

Case Report

Cerebral Venous Thrombosis in a Patient with Immune Thrombocytopenia, an Apparent Paradox

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Keywords

Anticoagulation · Cerebral venous thrombosis · Drug therapy · Immune thrombocytopenia · Side effects

Abstract

We present a paradoxical case of immune thrombocytopenia (ITP) that presented with cerebral venous thrombosis. A 39-year-old female patient diagnosed with chronic ITP, who failed treatment on multiple-line agents, was started on eltrombopag (thrombopoietin receptor agonist), which she was not compliant to. The patient later developed extensive cerebral venous thrombosis, along with venous infarcts, and intracranial and subarachnoid hemorrhage. She was treated with intravenous immunoglobulins as well as steroid therapy and was simultaneously started on anticoagulation. The patient improved clinically and radiologically. This case is among few reported cases which signify that patients with ITP are inherently prone to thrombosis despite low platelet count and treating these patients can be a dilemma. Judicious use of anticoagulation and immunosuppressive therapy is recommended based on available evidence pending further recommendations and guidelines about treatment of thrombosis in ITP.

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Published by S. Karger AG, Basel

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Introduction

Thrombocytopenia is a condition characterized by platelet counts less than normal (less than 150,000 platelets per microliter) in the blood. Thrombocytopenia may be inherited or acquired. The causes of thrombocytopenia can be classified into 3 groups: diminished production (caused by viral infections, vitamin deficiencies, aplastic anemia, drugs), increased destruction (caused by drugs, heparin [heparin-induced thrombocytopenia; HIT], idiopathic, pregnancy, immune system), and sequestration (caused by enlarged spleen, neonatal, gestational or pregnancy) [1].

Immune thrombocytopenia (ITP) is an autoimmune disorder manifested as isolated thrombocytopenia as a result of either increased platelet destruction or platelet production. The major culprits are autoantibodies against platelet surface glycoproteins, such as GPIIb/IIIa and GPIb/IX complexes. However, T cell-mediated cytotoxicity may also be involved [2, 3].

The diagnosis of ITP is mainly a clinical diagnosis that is made after other potential causes are ruled out by careful history, examination, and appropriate laboratory investigations [2, 3]. Initial presentation of ITP is usually related to bleeding. This may occur in up to two-thirds of patients; however, many are asymptomatic. Clinically significant bleeding is noted in individuals with lower platelet counts of $<20,000/\text{mL}$, although the correlation was deemed weak [2, 3].

Management of ITP consists of corticosteroids as first-line therapy. Splenectomy is recommended for corticosteroid-resistant patients as a second-line treatment. Patients who failed previous regimens are referred to as refractory ITP patients; many drugs have been tried as third-line treatments, including thrombopoietin receptor agonists (TPO-RAs) and rituximab [2, 3].

Case Presentation

A 39-year-old female presented with complaints of severe headache, nausea, and vomiting for 4 days. Her medical background was significant for type 2 diabetes mellitus and chronic ITP on eltrombopag, which she was not compliant to. There were no other complaints on systemic review. On examination, she was initially alert and oriented with Glasgow-Coma Scale (GCS) of 14/15. On neurologic exam, she had neck stiffness. Otherwise, no focal neurologic deficits were detected.

Laboratory tests revealed leukocyte count of $11.4 (4-10 \times 10^3/\text{mL})$, hemoglobin of $12.6 \text{ g/dL} (12-15 \text{ g/dL})$, and platelet count of $32 \times 10^3/\text{mL} (150-400 \times 10^3/\text{mL})$.

Computed tomography (CT) of the head and venogram were done and showed cerebral venous sinus thrombosis involving bilateral transverse sinuses, left sigmoid sinus, torcular Herophili, and posterior aspect of the superior sagittal sinus (Fig. 1, 2).

Within a couple of hours, her GCS dropped from 14/15 to 12/15. Repeat CT was done and showed extension of thrombosis involving the entire superior sagittal sinus, cortical veins, left transverse and sigmoid sinuses bilaterally as well as the left internal jugular vein.

The patient was admitted to the intensive care unit. Hematology and neurology stroke teams reviewed the case and reached a consensus to start platelet transfusion, steroids (intravenous dexamethasone), and intravenous immunoglobulins (IVIGs). She was also started on heparin infusion for thrombosis treatment. On the following day, her platelet count had improved to $56 \times 10^3/\text{mL} (150-400 \times 10^3/\text{mL})$. Anticoagulation with heparin infusion was continued.

