What cardiologists should know about essential thrombocythemia and acute myocardial infarction: report of two cases and advanced heart failure therapies considerations

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Abstract: We present the cases of two young male patients aged 22 and 31 without prior medical history nor cardiovascular risk factors, who presented to the hospital with large anterior ST-elevation myocardial infarction (STEMI). Urgent coronary angiography revealed acute thrombotic occlusion of the proximal left anterior descending artery in both patients. Persistent thrombocytosis was noted and subsequent investigations led to the diagnosis of essential thrombocythemia (ET) with positive JAK2-V617F mutation. Myocardial infarction as a first clinical manifestation of ET is rare but must be considered in patients without cardiovascular risk factors who show persistent thrombocytosis. In young patients without risk factors, there may be great delays before the diagnosis of STEMI is made. Longer time to revascularization of extensive STEMI is associated with adverse outcomes and cardiogenic shock which can lead to advanced therapies like heart transplant and left ventricular assist device (LVAD). Considering the favorable long-term prognosis of patients with ET, advanced therapies may be a valuable option in the presence of severe left ventricular dysfunction.

Keywords: thrombocytosis, JAK2 mutation, heart transplant, left ventricular assist device

Introduction

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm (MPN) characterized by an excessive clonal platelet production. JAK2-V617F mutation is involved in about 60% of the patients.^{1,2}

Common clinical manifestations of this disease result from thromboembolic events or from the thrombocytosis itself.³ Common vasomotor symptoms include headaches, dizziness, visual disturbances, and burning dysesthesia. Most people with ET experience at least one thrombotic or hemorrhagic event at some point during the course of their disease.⁴ For instance, patients can present with Budd-Chiari syndrome, multiple first trimester abortions or a hemorrhagic complication secondary to acquired von Willebrand disease associated with extreme thrombocytosis. The incidence of myocardial infarction (MI) in patients with known ET is under 10% and is uncommon as a first clinical manifestation of the disease.⁵

Case I

A 31-year-old male patient without medical history, familial history of coronary heart disease, or cardiovascular risk factors was evaluated at our hospital for acute retrosternal pain.

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Anterolateral ST-elevation myocardial infarction (STEMI) was diagnosed (Figure 1) and the patient underwent urgent coronary angiography, revealing an acute occlusion by an intramural thrombus of the proximal left anterior descending artery (LAD). There was no other significant lesion. A drug-eluting stent was successfully implanted in the proximal LAD (Figure 2). Echocardiography showed a depressed left ventricular ejection fraction (LVEF) at 15% with extended areas of akinesia in the LAD territory, left ventricular end-diastolic diameter (LVEDD) of 59 mm and left ventricular end-systolic diameter (LVESD) of 53 mm.

Blood tests revealed isolated but severe thrombocytosis with 1260×10^9 platelets/L, which persisted on controls. ET was confirmed by positive JAK2-V617F mutation,

negative BCR-ABL1 translocation, and compatible bone marrow biopsy. Hematology consultant started cytoreductive therapy with hydroxyurea, targeting less than 400×10^9 platelets/L, and recommended anticoagulation for primary prevention of ventricular thrombus given the diffuse area of akinesia and the prothrombotic state induced by ET. The patient underwent a favorable in-hospital evolution and was discharged 4 days later with warfarin for at least 6 months, acetylsalicylic acid 80 mg PO QD, clopidogrel 75 mg PO QD, bisoprolol 2,5 mg PO QD, perindopril 4 mg PO QD, eplerenone 25 mg PO QD, and hydroxyurea 500 mg PO TID. The follow-up complete blood count revealed a steady platelet count of 350×10^9 /L on hydroxyurea.

Figure 1 ECG, ST waves elevation in anterolateral leads, pathologic Q waves in lateral leads, ventricular ectopic beats.

Figure 2 (A) RAO 20-caudal 20 view left coronary angiography: proximal LAD thrombus and thrombolysis in myocardial infarction (TIMI) flow grade 0. (B) RAO 10-cranial 40 view: a 4.0x22 mm drug-eluting stent was placed in the proximal LAD to restore normal TIMI flow grade 3. Right coronary angiography (not shown) was normal.

Despite initial improvement, the patient experienced worsening of symptoms at 6 months and a control echocardiography showed a new severe functional mitral regurgitation and deterioration of LVEF to 20% with LVEDD of 63 mm and LVESD of 54 mm.

At this point, the patient was referred to our specialized heart failure clinic and full pre-transplant assessment was made. Fortunately, the patient benefited from the intensive follow-up which included the substitution of perindopril to sacubitril-valsartan. After up-titration of sacubitril-valsartan to 97–103 mg PO BID, a stable New York Heart Association (NYHA) functional class I was maintained as of now. Last echocardiography showed improvement in LVEF to 25%, stable left ventricular dimensions, and mild mitral regurgitation.

