Cerebral Venous Sinus Thrombosis in Immune Thrombocytopenia Patients Treated with Thrombopoietin Receptor Agonist: Case Series and Literature Review

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Abstract

Cerebral venous sinus thrombosis is an uncommon adverse event in immune thrombocytopenia (ITP) patients treated with thrombopoietin receptor agonists. We reported two cases of cerebral venous sinus thrombosis after eltrombopag administration. The first case is a 29-year-old ITP woman who recently initiated eltrombopag one month before admission. She presented with progressive headache, visual disturbance, and nausea for six days with unremarkable physical examination except for bilateral optic disc edema. She was treated with enoxaparin and switched to edoxaban when discharged. The second case is a 75-year-old man with a history of vaccine-induced ITP. He was initially treated with dexamethasone and eltrombopag. One month later, he developed acute cerebral venous thrombosis with hemorrhagic infarction in bilateral frontal lobes. Even though he was treated with intravenous heparin, his status was not improved. He received the best supportive care. The pathophysiology of TPO-RAs-associated cerebral venous sinus thrombosis remained unclear but might associate with platelet activation. Careful use and closed monitoring might prevent this event.

Background

Chronic immune thrombocytopenia (ITP) is an acquired hematologic autoimmune disease characterized by an isolated decrease in the amount of platelet.[1] Antibody against platelet surface glycoprotein, peripheral T-cell mediated platelet destruction and megakaryocyte dysfunction become the important pathogenesis in this disease. The initial presentation is usually associated with bleeding diathesis from low platelet count such as petechiae, purpura, and bleeding per mucosa. Platelet count less than 30 x 10^9/liter is correlated with fatal bleeding. However, secondary ITP, triggered by some infection such as *Helicobacter pylori o*r human immunodeficiency virus (HIV) and systemic autoimmune diseases like systemic lupus erythematosus (SLE) or rheumatoid arthritis, needed to be excluded.[2] The treatment goal is to prevent bleeding symptoms by maintaining an adequate platelet level. Prednisolone, dexamethasone, and methylprednisolone are considered the first-line treatment. In an emergency setting, intravenous immunoglobulin and anti-D are also effective, but their effect of raising platelet level become transient.[3] In case of first-line treatment failure, splenectomy may be considered. Thrombopoietin receptor agonists (TPO-RAs) such as romiplostim and eltrombopag are also considered if patients are unresponsive or contraindicated to prior treatment.[3] Even though TPO-RA is effective and safe, one of the most concerning adverse effects is thromboembolism, especially atypical site embolism like cerebral venous sinus thrombosis (CVT). This review showed the case illustrations with the literature review of TPO-RA-associated cerebral venous thrombosis.

Case Presentation

Case 1

A 29-year-old woman presented with an acute throbbing headache in the occipital area, visual blurring, and nausea with increasing severity for 6 days. Her underlying disease was immune thrombocytopenia (ITP), which she recently started eltrombopag a month ago. She denied a history of prior head trauma or using oral contraceptives. On arrival, her blood pressure was 145/90 mmHg, pulse rate was 120 beats per minute, the axillary temperature was 37.1-degrees Celsius, and she was fully conscious. On examination, she had bilateral optic disc edema from a fundoscopic examination without any focal neurological deficit. There was no neck rigidity. Other systemic examinations appeared unremarkable. On the day of admission, her platelet count was 212,000 /mm^3 and her D-dimer was 2131 ng/ml. Magnetic resonance imaging (MRI) and venogram of the brain were done to evaluate the intracranial lesion (See Fig. 1). The MRI brain showed acute thrombosis along the left transverse sinus, sigmoid sinus, and left internal jugular vein with vasogenic edema. CVT was diagnosed and she was admitted to the stroke unit for closed monitoring. Laboratory screening for a thrombophilic state and autoimmune panels were negative, including protein C, protein S, antithrombin, antiphospholipid antibodies, anti-nuclear antibody, rheumatoid factor, and hepatitis profiles. Therefore, eltrombopag-associated CVT was diagnosed. Eltrombopag was withheld and enoxaparin was initiated. Before discharge, enoxaparin was switched to edoxaban, a direct oral anticoagulant, to prevent CVT recurrence. Three months after onset, her clinical symptoms were improved without symptoms of headache. She continued to take edoxaban for at least six months.

