CASE REPORT

JIACM 2023; 24 (3-4): 221-23

Eltrombopag-induced Cortical Vein Thrombosis: A Case Report

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Abstract

Eltrombopag, a thrombopoietin receptor agonist is widely used in the treatment of immune thrombocytopenic purpura (ITP), aplastic anaemia and post-transplant cytopenia. Eltrombopag is used as second-line treatment in ITP. We describe a rare and life-threatening complication of this drug namely cortical venous thrombosis in a patient with ITP. Pathogenetic mechanisms behind the thrombosis may vary from case to case. Thrombosis may be linked to the platelet count or additional thrombophilic states. Regular monitoring of patients on therapy with Eltrombopag is required to avoid these complications.

Introduction

Eltrombopag is an agonist of thrombopoietin receptors (TPO-RA) used in immune thrombocytopenic purpura (ITP) and aplastic anaemia. There have been few case reports which showed episodes of treatment concomitant thromboembolism with the reports of thrombosis in the venous and arterial circulation[1-4]. Here we describe the development of cerebral venous thrombosis involving the sigmoid and transverse sinus in a patient with immune thrombocytopenic purpura, who was being treated with Eltrombopag. We also discuss the possible pathophysiology behind the thrombotic events and steps to prevent the adverse event.

Case

A 34-year-old female patient had a three-year history of Immune thrombocytopenic purpura (ITP) being treated with oral prednisolone. Clinical remission was achieved for two years. Six months earlier she developed fever, purpura, epistaxis, and lab investigations revealed a platelet count of 6 x $16^3/\mu L$. In view of the poor response to glucocorticoids, along with steroids, oral Eltrombopag 25 mg was started after the management of acute bleeding episodes with intravenous immunoglobulin. After two weeks of treatment, the patient experienced ongoing symptoms consistent with thrombocytopenia. Therefore, the dosage of Eltrombopag was escalated to 50 mg per day. Subsequently, the patient's platelet count showed improvement over the following week. She was discharged with a schedule for follow-up after 15 days for platelet measurement. But she failed to attend the scheduled follow-up. She received this medication for six weeks before presenting to us for emergency care for acute onset severe headache – which was throbbing in nature – and blurred vision.

Physical examination upon admission to the emergency care revealed normal vitals. The nervous system examination was unremarkable. Direct ophthalmoscopy revealed bilateral papilloedema. Laboratory investigations revealed elevated platelet counts, i.e., 658.0 x $10^3/\mu L$, normal haemoglobin (13 g/dL), and normal coagulation studies. Peripheral smear showed features suggestive of reactive thrombocytosis and enlarged platelets. Magnetic Resonance venography (MRV) showed features suggestive of right sigmoid sinus thrombosis as shown in Fig. 1. Anti-nuclear antibodies and antiphospholipid antibodies were within normal limits.

Treatment

She was treated with low molecular-weight heparin and enoxaparin. The headache was managed symptomatically with Mannitol and oral analgesics. Eltrombopag was withheld in view of thrombosis. Subsequently, she was started on warfarin with a target INR of 2 - 3 which was achieved. The oral prednisolone dose was increased to 10 mg per day.

Outcome

At the time of discharge, the patient was stable with platelet count of 195 x $10^3/\mu L$ and the headache resolved. The most recent follow-up platelet count was 272 x $10^3/\mu L$. MRV done during this time showed complete resolution of the thrombosis as shown in Fig. 2.

