Recurrent Cardiovascular Events Despite Antiplatelet Therapy in a Patient with Polycythemia Vera and Accelerated Platelet Turnover

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None related to this article

Patient: Male, 58
Final Diagnosis: STEMI
Symptoms: Angina pectoris
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Unusual clinical course
Background: Clopidogrel is commonly used in the prevention and treatment of cardiovascular events. However, despite clopidogrel treatment, some patients experience recurrent ischemic events.
Case Report: We present the case of a 58-year-old man with polycythemia vera and concomitant thrombocytosis who suffered 6 episodes of cerebral infarctions and 1 myocardial infarction, despite treatment with clopidogrel. Following his last ischemic event, the antiplatelet therapy was intensified from initially clopidogrel monotherapy to dual antiplatelet therapy with aspirin 75 mg once daily and ticagrelor 90 mg twice daily. Since then, no cardiovascular event has been reported.
Conclusions: This case report illustrates that insufficient platelet inhibition with clopidogrel monotherapy in a patient with thrombocytosis may be associated with recurrent arterial thrombosis. The exact reasons for the insufficient platelet inhibition are not known, but a plausible explanation may be an accelerated platelet turnover reflected by an increased number of immature platelets in this patient.
The findings in this case indicate that further studies are warranted to determine the role of immature platelets as markers of accelerated platelet turnover and poor response to antiplatelet treatment.

MeSH Keywords: Blood Platelets • Platelet Aggregation • Platelet Aggregation Inhibitors • Platelet Count • Purinergic P2Y Receptor Antagonists • Thrombocytosis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/904148

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Background

Clopidogrel is an antiplatelet drug widely used in the treatment and prevention of cardiovascular disease, including stroke and myocardial infarction (MI) [1]. Clopidogrel irreversibly inhibits the P2Y12 receptor, thereby inhibiting platelet aggregation and reducing the risk of cardiovascular events [2]. However, during clopidogrel treatment, recurrent cardiovascular events remain a significant cause of morbidity and mortality [3]. This may be partly explained by a reduced platelet response to clopidogrel [4,5]. Therefore, more potent P2Y12 antagonists have been developed to improve platelet inhibition [2]. Ticagrelor provides stronger and more consistent platelet inhibition compared with clopidogrel in patients suffering from MI or stroke and after percutaneous coronary intervention [2,6].

We report the case of a patient with polycythemia vera and concomitant thrombocytosis who had several recurrent cerebrovascular events and 1 event of ST-elevation myocardial infarction (STEMI), despite treatment with clopidogrel monotherapy.

Case Report

A 58-year-old man presented at the Neurology Department with symptoms and signs of cerebral infarction. His medical history included 5 previous ischemic strokes, as well as carotid artery disease with total occlusion of the left internal carotid artery treated with carotid endarterectomy. His cardiovascular risk factors included hypertension, hypercholesterolemia, and smoking. The patient was diagnosed with polycythemia vera with concomitant thrombocytosis 3 years prior to this episode of cerebral infarction. The diagnosis was made in accordance with the WHO criteria: 1) a hemoglobin level above 19.5 g/dL and the presence of *JAK-2* mutation as major criteria and 2) a bone marrow biopsy showing erythroid, granulocytic, and megakaryocytic proliferation and low erythropoietin as minor criteria to ensure the specific polycythemia vera diagnosis [7]. He was treated in accordance with recommendations for patients with polycythemia vera and a history of arterial thrombosis [8], thus receiving cytoreductive therapy (hydroxyurea alternating between 500 mg and 1000 mg every other day), venesection (target hematocrit below 0.45), uric-acid-reducing treatment (allopurinol 300 mg once daily), and antiplatelet therapy (clopidogrel 75 mg once daily). Clopidogrel monotherapy was chosen instead of aspirin due to his comprehensive thrombosis history and because previous data show that clopidogrel outperforms aspirin monotherapy [1,9]. A magnetic resonance imaging scan was performed in the acute phase and showed new infarctions in vermis and left cerebellar hemisphere. Biochemical parameters included: platelet count at 890×10^9/L (reference range (RR): 145–350), leucocytes at 22.1×10^9/L (RR: 3.5–10.0), and a hematocrit of 0.47 (RR: 0.40–0.50). The patient was successfully treated with tissue plasminogen activator 90 mg according to weight and was discharged the following day. At discharge, the patient was prescribed dual antiplatelet therapy (DAPT) consisting of clopidogrel 75 mg once daily and aspirin 75 mg once daily for 3 months followed by a maintenance dose of clopidogrel 75 mg once daily. Treatment of his polycythemia vera disease was intensified with cytoreductive treatment (hydroxyurea) and venesection. Other drugs, such as interferon-alfa and busulfan, were not used, primarily due to the patient's age.

