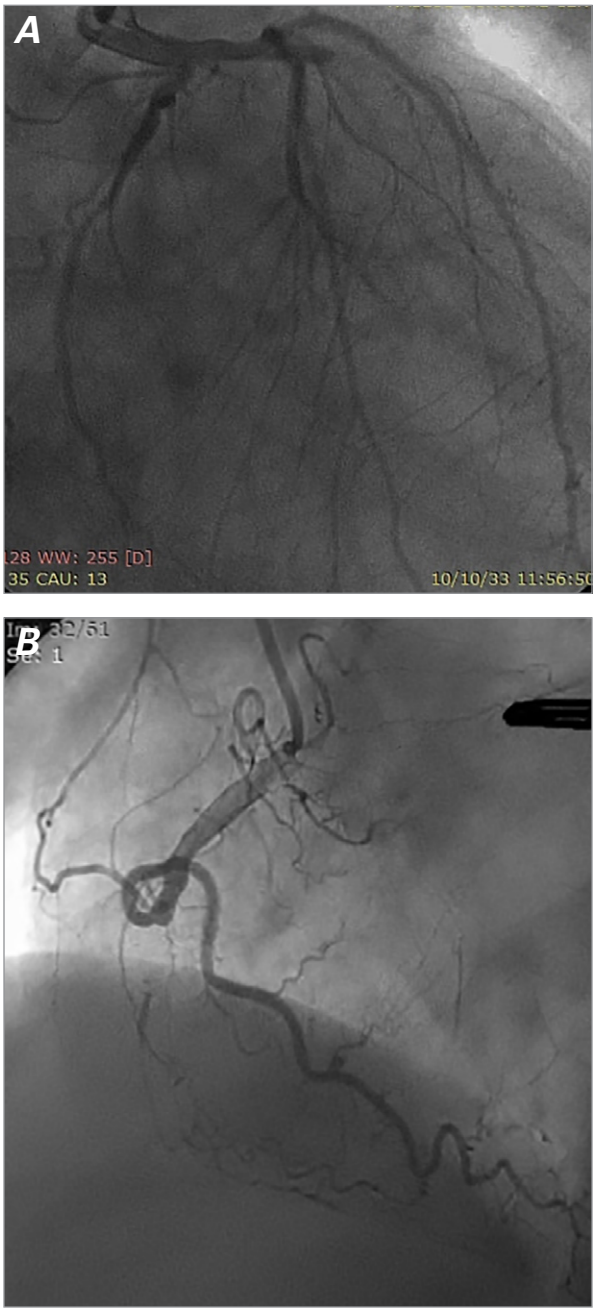

Fig. 3 *Preoperative coronary angiograms show complete occlusion of* ***A****) the left anterior descending coronary artery and* ***B****) the right coronary artery.*

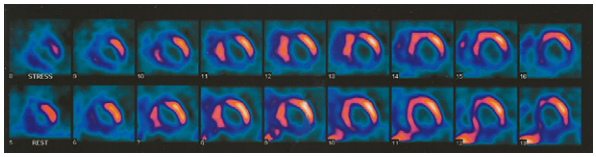

Fig. 4 *Stress thallium single-proton-emission computed tomogram shows a fixed defect at the ventricular apex with minimal redistribution of interventricular septum, denoting mild ischemia. A small area of reversible ischemia can be seen at the anterior surface.*

After 8 days, the patient was discharged on a daily regimen of hydroxycarbamide (1.5 g), aspirin, warfarin, amiodarone, and diuretics. He remained asymptomatic and active during 2 years of follow-up. Echocardiography showed improvement of the LVEF to 0.33 and a platelet count of 520 $\times 10^3/\mu L$.

Discussion

Essential thrombocythemia is a rare type of myeloproliferative disorder characterized by a sustained elevation in platelet count (more than 600,000/μL).[2]

The exact cause is still unclear. Excessive production of platelets from megakaryocytes can be caused by autonomous production, increased sensitivity to cytokines (interleukin-3), decreased inhibition of platelets by inhibiting factors (such as transforming growth factor-β), or defects in the accessory-cell microenvironment.[3] In 40% to 50% of patients, a mutation is found in the Janus kinase 2 gene.[4]

Patients with essential thrombocythemia have a high likelihood of thrombotic and hemorrhagic complications, as a consequence of abnormal platelet function. The exact mechanism by which such complications are produced is not known. Various factors are involved, among them a reduction in aggregation or hyperaggregation, decreased activity of von Willebrand ristocetin cofactor, and acquired deficiency of antithrombin III, protein C, and protein S.[5]

Clinically, up to one third of patients remain asymptomatic[6]; however, most present with vasomotor symptoms or complications from thrombosis or bleeding that affect small or large vessels of cerebrovascular, coronary, and peripheral arterial circulation.[6]

The effect of thrombocythemia in our patient was seen in his small vessels. His coronary arteries were severely diseased, despite the fact that the patient had no risk factors for coronary disease except for smoking. Both dizziness and transient ischemic attacks resulted from the condition of the small cerebral vessels—areas of vascular ischemia were readily apparent on magnetic resonance imaging. Occlusion of the small peripheral arterioles resulted in a reduction of capillary pulsations and in erythromelalgia.

