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Case Report

Recurrent Type 2 Myocardial Infarction due to Eltrombopag in a Young Man with Immune Thrombocytopenia: A Case Report

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Abstract

A 28-year-old man on eltrombopag for primary immune thrombocytopenia presented with recurrent type 2 myocardial infarction. Dual antiplatelet therapy rather than percutaneous coronary intervention was administrated in this case. Rapid increase of thrombocyte count, combination therapy with eltrombopag and corticosteroid may be the etiologies of this case.

Keywords: Primary immune thrombocytopenia; Eltrombopag; Type 2 myocardial infarction; Dual antiplatelet therapy

Introduction

Primary Immune Thrombocytopenia (ITP) is an autoimmune disease characterized by isolated thrombocytopenia. The pathogenesis mechanisms of ITP encompass increased antibody-mediated platelet destruction, impaired platelet production and enhanced non-antibody mediated clearance of platelet [1]. Standard and documented ITP therapy strategies include corticosteroid therapy, intravenous immunoglobulin, splenectomy, platelet transfusion, cytotoxic agents and so on. Moreover, Thrombopoietin Receptor Agonists (TPO-RAs) have provided excellent responses in ITP therapy [2].

Eltrombopag is a low molecular weight TPO-RA, a type of thrombopoietin mimetics, which enhances the production of platelet by binding to thrombopoietin receptor. Eltrombopag has been approved as a second-line therapy of ITP. Thromboembolic Events (TEEs) are serious adverse events with low incidence in ITP patients using eltrombopag. While Myocardial Infarction (MI) have been reported as adverse events in several clinical trials and scattered case reports, no case of Type 2 Myocardial Infarction (T2MI) was mentioned in previous literature.

Here we present a case of 28-year-old man on eltrombopag for ITP suffering recurrent T2MI. This is the first case report of raising recurrent type 2 myocardial infarction due to eltrombopag therapy, from which we can provide new ideas for clinical treatment.

Case Presentation

A 28 year-old male patient with a long-lasting (>2 hours) chest pain was admitted in our hospital. He had a long period of smoking and drinking history (between the ages of 15 and 28 years) and there were no other risk factors for coronary artery disease such as hypertension and hyperlipidemia. He was diagnosed with ITP at age 27 and treated with corticosteroid. Nine months ago, the peripheral blood platelet count of the patient has been persistently descending and has reduced to 5.0×10^9/L. Given the deterioration of disease, treatment with cytotoxic agent, ciclosporin, was initiated and had lasted for only 5 days due to low-efficiency. Because there was no adequate increase of platelets, the new therapeutic regimen, eltrombopag (25 mg daily) combined with prednisone (30 mg daily), was initiated 8 months ago. When eltrombopag was given, the platelet count gradually achieved a stable count (150.0×10^9/L - 300.0×10^9/L) and the Mean Platelet Volume (MPV) fluctuated within the normal range.

The physical examination of the patient was normal. Electrocardiography (ECG) indicated ST segment elevation in leads V2-5 with T wave inversion. For the laboratory examinations, there was a significant increase of high-sensitivity cardiac troponin I (hsTnI) 7479.5 ng/mL. The peripheral blood platelet count of the patient was 198.0×10^9/L. Because ITP is the relative contraindication of anti-platelet therapy, Computed Tomography Coronary Angiography

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(CTCA) rather than Percutaneous Coronary Intervention (PCI) was preferred on this occasion. The CTCA revealed mild stenosis (<50%) in the proximal segment of the left anterior descending branch (Figure 1). Additionally, further auxiliary examinations including Cardiac Magnetic Resonance (CMR) were conducted at the same time. CMR exhibited a delayed gadolinium enhancement in the Inferior segment of interventricular septum and left ventricular apex, which indicated myocardial infarction (Figure 2). During the first hospitalization, drug treatment for coronary artery disease was given in hospital, whereas the anti-platelet therapy was not initiated for the reason that the patient was not directed by the prescription. The patient was discharged when he had no complained of chest pain and ST-segment normalized. Furthermore, the serum concentrations of myocardial enzymes (hsTnI 292.3 ng/mL) were obviously declined and his platelet count (150.0×10^9/L) was still in normal range before discharge. Since there was neither recurrent cardiovascular symptoms nor ST-segment changes, the administration of eltrombopag (50 mg daily) had not ceased. The patient maintained a platelet count of 180.0×10^9/L after discharge.