Five months after discharge and only 2 months after the patient stopped aspirin, he was admitted with STEMI. At admission, the electrocardiogram showed atrial fibrillation, ST-elevation in leads II, III, AVF, and V1, and ST depressions in all precordial leads in accordance with an inferior STEMI. In the acute phase, the patient received standard loading DAPT, consisting of aspirin 300 mg and ticagrelor 180 mg, as well as intravenous heparin 10 000 IU. Coronary angiography was performed immediately and showed complete occlusion of the right coronary artery. Bivalirudin was initiated and thrombectomy of the right coronary arteria was performed. Due to slow flow after thrombectomy, bivalirudin was substituted with infusion of abciximab, which improved blood flow. DAPT was continued with aspirin 75 mg once daily and ticagrelor 90 mg twice daily. Echocardiography showed left ventricular ejection fraction at 50% with akinesia corresponding to the supply area of the right coronary artery. The control angiography 2 days later demonstrated a 70% stenosis of the right coronary artery and successful coronary stenting was performed. The patient was discharged 6 days after symptom debut. Ambulatory Holter monitoring showed no paroxysmal atrial fibrillation and a transesophageal echocardiography found no signs of thrombus formation in the left atrium.

We observed increased platelet count, immature platelet count (IPC), and immature platelet fraction (IPF) 3 days after STEMI: Platelet count at 682×10^9/L, IPC at 25.9×10^9/L (RR: 2.5–16.6) and IPF at 3.8% (RR: 1.1–6.1) (Sysmex, Japan) (Figure 1). Platelet aggregation was simultaneously analyzed using whole-blood impedance aggregometry (Multiplate® Analyzer), demonstrating increased platelet aggregation in response to ADP and arachidonic acid despite treatment with aspirin and ticagrelor (Figure 2). Seventeen days later, IPC, IPF, and arachidonic acid-induced platelet aggregation decreased but ADP-induced platelet aggregation remained increased (Figures 1, 2).

DAPT was continued with aspirin 75 mg once daily and ticagrelor 90 mg twice daily. Since then (12 months), no cardiovascular event has been reported.
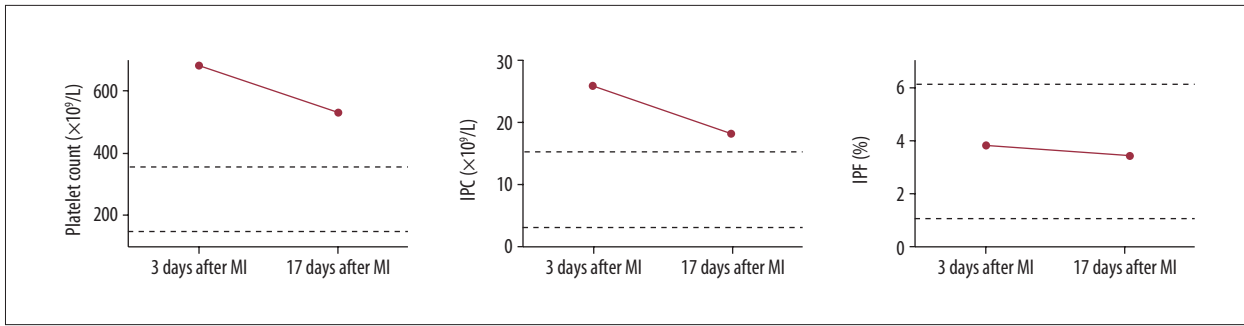
Figure 1. Platelet count, immature platelet count (IPC), and immature platelet fraction (IPF) 3 and 17 days after MI. Reference ranges for healthy individuals are shown as dotted lines. MI – myocardial infarction.
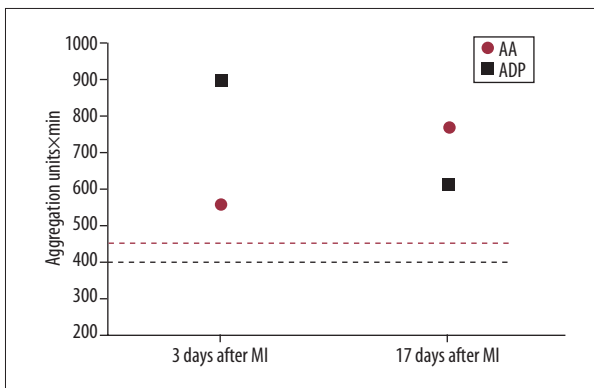
Figure 2. Platelet aggregation determined by Multiplate® Analyzer using arachidonic acid (AA) and adenosine diphosphate (ADP) as agonists during treatment with aspirin (75 mg once daily) 3 days after MI and ticagrelor (90 mg twice daily) 17 days after MI. Black dashed line represents cutoff values for low inhibition of cyclooxygenase-1 by aspirin [10]. Blue dashed line represents cutoff values for high platelet reactivity during treatment with P2Y12 inhibitor [11]. MI, myocardial infarction.