The treatment of patients who are undergoing coronary artery surgery in the presence of thrombocythemia is complicated because the number of patients in this circumstance is so small that there is no established protocol. Important variables to be considered when planning surgery include the need to achieve a balance between the prevention of bleeding and thrombotic complications, the use of platelet-lowering agents and their side effects, and the technique of cardiopulmonary bypass (CPB) to be used during surgery. The reduction of platelets is essential: it should be started before surgery and continued postoperatively. Effective platelet-

lowering agents include hydroxycarbamide, anagrelide, and interferon-α.[7] Hydroxycarbamide is a nonalkylating antineoplastic drug that substantially reduces platelet count and the rate of vascular complications; it is considered to be the drug of choice. However, its long-term risk of leukemogenic effect cannot be ruled out.[7]

Harrison and colleagues[8] found that hydroxycarbamide (when combined with aspirin) is superior to anagrelide, which was associated with a high incidence of arterial thrombosis, severe hemorrhage, and transformation to myelofibrosis. In unstable cardiac patients with extremely high platelet counts who require urgent surgery, plateletpheresis (uncommonly, but more accurately, called thrombocytapheresis) was found to be extremely effective in reducing counts and symptoms.[9]

The importance of reducing platelets preoperatively was well illustrated by the cases of Daya and colleagues[10] and Momiyama and coworkers,[11] whose patients successfully underwent urgent coronary surgery before receiving a platelet-lowering agent. Their patients experienced postoperative sequelae: pulmonary embolism, myocardial infarction, and cerebral infarction.

The number of platelets that is optimal for the safe performance of surgery is not clear. In previous studies,

TABLE I. Coronary Artery Surgery among Patients with Essential Thrombocythemia

Reference	Age (yr), Sex	Antiplatelet Therapy	Coronary Artery Lesion	Bypass Technique	Outcome
Pick RA, et al.[15] (1983)	26, M	Plateletpheresis	LAD	CCAB	Uneventful
Scheffer MG, et al.[1] (1991)	47, M	Busulfan	1 vessel	CCAB	Uneventful
	59, F	Busulfan	3 vessels	CCAB	Uneventful
	62, M	Aspirin	3 vessels	CCAB	Uneventful
	75, M	Busulfan	3 vessels	CCAB	Uneventful
Yoshida H, et al.[16] (1991)	52, M	Melphalan	LAD	CCAB	Uneventful
Iemura J, et al.[17] (1991)	53, M	Melphalan	LAD	CCAB	Uneventful
Momiyama T, et al.[11] (1993)	58, M	Melphalan	Left main	CCAB	Myocardial and cerebral infarction
Schött U[18] (1994)	67, F	Plateletpheresis	Left main and LCx	CCAB	Uneventful
Kohno K, et al.[19] (1997)	55, —	Interferon	—	CCAB	Uneventful
Ohto T, et al.[14] (1998)	78, M	Hydroxycarbamide	LAD and RCA	CCAB	Died after 5 mo
Haddad M, et al.[20] (2003)	26, M	Anagrelide	LAD	CCAB	LVAD and heart transplantation
Daya SK, et al.[10] (2004)	31, M	Hydroxycarbamide and anagrelide	Left main and LAD	CCAB	Pulmonary embolism
Nurkalem Z, et al.[21] (2006)	71, M	Thrombopheresis	Left main	CCAB	Uneventful
Yorukoglu Y, et al.[22] (2007)	61, M	Anagrelide	LAD and D	OPCAB	Died on 5th postoperative d
Kaya K, et al.[12] (2009)	65, M	Hydroxycarbamide	LAD and D	OPCAB	Uneventful
Schölzel BE, et al.[13] (2010)	36, M	Hydroxycarbamide	LAD and RCA	CCAB	Thrombosis of coronary arteries, pulmonary embolism, and tamponade
Das SS, et al.[9] (2011)	73, M	Plateletpheresis	Left main and LAD	CCAB	Uneventful
Current case	71, M	Hydroxycarbamide	LAD, D, and RCA	OPCAB	Uneventful

CCAB = conventional coronary artery bypass; D = diagonal artery; F = female; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVAD = left ventricular assist device; M = male; OPCAB = off-pump coronary artery bypass; RCA = right coronary artery

the number of platelets has varied from 350 to 1,000 $\times 10^3/\mu L$.[9,12,13] Patients with normal or near-normal numbers had no complications,[9,12] whereas patients with a platelet count of 1,000 $\times 10^3/\mu L$ experienced complications.[13] In our patient, the count was $600 \times 10^3/\mu L$, and the result of surgery was satisfactory.