Case 2

A 75-year-old man presented with petechiae on all extremities for 3 months. He previously received a shot of coronavirus vaccine 6 months prior to admission. On the day of admission, he had an upper gastrointestinal hemorrhage with gross hematuria. On arrival, his blood pressure was 140/50 mmHg, pulse rate was 78 beats per minute, the axillary temperature was 36.0-degrees Celsius, and he was fully conscious. Multiple petechiae were seen on his extremities, chest wall, and buccal mucosa. Other systemic examinations appeared unremarkable. His platelet level was 2,000/mm^3 with normal coagulogram. His bone marrow showed increased megakaryocytes which were compatible with ITP. Diagnosis of vaccine-induced ITP was made. Dexamethasone together with eltrombopag was administered. One month later, he had an acute throbbing headache in the frontal region and subsequently altered sensorium. Computed tomography (CT) with venogram of the brain showed hemorrhagic venous infarction in bilateral frontal lobes with evidence of venous sinus thrombosis along the anterior superior sagittal sinus and left transverse-sigmoid junction (See Fig. 2). Protein C, protein S, antithrombin, antiphospholipid antibodies, anti-nuclear antibody, rheumatoid factor, and hepatitis profiles were all negative. He was diagnosed with eltrombopag-associated CVT. Eltrombopag was withheld, and intravenous heparin was initiated. After a discussion with his family, his family denied the role of decompressive craniectomy. He was treated with the best supportive care.

Discussion

TPO-RAs, consisting of romiplostim, eltrombopag, avatrombopag, and lusutrombopag, are widely used for increasing platelet levels in various conditions including ITP. TPO-RAs bind to thrombopoietin receptors and activate numerous signaling such as JAK2/STAT5, PI3K/Akt, ERK, STAT3, MAPK, and STAT1 to

promote megakaryocyte proliferation. Romiplostim is a large peptide that directly and competitively binds to TPO receptors while eltrombopag is a small molecule drug that acts on the transmembrane receptor. Beyond platelet production function, they also have an immunomodulatory function by mediated transforming growth factor-beta (TGF-β) resulting as increase regulatory T-cell (Treg) production.

Romiplostim and eltrombopag have favorable outcomes reporting in many landmark studies. Several clinical trials showed that romiplostim could increase platelet levels and reduce symptomatic bleeding. Pool analysis consisting of 1,111 individuals showed 82% treatment response in the splenectomy group compared with 91% response in the non-splenectomy group.[5] Steroid reduction and concomitant medication discontinuation were observed in real-world studies.

However, there were some TPO-RAs adverse events reported in many studies. Thromboembolism was one of the concerning issues of prescribing TPO-RA. In the long-term randomized controlled study of romiplostim, nineteen out of 292 patients had thrombotic events. Venous thromboembolism was reported with 9 events including 3 deep venous thromboses (DVT), 2 pulmonary embolisms (PE), 1 portal vein thrombosis, 1 catheter-related thrombosis, 1 thrombophlebitis, and 1 transverse sinus thrombosis. From pool analysis of 13 studies of romiplostim, thromboembolic events were reported at 5.9%.[4] Focusing on eltrombopag, 2–6% of patients receiving this drug had thromboembolism. DVT became the most common thromboembolic event. Seven cases of cerebrovascular events were reported.[5] All reported cases had at least one risk factor of thromboembolism such as hypertension, smoking, or obesity. By the way, the most common site of venous thrombosis remained DVT and PE while other sites rarely occurred. Cerebral venous thrombosis associated with using of TPO-RAs was reported in 6 cases. The majority of the cases had a positive outcome. However, one patient died because of an anticoagulant adverse effect.[6] Interestingly, we observed that all cases were female. Female genders have a higher risk of CVT than male genders, owing to hormonal factors and a high frequency of autoimmune illnesses. (Table 1). When compared to our findings, we discovered that TPO-RAs-associated CVT can affect both men and women. Intracranial hemorrhage with additional intraventricular hemorrhage has a worse prognosis than the patient without intracerebral hemorrhage, compatible with the previously reported case.[6] Laboratory screening for thrombophilic state and autoimmune panels were negative in both cases. Unfractionated heparin and low molecular weight heparin are administered in the acute phase and subsequently switched to oral anticoagulants. However, no potential prothrombotic risk is founded in our patients.