Discussion

Patients with polycythemia vera have a high risk of thrombo-embolic complications, but the mechanisms of thrombosis are not fully understood [12]. The hyper-viscosity syndrome associated with the majority of chronic myeloproliferative syndromes may be important for the risk of thrombosis, and other suggested mechanisms include an overactive JAK/STAT pathway [8,12]. The present case report suggests that antiplatelet treatment in these patients may not have the expected protective effects, therefore resulting in a poor antiplatelet response. Our patient suffered 6 episodes of cerebral infarction and 1 episode of STEMI, despite the initial treatment with clopidogrel. During this period, the patient had a home nurse to confirm optimal compliance with medications. In general, the evidence supporting antiplatelet therapy in patients with polycythemia vera is based on 1 clinical trial, showing a favorable effect of low-dose aspirin compared to placebo [13]. We

are not aware of any clinical trial evaluating clopidogrel treatment in these patients.

Following the last event of ischemic stroke treated with thrombolysis, his antiplatelet treatment was changed for a 3-month period to dual therapy (clopidogrel 75 mg and aspirin 75 mg). Afterwards, the patient was switched back to clopidogrel monotherapy, and after only 2 months, he experienced STEMI. The antiplatelet treatment was then intensified again to aspirin 75 mg once daily and ticagrelor 90 mg twice daily.

Platelet aggregation was measured in this patient as a marker of antiplatelet effect, since the method has previously proved valid to investigate the antiplatelet effect in patients with myeloproliferative disorders [14]. Increased platelet aggregation observed 3 days after STEMI (Figure 2) supports the theory of insufficient platelet inhibition despite clopidogrel treatment. However, platelet aggregation measured by impedance aggregometry is highly dependent on platelet count [15], suggesting that the increased aggregation in this patient may be partly explained by thrombocytosis. ADP-induced platelet aggregation remained increased 17 days after STEMI, despite treatment with ticagrelor and aspirin.

It is difficult to determine the exact reasons for the insufficient platelet inhibition. However, a plausible explanation may be an accelerated platelet turnover. We measured IPC and IPF as a marker of increased platelet turnover [16] and found increased values 3 days after STEMI, consistent with previous findings [16]. The patient had thrombocytosis and was a smoker, which are both known to be associated with an accelerated platelet turnover [17, 18]. In patients with accelerated platelet turnover, an increased proportion of immature platelets are released from the bone marrow. These immature, reticulated platelets may be more hemostatic-reactive. They can produce proteins involved in hemostasis, due to residual mRNA derived from megakaryocytes, and are therefore more likely to participate in thrombus formation [18–20].

Seventeen days after the MI, we observed a decrease in IPC, but the values were still above the reference interval (Figure 1), consistent with accelerated platelet turnover in a more stable phase [21]. In addition to very high platelet counts (500–700×10^9/L), we found continually high values of IPF. Our patient's poor response to clopidogrel may therefore partly be explained by an accelerated platelet turnover, counteracting the antiplatelet effects of clopidogrel [18,22]. The poor response may also partly be a consequence of the thrombocytosis. Finally, other explanations may involve variations in pharmacogenetics, bioavailability, and drug interactions [23].

Conclusions

Patients with polycythemia vera have a high risk of thromboembolic complications. Exploring mechanisms of thrombosis in these patients is important, and this case report illustrates that poor response to antiplatelet therapy may be a contributing factor. However, the pathophysiological role of accelerated platelet turnover and immature platelets is not yet fully understood [24,25], and further studies are warranted to determine the role of IPC/IPF as markers of accelerated platelet turnover and poor response to antithrombotic treatment [26,27].

Competing interests

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