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Case Report

Cerebral venous sinus thrombosis in immune thrombocytopenia patients treated with thrombopoietin receptor agonist: Case reports and literature review

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ABSTRACT

Introduction and importance: Cerebral venous sinus thrombosis is an uncommon adverse event in immune thrombocytopenia (ITP) patients treated with thrombopoietin receptor agonists (TPO-RAs).

Case presentation: 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 the bilateral frontal lobes. Even though he was treated with intravenous heparin, his status was not improved. He received the best supportive care.

Discussion: The pathophysiology of TPO-RAs-associated cerebral venous sinus thrombosis remained unclear but might associate with platelet activation. Most cases of cerebral venous sinus thrombosis occur within two months, thus closed platelet monitoring is important.

Conclusion: Careful use and closed monitoring might prevent this event. Indications of initiation and tapering must be considered before TPO-RAs administration. Off-label use may enhance TPO-RA side effects.

1. Introduction

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 30×10^9/liter is correlated with fatal bleeding. However, secondary ITP, triggered by some infection such as *Helicobacter pylori* or 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. 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

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venous thrombosis.

2. Methods, search strategy, and selection criteria

The PubMed database was searched using the keywords: "*eltrombopag*", "*romiplostim*", "*cerebral venous thrombosis*", "*adverse event*", and "*case report*" with demarcation from 2011 to 2021. The search was limited to research articles published in the English language.

The manuscript has been reported in line with the 2013 CARE guideline for medical case reports [4].

3. Presentation of case

3.1. Case 1

A 29-year-old woman with widespread petechiae and a platelet count of 16,000/mm3 was taken to the hospital. Extensive examinations indicated that she had immune thrombocytopenia (ITP). The four-day course of dexamethasone 40 mg/day followed by prednisolone 1 mg/kg/day was commenced. Her platelet count rose to 150,000/mm^3 without clinical evidence of hemorrhage. She was readmitted three months later with buccal and mucosal hemorrhage and a platelet count of 20,000/mm^3 when the steroid was being reduced. After beginning steroid medication, her symptoms eased, and the platelet count jumped to 80,000/mm^3. Since a subsequent diagnosis of corticosteroid-dependent ITP, 50 mg/day of eltrombopag was administered as second-line treatment. A month later, she came with a severe throbbing headache in the occipital region, visual blurring, and nausea that increased in intensity over the course of six days. She denied a previous history of head trauma or oral contraceptive use. At the time of her arrival, her blood pressure was 145/90 mmHg, pulse rate was 120 beats per minute, the axillary temperature was 37.1° Celsius, and she was completely aware. Fundoscopic examination revealed bilateral optic disc edema without focal neurological deficit. There was no neck rigidity. Other systemic examinations were unremarkable. Her platelet count was 212,000/mm3 and her D-dimer was 2131 ng/ml on the day of admission. The intracranial lesion was evaluated with magnetic resonance imaging (MRI) and venography of the brain (See Fig. 1). The MRI of the patient's brain revealed acute thrombosis along the left transverse sinus, sigmoid sinus, and left internal jugular vein, accompanied by vasogenic edema. She was diagnosed with CVT and brought to the stroke unit for observation. Protein C, protein S, antithrombin, antiphospholipid antibodies, anti-nuclear antibody, rheumatoid factor, and hepatitis profiles were negative as were autoimmune panels. Therefore, eltrombopag-associated CVT was diagnosed. Eltrombopag was discontinued, and enoxaparin was started. To prevent CVT recurrence, enoxaparin was replaced with edoxaban, a direct oral anticoagulant, before discharge. After three months, her clinical symptoms had improved to the point that she no longer experienced headaches. She kept using edoxaban for a minimum of six months.

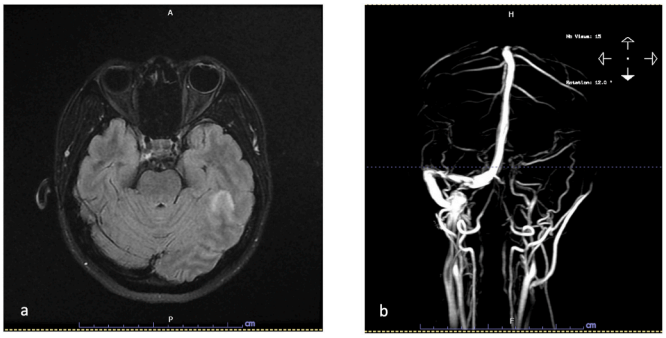

Fig. 1. Magnetic resonance imaging and venogram findings
Magnetic resonance imaging and venogram findings; **a** T2 weight imaging shows a hyperintense signal in the left posterior temporal lobe. Hyperintense signal consistent with a venous infarction or vasogenic edema in the left temporal lobe; **b** venogram shows thrombosis along left transverse sinus, sigmoid sinus, and left internal jugular vein.

3.2. 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 2000/mm^3 with a normal coagulogram. His bone marrow showed increased megakaryocytes which were compatible with ITP. Diagnosis of ITP was made, and 40 mg of dexamethasone per day was administered initially without response. He still had widespread petechiae and his platelet count was 15,000/mm^3. As considered the steroid-unresponsive ITP, 50 mg of eltrombopag was administered. One month later, he experienced a severe, throbbing headache in the frontal area, followed by an altered sensorium. Computed tomography (CT) with a 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). His platelet count was 81,000/mm^3. 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 heparin was administered intravenously. After a discussion with his family, his family denied the role of decompressive craniectomy. He was treated with the best supportive care.