She further deteriorated while in intensive care unit on day 3, when she became more drowsy. Repeated imaging showed extensive progression of the cerebral venous thrombosis along with bilateral frontal venous infarcts with frontal subarachnoid hemorrhage (Fig. 3).

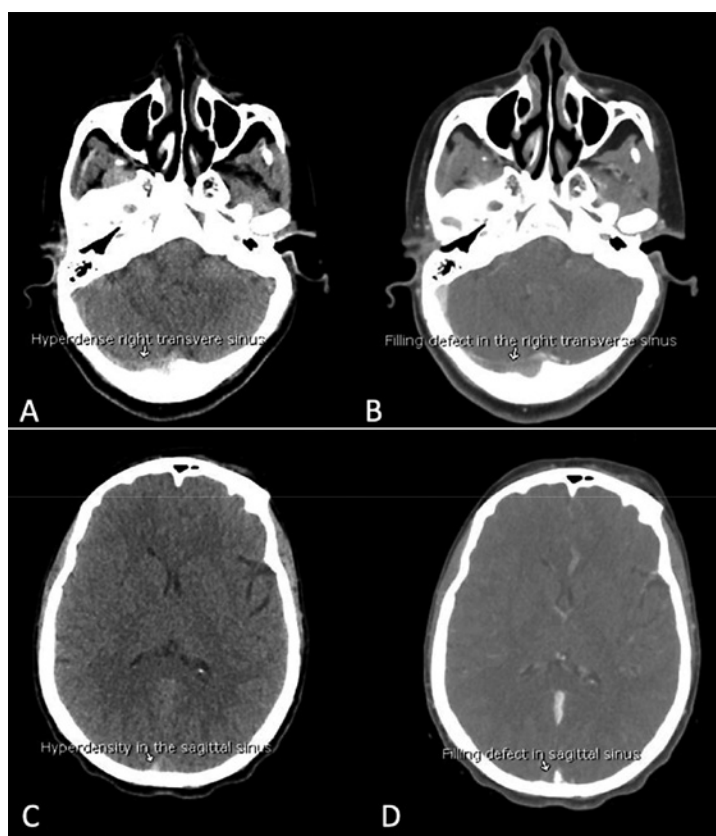


Fig. 1. Axial-plane single-slice plain CT scan showing hyperdensity in the right transverse (A) and superior sagittal sinus (C) with corresponding filling defects in CT venogram (B, D).

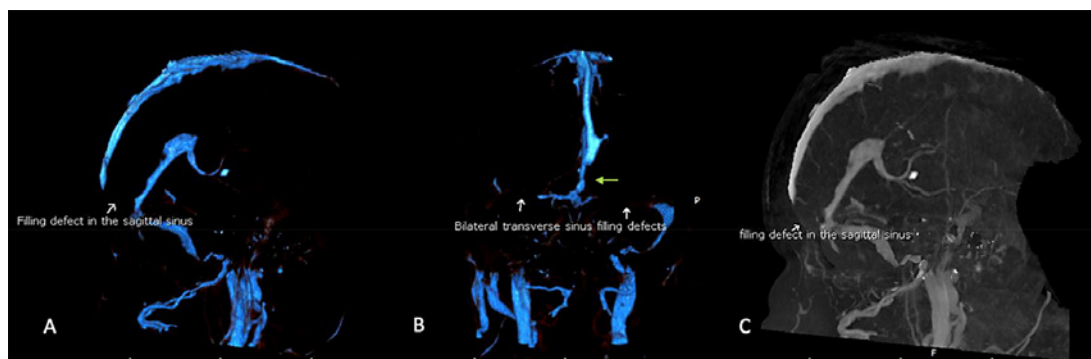


Fig. 2. 3D single-slice CT images of the cerebral venous sinuses demonstrating filling defects in the posterior lower superior sagittal sinus (A, C). B Bilateral transverse sinus filling defects, as well as partially opacified posterior part of the superior sagittal sinus (green arrow).

Her imaging was suggestive of ongoing thrombotic events. So, the heparin infusion was continued with target activated partial thromboplastin time of double the normal target. She received IVIGs for 2 days and steroids for 4 days. The platelet counts remained greater than $50 \times 10^3/\text{mL}$.

Her hospital course was complicated by significant bleeding requiring blood transfusions with widespread ecchymosis so that anticoagulation was held, which was resumed on the following day due to newly discovered partial right internal iliac artery thrombosis and left common iliac vein thrombosis.

