Cerebral Venous Thrombosis after Intravenous Immunoglobulin Therapy in Immune Thrombocytopenic Purpura

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Abstract

A common misconception is that immune thrombocytopenic purpura (ITP) causes only bleeding diathesis. From this case vignette of a young male with ITP who had cerebral venous thrombosis, we highlight the importance of considering venous thrombosis in such patients when they present with focal cerebral signs.

Keywords: Immune thrombocytopenic purpura, intravenous immunoglobulin, venous thrombosis

Introduction

Immune thrombocytopenic purpura (ITP) is a disorder characterized by autoimmune destruction of platelets, which commonly presents as bleeding diathesis. However, thromboembolic complications can also occur in ITP. Here, we describe a case of ITP who presented with cerebral venous thrombosis (CVT) after treatment with high-dose intravenous immunoglobulin (IVIg).

Case Report

A 26-year-old-male with a history of ITP, presented with occipital headache and one episode of left-sided focal seizure with secondary generalization of 1-day duration. He was diagnosed to have ITP 1-month back when he presented with petechial spots, bleeding gums, and hematuria. Bone marrow examination had shown megakaryocyte hyperplasia consistent with ITP. During that hospital stay, his initial platelet count was 6000/mm^3 which decreased to 1000/mm^3 over the next few days. He also had melena with rapid decline in hematocrit and was treated with single dose of IVIg 75 g. His platelet count increased to 82,000/mm^3 and was discharged on prednisolone 75 g once daily.

On examination, he was alert, oriented, and hemodynamically stable. There were no petechial spots, significant lymphadenopathy or hepatosplenomegaly. Neurological examination was normal. Investigations showed a total white blood cell count of 21,800/mm^3 with 84% neutrophils, 12% lymphocytes, and 4% mixed cells; hemoglobin of 11.2 g/dl; and platelet count of 65,000/mm^3. Serum sodium was 136 mEq/L, potassium 3.9 mEq/L, calcium 9.1 mg/dL, and plasma glucose 105 mg/dL. Serum creatinine was 1.1 mg/dL, total bilirubin was 1.5 mg/dL, and alanine aminotransferase was 30 IU. International normalized ratio was 1.03 and activated partial thromboplastin time was 31.3 (reference <28). Anti-nucleosome antibody, anti ds-DNA, C3 and C4 levels were normal. HIV, HBsAg, and HCV serology were negative. Computed tomography (CT) of the head showed a small intraparenchymal hematoma in the right frontal lobe [Figure 1a]. Magnetic resonance imaging (MRI) of the brain showed T2 and T2-fluid-attenuated inversion recovery hyperintensity in the right inferior and middle temporal gyrus [Figure 1b]. Magnetic resonance venogram (MRV) showed CVT of superior sagittal and right transverse sinus. Antiphospholipid antibody panel (IgG and IgM anti-β_2 glycoprotein I, anticardiolipin antibody, and lupus anticoagulant) was negative. He was started on warfarin and dexamethasone 40 mg pulse therapy was given for 3 days. His headache subsided and platelet count increased to 1.68 x 10^5/mm^3 and was discharged.

Access this article online

Quick Response Code:

Website: www.ijccm.org

DOI: 10.4103/ijccm.IJCCM_308_17

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How to cite this article: James J, Shiji PV, Radhakrishnan C. Cerebral venous thrombosis after intravenous immunoglobulin therapy in immune thrombocytopenic purpura. Indian J Crit Care Med 2017;21:869-71.