4. Discussion

TPO-RAs, which comprise of romiplostim, eltrombopag, avatrombopag, and lusutrombopag, are commonly used to increase platelet counts in a variety of conditions, including ITP. To enhance megakaryocyte proliferation, TPO-RAs bind to thrombopoietin receptors and activate many signaling pathways, including JAK2/STAT5, PI3K/Akt, ERK, STAT3, MAPK, and STAT1 [5]. Romiplostim is a large peptide that directly and competitively binds to TPO receptors, whereas eltrombopag is a small molecule drug that acts on the transmembrane receptor. In addition to their platelet synthesis function, they also have an immunomodulatory activity by mediating the development of regulatory T-cells (Tregs) via transforming growth factor-beta (TGF- β).

Numerous landmark studies demonstrate positive results for romiplostim and eltrombopag. Several clinical trials demonstrated that romiplostim can boost platelet levels and lessen bleeding symptoms. Pool analysis consisting of 1111 individuals showed 82% treatment response in the splenectomy group compared with 91% response in the non-splenectomy group [6]. 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-RAs. In the long-term randomized controlled study of romiplostim, 19 out of 292 patients had thrombotic events. Venous thromboembolism was reported with nine events including three deep venous thromboses (DVT), two pulmonary embolisms (PE), one portal vein thrombosis, one catheter-related thrombosis, one thrombophlebitis, and one transverse sinus thrombosis. The 5.9% of thromboembolic events were observed in a meta-analysis of thirteen trials on romiplostim [7]. 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. All reported

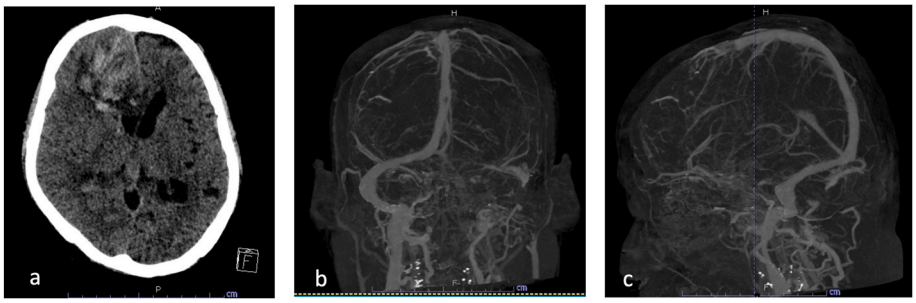

Fig. 2. Computed tomography imaging and venogram findings of **case 2**
Computed tomography (CT) imaging and venogram findings; an axial view of brain CT shows intracranial and intraventricular hemorrhage with midline herniation, **b and c** venogram shows thrombosis along the anterior superior sagittal sinus and left transverse-sigmoid junction.

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. CVT associated with using of TPO-RAs was reported in six cases. The majority of cases had favorable outcomes. However, one patient died because of an anticoagulant adverse effect. Interestingly, we observed that all cases were female. As a result of hormonal factors and the high frequency of autoimmune diseases, women have a greater risk of CVT than men (see Table 1). Compared to our findings, we discovered that CVT related to TPO-RAs can impact both men and women. Intracranial hemorrhage with additional intraventricular hemorrhage has a worse prognosis than the patient without

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	Reference
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	[11]
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	[12]
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	[13]
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	[14]
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	[8]
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	[15]

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

intracerebral hemorrhage, compatible with the previously reported case [8]. Unfractionated heparin and low molecular weight heparin were administered in the acute phase and subsequently switched to oral anticoagulants. However, no potential prothrombotic risk is founded in our patients. Laboratory tests for thrombophilic conditions and autoimmune panels in both cases were negative.

TPO-RAs are related to enhanced P-selection, an adhesion molecule that is predominantly expressed on activated platelet and endothelial cell surface [9,10]. 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 [10].

The 2019 edition of the American Society of Hematology guideline for ITP recommends either romiplostim or eltrombopag as the second-line therapy for people suffering from ITP who are corticosteroid-dependent or resistant to corticosteroids for at least 3 months. After the symptoms are free and achieve a platelet count of more than 50,000/mm3 for 6 months, eltrombopag could be tapered [3]. In our cases, CVT occurred within one month of initiating eltrombopag therapy. Compared to other published cases, most patients developed CVT within two months after treatment began. Only one case developed within nine months. Even though it has been deemed appropriate for eltrombopag treatment, the risk of eltrombopag-associated CVT must be taken into consideration during the first two months of treatment. Prior to administering TPO-RAs, initiation and tapering indications must be taken into account. Off-label usage may unnecessarily increase the incidence of TPO-RAs adverse events.

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

5. 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. Before providing TPO-RAs, one must consider initiation and tapering indications. Off-label use may raise the frequency of TPO-RA adverse effects unintentionally.

Data availability

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

Provenance and peer review

Not commissioned, externally peer-reviewed

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Ethical approval

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

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

All images/figures/photos are suitably anonymized with no patient information or means of identifying the patient.

Author contribution

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.

Registration of research studies

1. Name of the registry: Research Registry
2. Unique Identifying number or registration ID: researchregistry8043
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/62b9360ffd60bc001f960d8b/

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Declaration of competing interest

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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List of 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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104116.

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