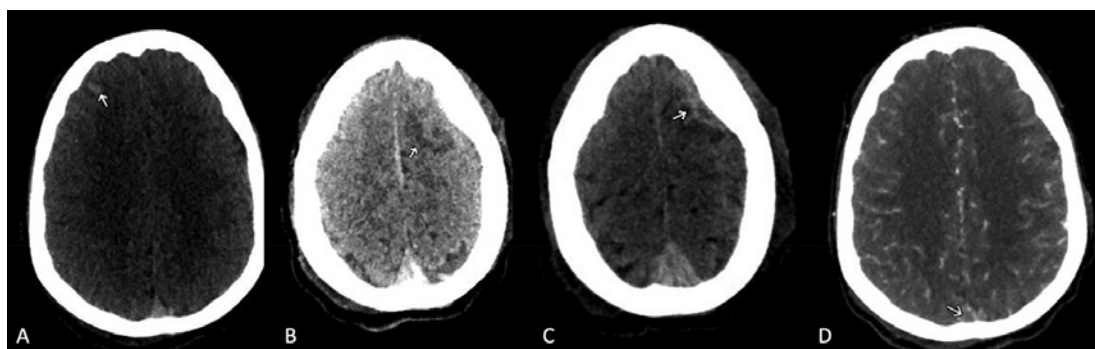


Fig. 3. CT images showing hemorrhage and thrombosis simultaneously. **A** Hemorrhagic focus (arrow) in the right frontal lobe. **B** Hypodensity (arrow) in the left frontal lobe. **C** Left frontal sub-arachnoid hemorrhage (arrow). **D** Superior sagittal sinus filling defect also called “the empty delta sign” (arrow), denoting persistent thrombosis.

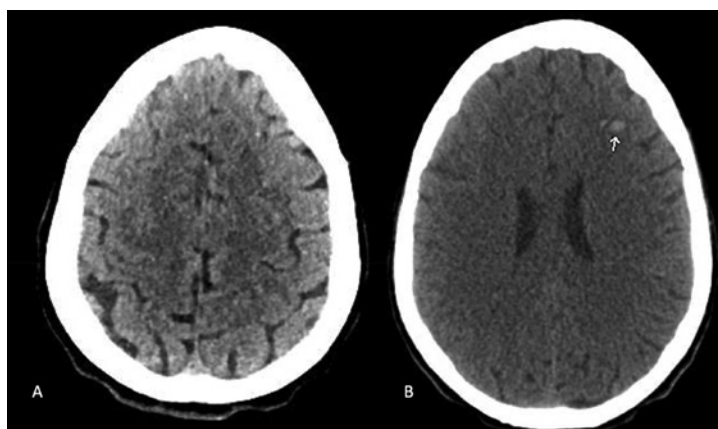


Fig. 4. Follow-up CT scan images. **A** Single-slice axial image of plain CT scan follow-up showing resolved previously seen hypodense focus in the left frontal lobe. **B** Single-slice axial plain CT image showing a new hemorrhagic focus in the left frontal lobe.

Extensive thrombophilia workup, including HIT study, was sent. The workup showed that ANA was positive, anticardiolipin IgM weakly positive, anti-DsDNA negative, β 2-glycoprotein equivocal, and lupus anticoagulant not detected. However, anti-Ro was weakly positive, raising suspicion for Sjogren’s syndrome. The rheumatology team started the patient on hydroxychloroquine for that.

Other workup for thrombophilia showed negative factor V Leiden, homocysteine, and antithrombin III and normal antithrombin activity. Proteins C and S were also normal. Hemolysis workup was also negative. Echocardiography was not suggestive of showering thrombus.

After 2 weeks, the patient became more alert. Repeated imaging showed near complete resolution of previous thrombosis with new evolution of the right anterior frontal small hemorrhagic infarction (Fig. 4).

After resolving thrombosis with reduction in areas of infarction and bleeding on repeated consecutive images, the anticoagulation was shifted to oral warfarin with bridging with intravenous heparin and she was stepped down to the medical floor for continuity of care. Magnetic resonance imaging (MRI) was done before discharging the patient, which revealed improving cerebral venous thrombosis and no increase in intracerebral bleed and subarachnoid hemorrhage (Fig. 5).



Fig. 5. Final follow-up MRI venogram before discharge shows improving thrombosis: well-opacified bilateral transverse (A) and superior (B, C) sigmoid sinuses.

