

Acute Ischemic Stroke related to Intravenous Immunoglobulin

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Abstract

A 26-year-old man with a history of Philadelphia chromosome (Ph)-negative B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) and prior chemotherapy and stem cell transplant was admitted due to thrombocytopenia and diffused interstitial bone marrow infiltration by atypical immature mononuclear cell. After being treated with chemotherapy, the patient developed prolonged fever despite getting antibiotics. Bronchoscope was done and human metapneumovirus pneumonia due to hypogammaglobulinemia was diagnosed. Three days after the 5 days course of IVIg, the patient developed sudden deterioration of consciousness and right hemiparesis. Imaging studies showed large left internal carotid artery (ICA) territory infarction. He died 4 days after the onset of stroke.

Keywords: Thromboembolic, immunoglobulin, ischemic stroke (J Thai Stroke Soc. 2018;17(3): 44-48)

Introduction

To date, intravenous immunoglobulin (IVIg) therapy has been widely used to prevent and treat various conditions such as hypogammaglobulinemia associated with malignancies and autoimmune disorders.¹ IVIg has been considered safe with minor adverse effects including hypertension, fever and chills, nausea, myalgia, and headache.² However, it is potential for serious adverse events such as acute renal tubular necrosis, aseptic meningitis, anaphylaxis

in patients with IgA deficiencies, and thrombotic manifestations.² We report here a case of cerebral infarction after IVIg treatment.

Case report

A 26-year-old man has a 2-year history of Philadelphia chromosome (Ph)-negative B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) which presented with fever and chest pain. The disease was refractory to hyper CVAD chemotherapy, and the salvage protocol was

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initiated after 2 months of the diagnosis then was continued for 5 phases with good response. Two months after the last phase of salvage protocol, allogenic stem cell transplantation was done and the donor was his younger brother. He has taken cyclosporine A 150 mg/day orally since then.

The patient had been well until 6 months later, he had back pain and was prescribed non-steroidal Anti-inflammatory drug (NSAID) to relieve the symptom. One week later, the patient came to a routine clinic visit and had complete blood count (CBC) tested which showed a decrease in white blood cells (WBC) and platelet (HCT 34.6%, WBC 3,700/cu.mm and platelet 38,000/cu.mm). Bone marrow aspiration and biopsy were done and showed diffused interstitial infiltration by atypical immature mononuclear cell. The patient was admitted and chemotherapy was given for 7 days.

After chemotherapy, the patient developed fever and diarrhea and stool culture showed an excess of *Aeromonas* and *Escherichia coli*. Antibiotics were given but fever still persisted, so bronchoscope was done and human

metapneumovirus pneumonia was diagnosed. Recurrent infections were thought to result from hypogammaglobulinemia, so IVIg was administered at the dose of 2 gm/kg divided into 5 days.

Three days after completing IVIg administration, the patient developed deterioration of consciousness, right hemiparesis and was unable to follow command after waking up in the morning. Neurological examination revealed forced deviation of both eyes to the left side with normal reactive pupils bilaterally. CBC on that period showed WBC 3,000/cu.mm, HCT 25% and PLT 10,000/cu.mm. Computed tomography (CT) and magnetic resonance imaging (MRI) (diffusion-weighted imaging) of the brain which were performed immediately and in the next 2 days, respectively showed acute infarction of left internal carotid artery (ICA) territory (figure 1 and 2). Magnetic resonance angiography (MRA) of the brain demonstrated total occlusion of left supraclinoid ICA to left anterior cerebral artery (ACA) and left middle cerebral artery (MCA) (figure 3).