One month later after discharge, the patient suffered a short duration (about 0.5 hour) of severe chest pain and was admitted in emergency room once again. ECG abnormalities demonstrated ST segment depression and T-wave changes. Additionally, hsTnI (884.37 ng/mL), biomarker of cardiomyocyte injury, had a conspicuous elevation and platelet count was 150.0×10^9/L at emergency room. Recurrent myocardial infarction was highly suspected and CTCA was conducted, which suggested no discernible stenosis and thrombosis. Considering the recurrent myocardial infarction, a Dual Aantiplatelet Therapy (DAPT, Indobufen 100mg twice a day and clopidogrel 90 mg twice a day) was administrated and eltrombopag was discontinued after comprehensively weighing the trade-off between the benefit of anti-ischaemia and the risk of bleeding. Two days after cessation of eltrombopag, his platelet count expeditiously declined to 84.0×10^9/L after 2 days of cessations. Since the significant slump of platelet count, eltrombopag was reinitiated and therapeutic dose (50 mg every other day) was switched. Moreover, DAPT was sustained to prevent the recurrence of cardiovascular events. His platelet count escalated to the normal range after discharge.

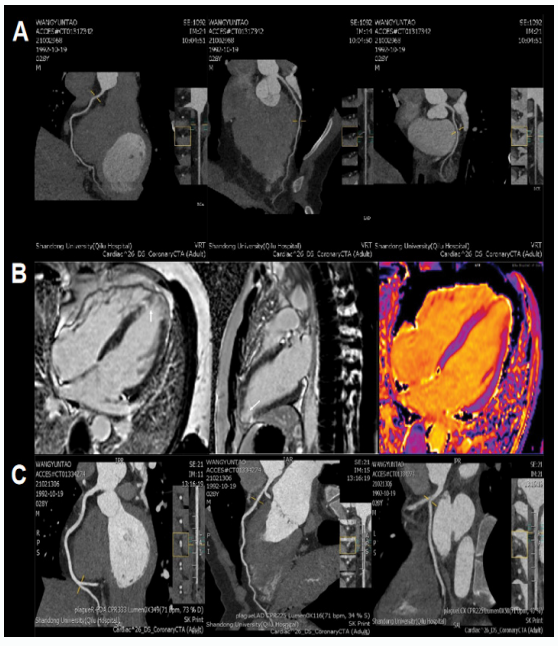

Figure 1: (A) Computed tomography coronary angiography revealing mild stenosis in the first hospitalization. (B) Cardiac magnetic resonance indicting myocardial infarction. (C) Computed tomography coronary angiography revealing no obvious stenosis and thrombus in the second hospitalization.

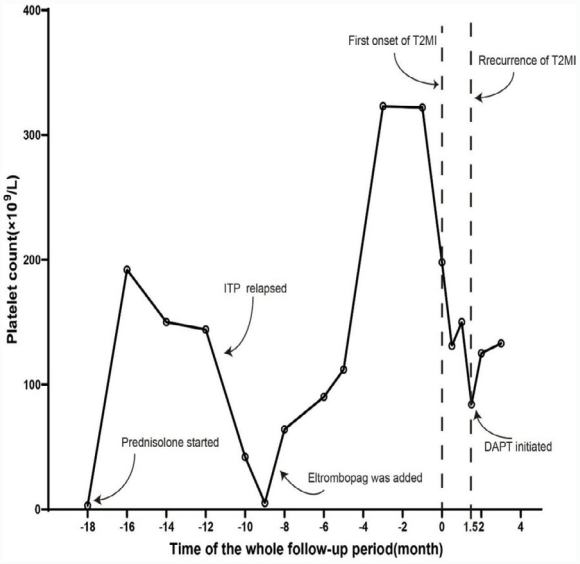

Figure 2: Changes of platelet count during the whole follow-up period. ITP: Primary Immune Thrombocytopenia; T2MI: Type 2 Myocardial Infarction; DAPT: Dual Antiplatelet Therapy

Discussion

We report a case of recurrent T2MI in an ITP patient using eltrombopag. Although there are increasing reports concerning MI in ITP patients receiving TPO-RA treatment, case of T2MI as severe adverse event is never mentioned.