Currently, the patient is being treated with warfarin for cerebral venous thrombosis and hydroxychloroquine for suspected Sjogren's syndrome. Her platelet counts remain stable (last count $286 \times 10^3/\text{mL}$). She is being followed up but currently not on any medications for ITP.

Discussion

Cerebral venous thrombosis is a rare type of cerebrovascular disease that can occur at any age and accounts for 0.5% of all strokes [4]. Generally, cerebral venous thrombosis is associated with prothrombotic states which can be transient or permanent. The most common risk factors include genetic thrombophilia, such as antithrombin deficiency, protein C deficiency, or protein S deficiency, factor V Leiden mutation, homocysteinemia, or acquired conditions like pregnancy and puerperium, oral contraceptive pills, malignancy, or infections. In more than 85% of adult patients, at least 1 risk factor for cerebral venous thrombosis can be identified, most often a prothrombotic condition [5].

ITP is an autoimmune condition characterized by an isolated thrombocytopenia due to increased peripheral destruction of platelets and decreased production. However, despite the low platelet counts, severe bleeding episodes are relatively infrequent, suggesting a possible protective mechanism [5].

Although association between thrombosis and ITP has not been clearly established, evidence has shown that platelet microparticles (PMPs) play a role in thrombus formation in ITP. PMPs are small vesicles (less than $0.5 \mu\text{m}$) originating from platelet membranes that cannot be detected in routine platelet counting. They most likely arise in association with platelet activation [6].

Multiple studies have shown increased levels of PMPs in patients with ITP as compared to a control population without ITP, which was found to be protective against hemorrhage [7]. In excess, PMPs can also promote thrombin formation. Thus, PMPs are thought to play a role in clot formation [8].

One of the possible contributing mechanisms of thrombus formation in ITP is the treatment with IVIGs. IVIGs can promote thrombosis by increasing blood viscosity and thrombin production, and also by directly affecting the vascular endothelium with associated cerebral arterial vasospasm [9].

Another possible mechanism for increased risk of thrombosis can be attributed to increased levels of von Willebrand factor (vWF) antigen. At least one study shows increased levels of vWF antigen levels in patients with ITP, especially old-age patients or patients with a longer duration of disease. Thromboelastography was done to investigate the effect of higher levels, which showed a relatively higher thrombotic tendency that correlated with the vWF antigen levels [10].

Platelet growth factors are commonly used to treat ITP. The TPO-RAs are a class of platelet growth factors that mimic the action of endogenous TPO on megakaryocytes and megakaryocyte precursors, promoting their growth and differentiation and increasing platelet production. The efficacy of TPO-RAs in ITP is attributed to their ability to promote megakaryocyte survival and increase platelet production, thereby improving the platelet count through reversal of the underproduction defect [11].

Increasing platelet count above the normal target is a potential side effect and might contribute to the adverse effect of thrombosis with TPO-RAs. However, nonrandomized observational studies have suggested only a modestly higher rate of thrombosis in patients with ITP treated with TPO-RAs as compared to similar observational studies of patients with ITP treated with immunosuppressive agents [11, 12].

Therefore, if a thrombotic event occurs in an ITP patient receiving TPO-RA treatment, it should be investigated as a new case of thrombosis. Even if no obvious reason is found, it is advised to switch to another ITP treatment, such as immunosuppression. This is in order to maintain a safe platelet count to allow for anticoagulation. In patients with ITP and thrombosis, anticoagulation should be continued despite low platelet counts along with appropriate treatment for ITP unless there is significant bleeding risk or a very low platelet count ($<20 \times 10^9/\text{mL}$) [11, 12].

Conclusion

ITP is a condition with inherent risk of thrombosis despite low platelet count and presents a dilemma to the treating physician to weigh risk and benefits of anticoagulation. Appropriate treatment with anticoagulation and immunosuppression can lead to successful treatment as in our case.

Acknowledgement

We all thank and acknowledge the Program Directors of the Internal Medicine Residency program in HMC for continuous support. We also acknowledge the Qatar National Library for support in printing and publications.

Statement of Ethics

We have obtained written informed consent from the patient to publish this case report.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was funding by the Qatar National Library for the purpose of publication.

Author Contributions

Maimoonah A. Rasheed: literature review and manuscript writing. Arwa E. Alsaud: editing and proof reading. Sania Razzaq: radiographs and images. Afraa Fadul: clinical follow-up. Mohamed A. Yassin: editing and proof reading, literature review (mentor).

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