Discussion

Immune thrombocytopenic purpura is distinguished by

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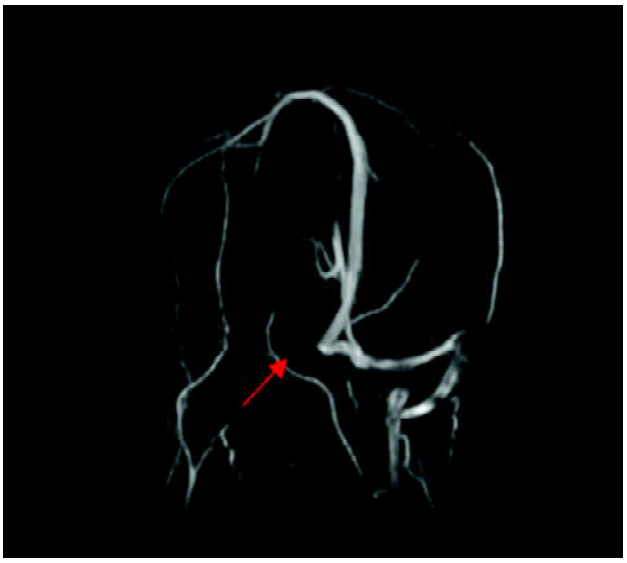

Fig. 1: *MRV showing absence of flow in the right sigmoid sinus, (red arrow) compared to left sigmoid sinus (white arrow).*

immune-mediated destruction of platelets and diminished production of platelets which leads to bleeding. Corticosteroids are the first-line drugs in the management of ITP. In the cases which are steroid-dependent or resistant, thrombopoietin receptor agonists like Eltrombopag are

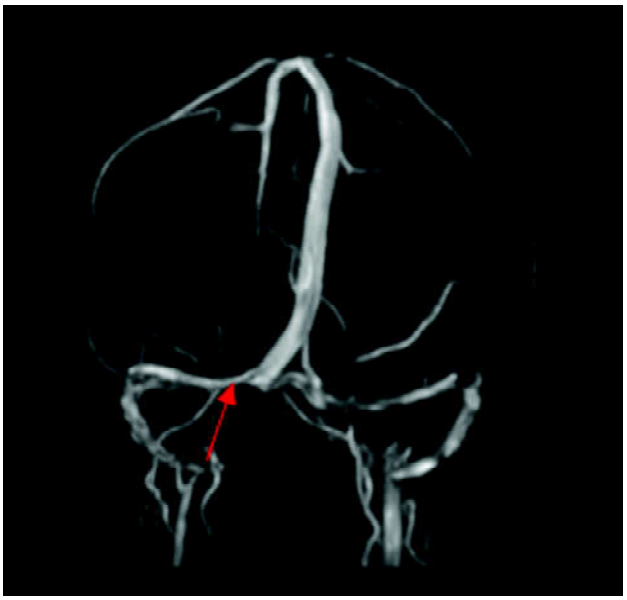

Fig. 2: *MRV showing flow established in the right sigmoid sinus, suggesting recanalisation (as pointed by arrow).*

used. It acts by its agonist action at thrombopoietin receptors leading to an increase in platelet counts compensating for increased destruction of platelets in ITP[5]. Eltrombopag has also been used for aplastic anaemia and post-transplant cytopenia.

Few adverse effects are reported with the use of Eltrombopag. The commonest of them is nasopharyngitis. Less common ones are thromboembolic episodes, transaminitis, and myelofibrosis. Sporadic cases of deep vein thrombosis[2], portal vein thrombosis[4], as well as myocardial infarction[6] due to thrombosis in those who have been taking Eltrombopag are reported. The incidence of thrombotic episodes was 6% in the EXTEND trial[7] which was aimed at long-term safety and efficacy of Eltrombopag in ITP whereas the RAISE trial by Cheng *et al*[8] had 2% thrombotic episodes. The relation between exposure to the drug and the development of thromboembolic has not yet been well described in the literature. In the EXTEND study, the rates of VTE did not increase beyond the first year of treatment. Similarly, in the majority of cases reported thromboembolic episodes occurred within the first 2 years.