TEEs, especially myocardial infarction, are severe adverse events with relatively low incidence in the utilization of eltrombopag. The RAISE trial and the EXTEND study both reported sporadic TEEs (3 patients in the RAISE trial and 19 patients in the EXTEND study) [1,2], whereas no TEE was reported in the REPEAT trial [3]. The etiologies of TEEs induced by eltrombopag have not been identified. Neither of vitro and vivo studies revealed that eltrombopag had effect on the aggregation or activation of platelet [4].

T2MI, characterized by the imbalance in myocardial oxygen supply and demand, is in the absence of acute atherothrombosis. The pathological etiologies of T2MI encompass Coronary Artery Spasm (CAS), coronary endothelial dysfunction, coronary artery embolism, severe hypoxia, inflammation and so on. In our case, the patient has a cardiovascular risk factor, smoking history, and lacks coronary angiography and optical coherence tomography data, however, his first Computed Tomography Coronary Angiography (CTCA) diagnostic report suggests just mild stenosis (<50%) in the proximal segment of the anterior descending branch and his second shows no, which illustrated that the main mechanism of MI recurrence in this case is thromboembolism rather than atherothrombosis.

In this case, existing evidence can clarify the mechanism of T2MI induced by eltrombopag. We speculate that ITP could have pro-thrombotic characteristics and TEEs probably correlated to the amelioration of thrombocytopenia [5]. On the one hand, MPV

of platelet in ITP patients is higher and immature platelets, newly synthesized by the stimulation of eltrombopag, are larger than the ordinary [6]. MPV correlates with platelet function. Larger platelets are more active in platelet aggregation, thromboxane synthesis and expression of adhesion molecules, thus they have greater prothombotic potential. In addition, ITP patients exhibit a slightly increased resistance to fibrinolytic system and protein C [5]. Coexistence of these factors facilitates the thrombosis in ITP patients. On the other hand, inflammation is associated with the pathogenesis of CAS, which also plays an important role in the etiopathogenesis of ITP [7]. Under inflammatory circumstance, both of the reactivity of vascular smooth muscle cells and adventitial release of vasoconstrictor substances increase, which may contribute to the trigger of CAS [8]. Apart from these factors, patients receiving eltrombopag combined with corticosteroid therapy are more vulnerable to TEEs. In our case, the patient has a satisfactory response to eltrombopag therapy and the platelet count briskly increased about sixty-fold versus on-set of administration during the 8-month follow-up period. The rapid refinement of thrombocytopenia and combination therapy with eltrombopag and corticosteroid may account for the first T2MI. Furthermore, it is a conundrum to balance hemorrhagic risk and thrombosis risk in ITP patients with myocardial infarction, but the safety and validity of antiplatelet therapy in acute myocardial infarction caused by eltrombopag are uncertain, especially for T2MI. Case of T2MI in ITP patients using eltrombopag has not been reported. The cause of the second T2MI may be the mere ITP therapy with the absence of DAPT after the first T2MI, which indicates the necessity of DAPT for ITP patients with T2MI due to eltrombopag therapy.

This is the first report of raising those ITP patients with recurrent T2MI owing to eltrombopag therapy. We hypothesized that numerous factors, such as accelerated thrombopoiesis, immature platelets with larger size, inflammation and combination therapy with eltrombopag and corticosteroid are presumably responsible for T2MI in ITP patients on eltrombopag therapy. Further studies should be conducted to investigate potential mechanisms for this phenomenon. It is worth highlighting that DAPT is indispensable and effective in ITP patients with T2MI owing to eltrombopag therapy.

Conclusion

Our case showed the effectiveness and safety of giving a Dual Antiplatelet Therapy (DAPT) in ITP patients using etrombopag. Moreover, combining this case with previous literature, we can conclude that Percutaneous Coronary Intervention (PCI) could be harmful for ITP patients using etrombopag, and extrapolation of the benefit of DAPT to alternative scenarios should be cautiously assessed.

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