Case 2

A 22-year-old male patient without medical history nor family history of coronary heart disease presented to the emergency department of a regional hospital after 3 days suffering from vague retrosternal pain and nausea.

A recent transmural MI with anterolateral Q waves and persistent ST-elevation was diagnosed on electrocardiogram (Figure 3). Thrombolytics were not administered because of the late presentation. Intravenous furosemide and oxygen supplementation were begun for acute lung edema, and the patient was immediately transferred to our institution. Coronary angiography revealed a complete occlusion of proximal LAD (Figure 4). No coronary angioplasty was performed considering the late presentation with complete transmural cardiomyonecrosis that was confirmed by cardiac magnetic resonance imaging. An

intra-aortic balloon pump (IABP) was installed at the end of the procedure for hypotension and signs of organs hypoperfusion. Echocardiography showed a LVEF of 10%, LVEDD of 52 mm, LVESD 40 mm, diffuse akinesia in the LAD territory and severe apical stasis, for which intravenous heparin as primary prevention of thrombus formation was continued.

Blood tests revealed initial and persistent thrombocytosis with platelets level of $700 \times 10^9/L$ but otherwise normal complete blood count. ET was eventually confirmed by positive JAK2-V617F mutation, negative BCR-ABL1 translocation, and compatible bone marrow biopsy. Cytoreductive therapy with hydroxyurea was started.

The patient was weaned from the IABP within 48 hrs but the initiation of usual heart failure therapies was limited due to symptomatic hypotension with systolic blood pressure of 85 mmHg and lower. Considering his NYHA class IV heart failure and poor tolerability of medication, the patient underwent a complete pre-transplant assessment.

On day 7, the patient developed an acute right thumb pain with blue discoloration that coincided with a drop in the platelets level to $340 \times 10^9/L$. Considering the high probability of heparin-induced thrombocytopenia (HIT), intravenous heparin perfusion was immediately stopped and argatroban was initiated. The testing for anti-platelet factor 4 antibody was positive, and the diagnosis of HIT was confirmed with positive serotonin release assay. Substitution of argatroban by warfarin was then accomplished.

After 4 weeks of gradual up-titration of medication and slow improvement to NYHA class III, the patient was discharged with warfarin for at least 6 months, hydroxyurea 500 mg PO BID, acetylsalicylic acid 80 mg PO

Figure 3 ECG, sinus tachycardia with ST waves elevation and pathologic Q waves in the anterolateral leads.

Figure 4 (A) LAO 45-cranial 25 view left coronary angiography: complete proximal LAD occlusion. (B) Left ventriculography revealing severe left ventricular systolic dysfunction and antero-apical akinesia. Right coronary angiography (not shown) was normal.

QD, metoprolol 50 mg PO BID, ramipril 5 mg PO BID, and spironolactone 12,5 mg PO QD. Echocardiography on discharge revealed a LVEF of 25%, LVEDD 56 mm, and LVESD 40 mm.

A long-term steady platelet count around $250 \times 10^9/L$ was achieved with hydroxyurea and the patient did not experience any other thrombotic event. Despite difficult up-titration of medications due to orthostatic hypotension, patient slowly attained NYHA functional class II and the LVEF reached 35% 8 months after the event. Consequently, the heart transplant was no longer considered.

Discussion

ET is characterized by monoclonal proliferation of hematopoietic stem cells resulting in overproduction of platelets. It is a MPN, like polycythemia vera (PV), primary myelofibrosis, and chronic myeloid leukemia. The JAK2 enzyme mutations (V617F and exon 12 mutations) are identified in almost all patients with PV and in 60% of ET (V617F).² This enzyme is involved in signal transduction for erythropoietin and thrombopoietin. CALR exon 9 and MPL exon 10 mutations can be identified in 30% of JAK2 negative ET patients, but the JAK2-V617F mutation clearly confers the highest risk for thrombosis, with a hazard ratio of 1.43 and 2.56 for venous and arterial thrombosis, respectively.⁶ According to the World Health

Organization (WHO), the diagnosis of ET needs a persistent platelet count of $\geq 450 \times 10^9/L$, the identification of typical ET-associated mutations, a negative BCR-ABL1 rearrangement to exclude chronic myeloid leukemia and the histopathological confirmation with bone marrow biopsy.⁷

MI in patients with ET often results from in situ thrombosis without associated coronary atherosclerosis. Vianello et al,⁴ demonstrated that ET patients have endothelial dysfunction and lower coronary flow reserve. In two large cohorts of ET patients,^{5,6} incidence of MI ranged from 2 to 9, 4% and most had other significant cardiovascular risk factors. None of them were younger than 40 years old.⁵ However, more recent case reports described STEMI as the first thrombotic event that led to the diagnosis of ET in younger patients.^{8–13} Reactive thrombocytosis is frequent during acute MI but should not be overlooked. Normalization of platelets level must be confirmed with subsequent complete blood count.