The pathophysiological mechanisms behind thrombotic episodes with Eltrombopag use in ITP are manifold. First, is the relation of thrombotic events with increased platelet counts with therapy. Cheng *et al* in the RAISE trial reported that 2% of the patients receiving eltrombopag had episodes of thrombosis with a platelet count between 50 - 400 x $10^3/mm^3$. However, thrombocytosis was seen in 44.7% of cases with arterial thrombosis and 50% of venous thrombosis cases. Second is the presence of a concomitant thrombophilic state like protein C/S deficiency, or antiphospholipid antibody syndrome. Lastly, whether ITP predisposes to thrombosis inherently is a question to ponder as reported by several studies[8,9].

The onset of thrombus formation in the cerebral venous circulation may have been triggered by the eltrombopag administration induced thrombocytosis in our case. Other causes of thrombosis were ruled-out through appropriate tests. We immediately stopped the administration of Eltrombopag. Enoxaparin was used to achieve anticoagulation. Warfarin was initiated after the acute phase to prevent a recurrence.

Eltrombopag therapy requires regular monitoring. The initiation dose is 50 mg per day for the Western population. Whereas for the East Asian population recommended initiation dose is 25 mg/day. Recommended intervals for platelet monitoring:-

- One week after the initiation of treatment with TPO agonists.
- One week after the dose titration.
- One month after achieving a stable dose.

Table I below is a guide for dose adjustment of Eltrombopag as per platelet counts.

Table I:

Platelet Count Range	Action
>250 x 10^3/mm^3	Hold back the dose. Restart at 50% lower dose once platelet count is < 150 x 10^3
150 - 250 x 10^3/mm^3	Reduce the dose by 50% and monitor platelets 2 weeks after
50 - 150 x 10^3/mm^3	Continue with the same dose
< 50 x 10^3/mm^3 (after 2 weeks)	Increase the dose by 25 mg/day to a maximum of 75 mg/day

To summarize, albeit there have not been designated clinical trials, retrospective data have shown two to three times higher rates of thrombosis in adults treated with TPO-RA than in the population of ITP not administered TPO-RA, and even higher if compared to the general population.

Conclusion

Before initiating treatment with TPO-RA it is prudent to consider the individual's risk profile for thromboembolism. Also, thrombosis can occur following an increase in the dose of Eltrombopag.

Frequent observation of platelet count after start of Eltrombopag is an important aid in thwarting the episodes of thrombosis as they are associated with dramatic oscillation in the number of platelets, despite the platelet number remaining depressed.

Also it is important to individualise the dosing during the treatment using Eltrombopag. Attempts must be made to rectify the alterable risk factors.

If thrombosis is dose-dependent can we start the therapy at a lower dose? Further studies are required to check the beneficence/feasibility of this approach.

References

1. Saleh MN *et al*. Hepatobiliary and Thromboembolic Events during Long-Term EXTENDed Treatment with Eltrombopag in Adult Patients with Chronic Immune Thrombocytopenia (ITP). *Blood* 2016; 128 (22): 1368.
2. Wu C, Zhou X-M, Liu X-D. Eltrombopag-related renal vein thromboembolism in a patient with immune thrombocytopenia: A case report. *World J Clin Cases* 2021; 9 (11): 2611-8.
3. Spencer FA *et al*. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. *J Thromb Thrombolysis* 2009; 28 (4): 401-9.
4. Kawano N *et al*. Portal vein thrombosis during eltrombopag treatment for immune thrombocytopenic purpura in a patient with liver cirrhosis due to hepatitis C viral infection. *J Clin Exp Hematop* 2013; 53 (2): 151-5.
5. Gómez-Almaguer D. Eltrombopag-based combination treatment for immune thrombocytopenia. *Ther Adv Hematol* 2018; 9 (10): 309-17.
6. Gunes H, Kivrak T. Eltrombopag-Induced Thrombosis: A Case with Acute Myocardial Infarction. *Curr Drug Saf* 2016; 11 (2): 174-6.
7. Wong RSM *et al*. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. *Blood* 2017; 130 (23): 2527-36.
8. Cheng G *et al*. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011; 377 (9763): 393-402.
9. Rodeghiero F. Is ITP a thrombophilic disorder? *Am J Hematol* 2016; 91 (1): 39-45.