Table 1
Reported Cerebral Venous Sinus Thrombosis in Immune Thrombocytopenia Patients Treated with Thrombopoietin Receptor Agonist

Sex, Age	Initial Presentation	Duration of disease	TPO-RA, dose	Duration of TPO-RA treatment	Splenectomy	OCP	Platelet level (/mm^3)	Autoantibody screening	Thrombosis area from imaging	Treatment and outcome	R
female, 55	headache, nausea, vomiting	18 years	Eltrombopag, 25 mg then 50 mg	13 days with dose increment 6 days	no	no	124000	negative	right transverse sinus, sigmoid sinus, internal jugular vein with hemorrhagic infarction	heparin then discharge with warfarin	9
female, 39	headache, nausea, vomiting	NA	Eltrombopag, (dosage was not stated)	NA	no	no	32000	ANA (+) anticardiolipin IgM (weakly +) B2-glycoprotein (+/-) anti-Ro (weakly +)	superior sagittal sinus and bilateral transverse sinuses with hemorrhagic infarction	heparin then discharge with warfarin	10
female, 36	headache, left hemiparesis	11 years	Eltrombopag, 75 mg	9 months	no	no	NA	negative	superior sagittal sinus and right parietal cortical vein with left parietal hemorrhagic infarction	enoxaparin then discharge with warfarin	11
female, 36	headache, speech problem, left hemiparesis	5 years	Eltrombopag, 50 mg	3 days	yes	no	95000	negative	superior sagittal sinus and transverse sinuses	enoxaparin then discharge with warfarin	12
female, 44	headache, blurred vision, phonophobia, nausea, vomiting, left hemiparesis	1 year	Romiplostim, 1 mg/kg	2 months	no	no	160000	negative	right jugular vein, right sigmoid sinus, right transverse sinus	enoxaparin, dead due to EDH, SDH	6
female, 45	headache	NA	Romiplostim, 6 µg/kg	NA	yes	no	31000	Anticardiolipin IgM (+)	right internal jugular bulb with brain edema without bleeding	heparin then discharge with warfarin	13

Abbreviations: ANA; anti-nuclear antibody, EDH; epidural hematoma, NA; not available, OCP; oral contraceptive pills, SDH; subdural hematoma, TPO-RA; thrombopoietin receptor agonist

From previous studies, we found that TPO-RAs are associated with increased P-selection, an adhesion molecule mainly expressed on activated platelet and endothelial cell surface.[7, 8] The platelet activation from TPO-RAs was hypothesized as the main pathogenesis of venous thromboembolism. Even though there was no agreement on how platelet takes part in venous thrombosis, a study found that DVT patients had a high level of platelet activation measured by mean platelet volume, mean platelet component, and mean platelet mass.[8]

We could infer that thromboembolism associated TPO-RAs was not uncommon from these findings. Patients with thromboembolic risks should be aware and used TPO-RAs with caution. Starting with the lower dose, slow titration and frequent platelet monitoring might help prevent these unfavorable events.

Conclusion

Cerebral venous sinus thrombosis from TPO-RAs was not uncommon. The pathophysiology remained unclear but might associate with platelet activation. Careful use and closed monitoring might prevent this event.

In summary, we describe an unusual case of CVT, but the serious adverse event of using TPO-RAs. The mechanisms by which using TPO-RAs causes CVT has not been fully elucidated, but platelet activation has been proposed as the possible mechanism. Physicians should be aware of the potential of developing this adverse event and warn patients when prescribing the TPO-RAs.