Treatment of ET

General treatment of ET includes controlling the usual cardiovascular risk factors and cytoreductive therapy such as hydroxyurea in high-risk patients. Patients are considered at high risk if they fulfill any of the following criteria: age ≥ 60 years, history of thrombosis or major bleeding and platelets count $\geq 1500 \times 10^9/L$.¹⁴ Additionally, the presence

of cardiovascular risk factors or positive JAK2 mutation confers a significant risk of thrombosis. Low dose acetylsalicylic acid is the mainstay for primary and secondary prevention of thrombosis.¹⁴

Cytoreductive therapy is to be added in high-risk patient, including all those who have suffered from a thrombotic cardiac event. Hydroxyurea is the first line choice in the majority of patients because of its favorable side effects profile and its effective lowering of thrombotic events.¹⁴ However, hydroxyurea has long-term irreversible gonadal toxicity and is contraindicated in the first trimester of pregnancy. Interferon alpha may be the preferred option in young patients with reproductive intention but is associated with more frequent side effects such as hyperthermia, general malaise, and gastrointestinal upset. The objective of treatment is to maintain a platelet level of less than $400 \times 10^9/L$ and if concomitant leukocytosis is present, a white blood cell count of less than $11 \times 10^9/L$.

HIT associated with ET

The second case described a challenging diagnosis of HIT in a patient without thrombocytopenia but a relative platelet count fall of more than 50% and a new thrombotic episode. According to few case reports, ET may be associated with a higher prevalence of HIT so that new thrombotic episodes while patient is receiving unfractionated heparin or low molecular weight heparin should not be overlooked.^{15–21} Clinicians should be aware that ET patients will not present an absolute thrombocytopenia but a faster than expected fall in platelets count with cytoreductive therapy associated with new thrombosis, skin necrosis, or lesions or systemic reaction to heparin bolus. The approach to diagnosis and treatment of HIT in patient with ET is the same as usual.

Prognosis of ET

ET is associated with a better prognosis than other BCR-ABL1 negative MPN and therefore, WHO diagnostic criteria must be strictly respected to estimate long-term evolution. Life expectancy of ET patients is only slightly worse than general population.^{22,23} Median survival time of overall ET patients is about 20 years and increases to 33 years in patients diagnosed before 60 years.²⁴ Comparatively, median survival time of PV and primary myelofibrosis patients under 60 years is 24 and 15 years, respectively. Most important predictors of poor prognosis are age of ≥ 60 years, white blood cell count of $\geq 11,000/\text{microL}$ and history of thrombosis.²⁵

Even for patients considered at high risk, median survival is about 14 years. Among all BCR-ABL negative MPN, ET has the lowest 15 years incidence of blast transformation and myelofibrosis of only 2–3% and 4–10%, respectively.^{22,23,26,27}

Advanced heart failure therapies and ET

Those two cases raised many questions regarding advanced heart failure therapies. There is only one published case of a patient with ET who had a left ventricular assist device (LVAD) implanted for 3 months without complication, and eventually benefited from orthotopic heart transplantation.²⁸ Unfortunately, the authors do not report the long-term evolution of the patient. Even with the improved management and risk categorization of ET patients in the last years, there is a persistent prothrombotic state that confers up to 3.6% annual risk of thrombosis in high-risk patients.²⁹ Therefore, we do not consider ET as an absolute contraindication to LVAD implantation. If long-term LVAD is considered, close follow-up with hematologists and active monitoring for device thrombosis would be a standard of care. In addition to usual LVAD management, twice daily acetylsalicylic acid may be considered owing to the high platelets production.^{30–32}

Considering the favorable long-term prognosis of ET patients, heart transplantation may also be considered if clinically indicated.³³ As for medication, hydroxyurea or alternatives do not have prohibitive drug interaction with usual immunosuppressive medication but special attention must be paid to cytopenias caused by increased myelosuppressive effect.

Conclusion

Although close to 10% of the patients with ET will eventually suffer from MI at some point during the course of their disease, MI as the first clinical manifestation leading to the diagnosis of ET is uncommon. Our two cases emphasize the importance of pursuing the investigations for ET in young adults presenting with MI and thrombocytosis. Considering the favorable prognosis of ET, advanced therapies like heart transplantation or LVAD may be considered in the presence of severe left ventricular dysfunction.

Consent

Written informed consent was obtained from the patients for publication of this case series and accompanying images.

Ethical considerations

Considering the non-nominal and descriptive nature of this case series, it was exempted from ethical approval.

Disclosure

The authors report no conflicts of interest in this work.

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