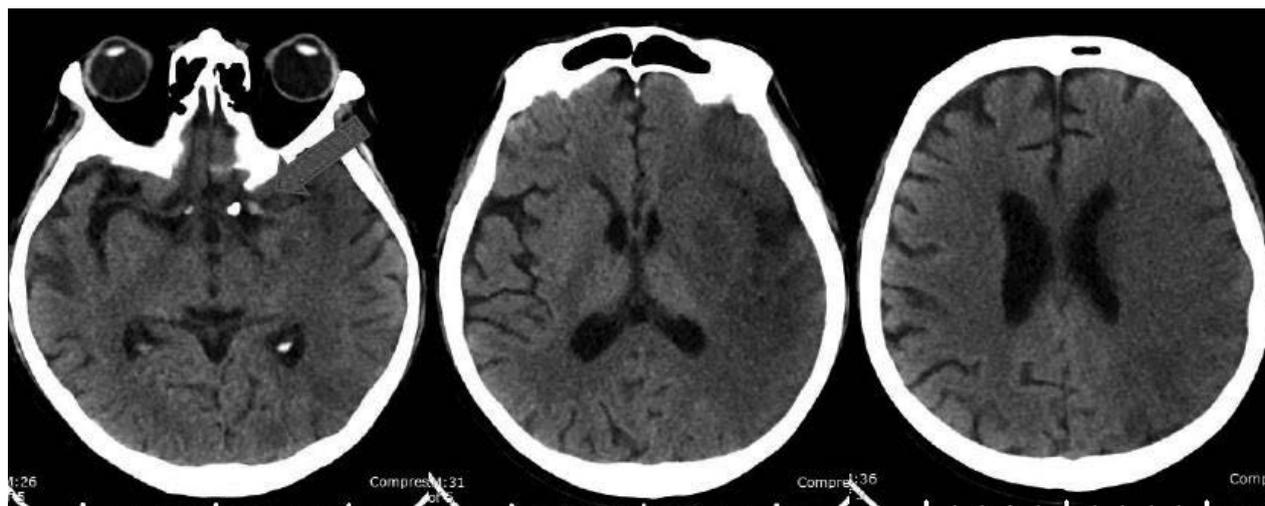


Figure 1. Computed tomography (CT) of the brain showed acute large left middle cerebral artery (MCA) territory infarction involving left fronto-parieto-temporal lobes, left basal ganglia and left insular cortex. A hyperdense clot at left M1 MCA is seen (arrow).

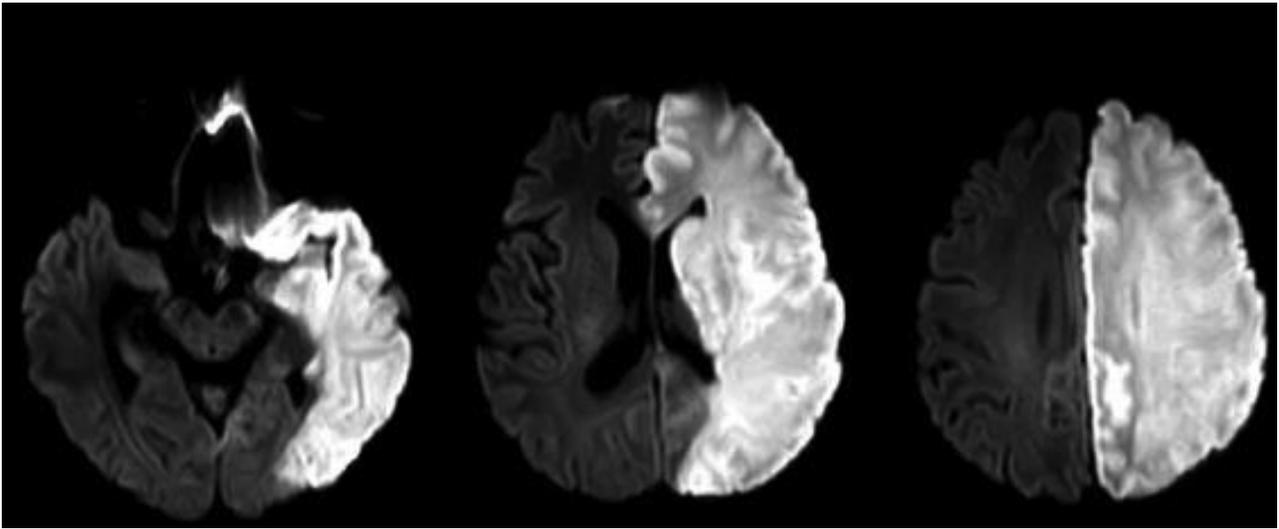


Figure 2. Magnetic resonance imaging (MRI) (Diffusion-weighted imaging) of the brain showed restricted diffusion involving left fronto-parieto-occipito-temporal lobes, left basal ganglia and left insular lobe representing acute left internal carotid artery (ICA) infarction