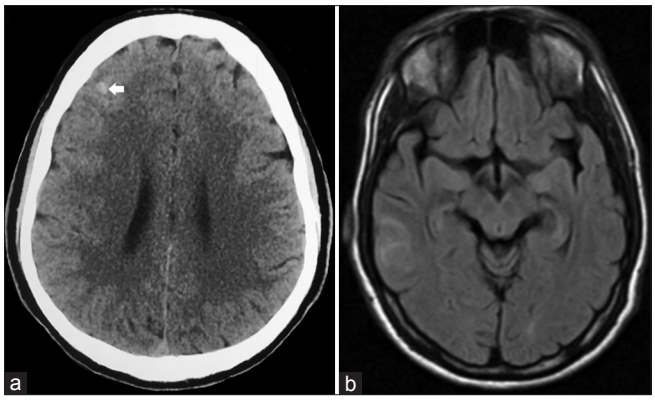

Figure 1: (a) Computed tomography showing intracerebral hemorrhage involving cortex of the right frontal lobe (arrow), (b) magnetic resonance imaging of the brain showing T2-fluid-attenuated inversion recovery hyperintensity in the right inferior and middle temporal gyrus due to transverse sinus thrombosis

Discussion

This case demonstrates a rare combination of thrombosis, despite thrombocytopenia in a case of ITP. In ITP, risk of intracranial bleed increases when the platelet count is <20,000/mm^3.[1] However, our patient had a platelet count of 60,000/mm^3 at presentation, and hence, primary intracerebral bleed was unlikely. On subsequent evaluation, he was found to have CVT, and the intracranial bleed was secondary to this. Apart from bleeding risk, ITP also increases the risk of both arterial and venous thrombosis. Deep vein thrombosis, pulmonary embolism, CVT, and peripheral arterial thrombosis have been described in ITP.[2,3] There are many mechanisms that lead to thrombosis in ITP. Proinflammatory cytokines such as interleukin-6 and interleukin-21 are increased in ITP, suggesting that a chronic inflammatory state exists in these patients. Chronic inflammation is a risk factor for thrombosis. Second, ITP may be a manifestation of an evolving connective tissue disorder, associated with increased risk of thrombosis.

Many drugs used in the treatment of ITP also increase the risk of thrombosis. IVIg is used in ITP to rapidly increase the platelet count in patients with impending major bleed. Cerebral infarction, pulmonary embolism, CVT, and myocardial infarction have been described as complication of IVIg therapy for various disorders.[4,5] IVIg increases blood viscosity and increases risk of thromboembolic complications.[6] The increase in blood viscosity is proportional to the dose and concentration of IVIg infusion.[7] The high-dose IVIg used in emergent therapy in ITP is particularly more likely to lead to thrombosis due to rapid increase in blood viscosity. Some preparations of IVIg may have coagulation factor XI as a contaminant. This can lead to production of thrombin and further increases the risk of thrombosis.[8] However, a recent meta-analysis of IVIg and thromboembolic events suggest that the absolute risk of combined arterial and venous thrombosis with IVIg therapy is low.[9] However, the study noted higher number of venous thrombosis than arterial thrombosis among IVIg-treated patients. Moreover, the study had underrepresentation of ITP and other autoimmune hematologic conditions and hence cannot be generalized. Anti-D immunoglobulin is an alternative to IVIg that can be used in ITP patients with Rh-positive blood group. CVT has been reported in children with ITP after anti-D immunoglobulin therapy.[10] Glucocorticoids are another class of first-line agents used in the treatment of ITP. In a nationwide case–control study, the use of glucocorticoids increased the risk of venous thromboembolism by a factor of 2.31.[11]

To conclude, CVT in our patient was caused by ITP and high-dose IVIg with a contribution from glucocorticoids. Intracerebral bleed in ITP should alert the physician to consider CVT, if there are atypical features such as high platelet count, or if it follows treatment with IVIg. CT and plain MRI may miss CVT, and in such cases, MRV should be obtained for a definitive diagnosis.

Conclusion

ITP patients have increased risk of venous thrombosis even with thrombocytopenia. High-dose IVIg used in the treatment of ITP increases blood viscosity and further provokes thrombosis. When an intracerebral bleed is seen in ITP patients with a platelet count of >50,000/mm^3, CVT should be considered.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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