Abbreviations

ANA anti-nuclear antibody

CT computed tomography

CVT cerebral venous sinus thrombosis

DVT deep venous thrombosis

EDH epidural hematoma

HIV human immunodeficiency virus

ITP immune thrombocytopenia

MRI magnetic resonance imaging

NA not available

OCP oral contraceptive pill

PE pulmonary embolism

SDH subdural hematoma

SLE systemic lupus erythematosus

TGF-β transforming growth factor-beta

TPO thrombopoietin

TPO-RA thrombopoietin receptor agonist

Treg regulatory T-cell

Declarations

Ethics approval and consent to participate

This study is reviewed by Research Ethics Committee of Faculty of Medicine, Chiang Mai University. STUDY CODE: MED-2564-08692 Research ID: 8692

Consent for publication

All included patients provided written informed consent.

Data availability

According to an ethical issue, the data can be disclosed upon appropriate request.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

CT, conceptualization, methodology, writing - original draft, visualization, project administration; AN, ST, AS, KTh, and CW, revision, literature review; KTe, writing – original draft, literature review; CC, final approval, supervision; All authors read and approved the final manuscript.

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Figures

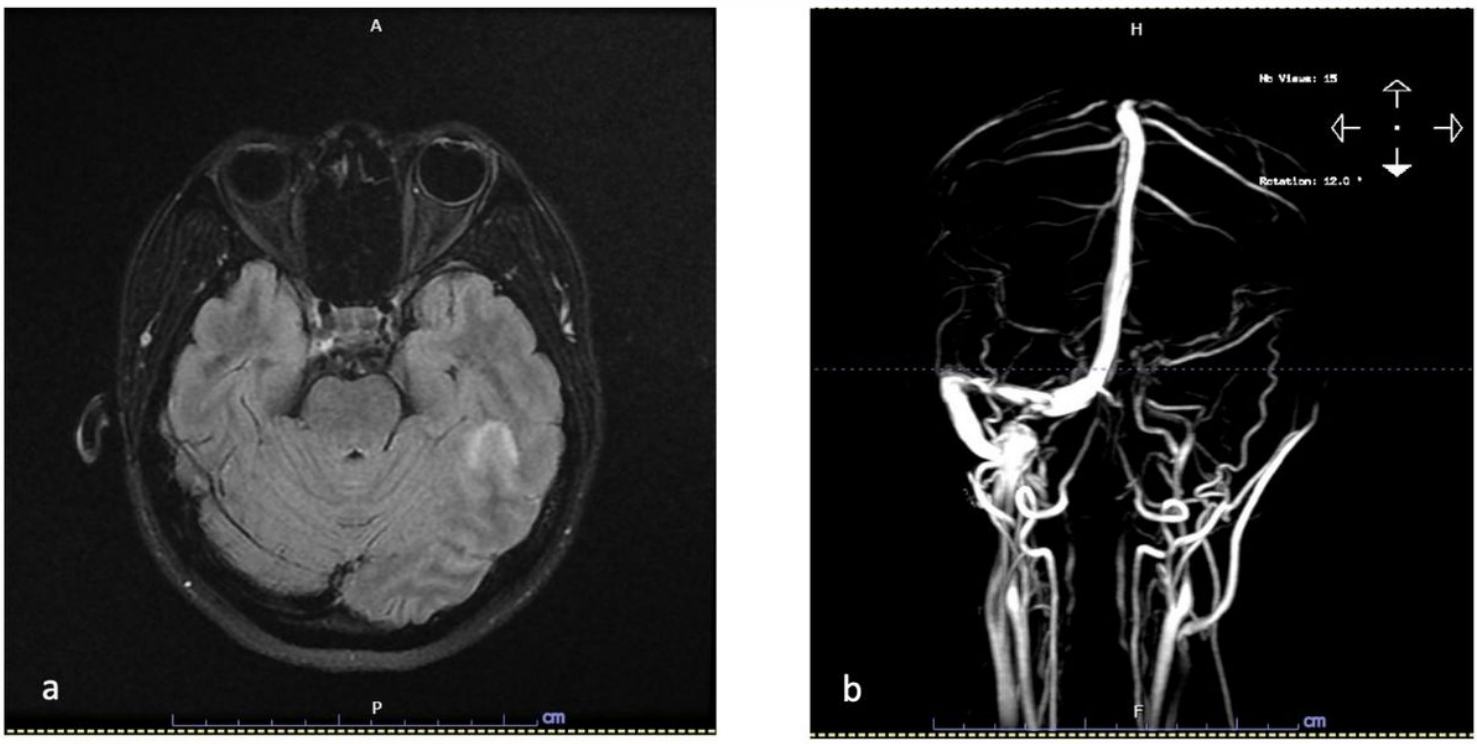

Figure 1

Magnetic resonance imaging and venogram findings

Magnetic resonance imaging and venogram findings; **a** T2 weight imaging shows a hyperintense signal in the left posterior temporal lobe. Hyperintense signal consistent with a venous infarction or vasogenic edema in the left temporal lobe; **b** venogram shows thrombosis along left transverse sinus, sigmoid sinus, and left internal jugular vein.

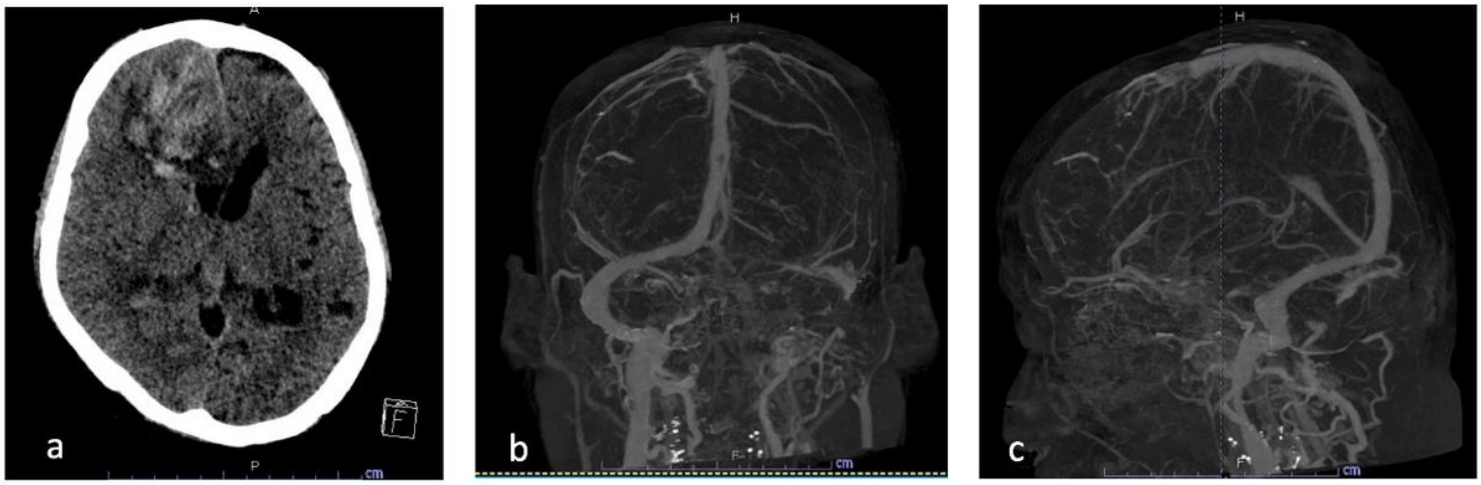

Figure 2

Computed tomography imaging and venogram findings of **case 2**

Computed tomography (CT) imaging and venogram findings; **a** axial view of brain CT shows intracranial and intraventricular hemorrhage with midline herniation, **b and c** venogram shows thrombosis along the anterior superior sagittal sinus and left transverse-sigmoid junction.