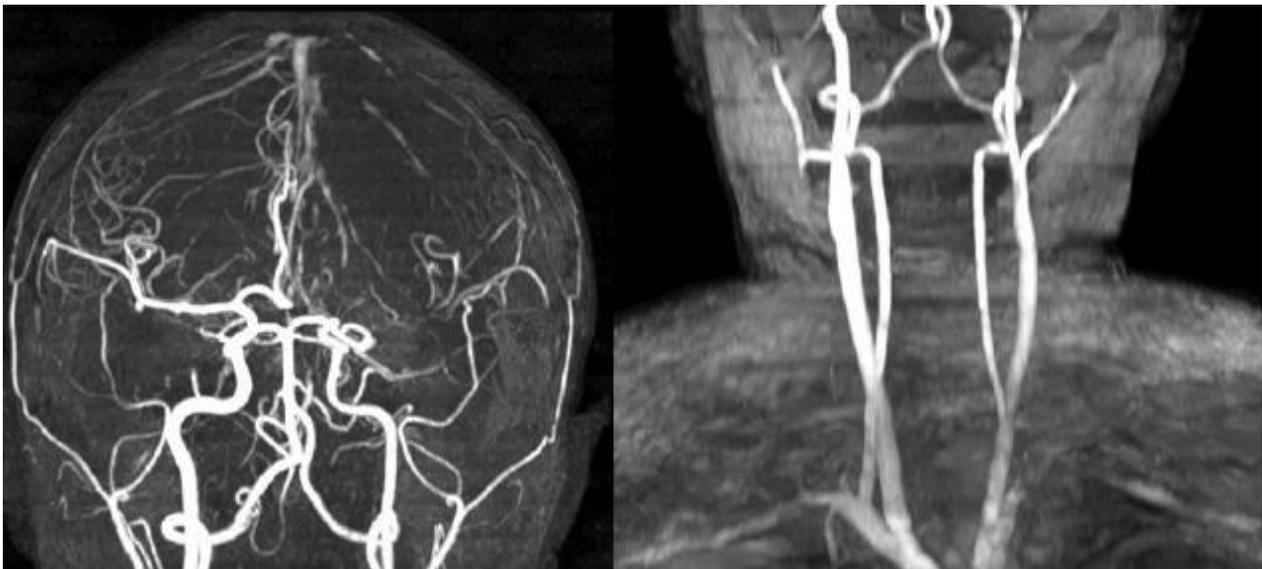


Figure 3. Magnetic resonance angiography (MRA) of the brain demonstrated total occlusion of left supraclinoid ICA to left A1 anterior cerebral artery (ACA) and left M1 middle cerebral artery (MCA)

The patient was intubated and his relatives decided to give him only best supportive care. He died 4 days after stroke onset, so full investigation to exclude other potential cardiac sources of stroke could not be performed.

Discussion

This is a patient who developed acute large ICA infarction 72 hours after IVIg administration. A close temporal association

between the cerebrovascular event and IVIg infusion suggested that the stroke was associated with IVIg use.

The mechanism by which IVIg may cause stroke has not been elucidated but several theories have been proposed. One of the strongest - evidenced mechanisms is an immediate increase in serum viscosity following IVIg infusion that is related to dose.³ Additionally, patients with preexisting high-normal serum viscosity (e.g.,

hypercholesterolemia) or stroke risk factors (e.g., carotid artery disease, diabetes mellitus, and thrombocytosis) may be at a greater risk of developing a thromboembolic event.⁴ Underlying disease of leukemia in this case may be prone to hyperviscosity due to increased cellular component. However, CBC did not show an increase in WBC. Increase in serum viscosity may also have an accumulative effect which persists in certain patients, thereby explaining delayed thrombosis after several doses of IVIg.⁵ In case series by Vuvic and colleagues reported 7 patients having thrombotic event after IVIg infusion, all events occurred after the last dose of IVIg (range from 0.5 to 336 hours).⁶ Similarly, our patient experienced acute left ICA infarction 72 hours after the last dose of IVIg.

Apart from the hyperviscosity theory, other mechanisms are an activation of platelets by IVIg, a contamination of an IVIg product with coagulation factor XI, and a passive infusion of antiphospholipid antibodies via IVIg administration that would trigger the thrombotic cascade and lead to in situ thrombosis and embolism.^{2,3} In addition, an IVIg therapy may cause cerebral vascular spasm and have a direct effect on vascular endothelium leading to cerebral ischemia and possible thrombosis.⁷

A previous report demonstrated the pattern of stroke in multiple vascular territories portends to a thromboembolic mechanism of stroke rather than occlusion of atherosclerotic cerebral arteries or small vessel disease.⁸ Our patient had total occlusion of left ICA without arteriosclerotic change of other intracranial vessels, suggesting of thromboembolic mechanism. There have been conflicting evidences on the potential risk of thrombotic events concerning the dosage and rate of IVIg

administration. A retrospective study among 303 patients who received IVIg infusion showed thromboembolic events in 50 patients with dose dependence (mean 589.4 mg/kg/day vs 387.0 mg/kg/day).⁹ The Food and Drug Administration (FDA) identifies high dosage and rapid infusion of IVIg in susceptible patients as possible risk factors for thrombosis. However, exact parameters for the IVIg dosage and infusion rate are not specified by FDA.² Conversely, it is believed that strokes are not related to an infusion rate, specific products, or concentration of IVIg solution as shown in the case series by Vuvic and colleagues. The patients who developed thrombotic events after IVIg administration received a variety in dosage and rate of IVIg.⁶

Conclusion

In conclusion, we reported a patient who developed acute ischemic stroke after IVIg treatment for hypogammaglobulinemia. Multiple mechanisms including hyperviscosity, platelets activation, a contamination with coagulation factor and antiphospholipid antibodies infusion were proposed.

Originality and Body of Knowledge

Acute ischemic stroke is rarely associated with IVIg administration. Patients at risk for thrombotic complications should be monitored closely for adverse events during any period of IVIg therapy. This suggests that IVIg should be prescribed cautiously, after judiciously weighing the risks and benefits.

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