Similarly, the postoperative observation of platelet count and the continuation of antiplatelet therapy are crucial. Discontinuation of these medications can result in death.[14]

Scheffer and colleagues[1] found that controlling platelet activation and aggregation by platelet-lowering agents is effective both in preventing and in terminating thrombotic events after surgery.

The performance of coronary surgery in patients with thrombocythemia is infrequent (Table I). In most cases, myocardial revascularization has been performed with the aid of CPB[1,9-22] and was usually successful. However, 31% of patients developed postoperative sequelae in the form of coronary artery thrombosis, tamponade, pulmonary embolism, or myocardial and cerebral infarction.[10,11,13]

The application of off-pump CPB among these patients has apparently been limited to 2 instances.[12,22] Although the surgery itself was satisfactory, one patient died early of an unexplained postoperative cardiac arrest.[22]

We chose an off-pump CPB technique in the present case on the basis of several factors. Aside from the hematologic sequelae that can follow CPB, our patient was considered to be at high risk in accordance with the risk-stratification protocol of thrombocytosis.[7] In addition, our patient had associated comorbidities in the form of impaired left ventricular function, chronic obstructive pulmonary disease, and associated cerebral ischemia. In order to obtain the best surgical outcome, we took precautions to avoid preoperative, operative, and postoperative bleeding and thrombosis.

The use of hydroxycarbamide was effective in reducing our patient's platelets to almost one third their original level. Both aspirin and clopidogrel were omitted 5 days before surgery and replaced by clexane. Adopting an off-pump technique enabled us to use half the dose of heparin during operation—nor did we reverse heparin with protamine at the end of the procedure. After checking our patient's coagulation profile and his drainage tubes for blood loss, we administered a single early postoperative dose of unfractionated heparin (5,000 IU). A combination of hydroxycarbamide, aspirin, and clexane was resumed on the day after the operation. Warfarin was begun after the passage of 2 postoperative days, and clexane was stopped when the international normalized ratio level reached 1.8.

In addition to the above regimen, which we applied as successfully as have others before us, 2 groups of investigators (Kaya and co-authors[12] and Ahmed and colleagues[23]) have reported the occasional prophylactic use of aprotinin and fresh frozen plasma to counteract possible postoperative bleeding.

The early and long-term patency of the grafts used in our patient was of great concern not only because of thrombocythemia, but because there is some evidence that the use of an off-pump technique is associated with lower graft patency than is the use on-pump CPB. The differences in patency were initially attributed to such technical factors as patient selection, surgical expertise, operative technique, and the antithrombotic medications used postoperatively.[24] However, factors related to the inflammatory and prothrombotic state that occurs after surgery seem to be involved. Stable platelet aggregation, endothelial cell disruption of vein grafts, and the aspirin resistance seen among patients undergoing off-pump CPB could be responsible for early graft occlusion.[25]

Studies of this issue have produced conflicting results. Some investigators have found significantly lower patency rates among off-pump CPB patients,[26,27] whereas others[28,29] have found no significant difference in patency regardless of CPB method.

Sousa Uva and colleagues[24] found that antithrombotic protocols greatly affect graft patency. In their study, patients undergoing on-pump CPB had significantly better graft patency than did the off-pump group. However, when their results were adjusted to account for the total dose of heparin, the difference was not significant.

It seems that lower anticoagulation levels during the intraoperative and postoperative periods greatly affect graft patency, whether off-pump or on-pump CPB is used. In our patient, we did not intraoperatively neutralize heparin with protamine; rather, we ensured graft patency by using (postoperatively) a combination of antiplatelet and anticoagulant, together with a platelet-lowering agent. Such a protocol was efficient, as shown during follow-up of the patient.

We conclude that the use of off-pump CPB in high-risk patients with essential thrombocythemia is safe. Reducing platelet count via the administration of hydroxycarbamide and the careful balancing of antiplatelets and anticoagulants is crucial in determining the outcome of surgery.

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