A 43-year-old black man with pemphigus vulgaris was started on intravenous immunoglobulin (IVIg) therapy after his disease was found to be refractory to prednisone alone and prednisone in combination with mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, and oral cyclophosphamide. The patient subsequently developed a deep venous thrombosis (DVT) that was attributed to the IVIg. IVIg has been associated with numerous thrombotic complications such as pulmonary embolism and myocardial infarction. Traditional risk factors for thrombotic complications, such as hypertension, a history of coronary artery disease, and immobility, should
be considered as relative contraindications to IVIg therapy.


Intravenous immunoglobulin (IVIg) has been advocated as therapy for several immune-mediated and autoimmune skin disorders, and side effects such as vasomotor symptoms, anaphylactic reactions, and renal failure have been well documented.1 Thrombotic complications, such as stroke and myocardial infarction, also have been documented in the neurologic and cardiologic literature but have received little notice from dermatologists.2,3 One recent report in the dermatologic literature described 2 cases of thrombotic events, including a 65-year-old woman with pemphigus vulgaris who developed an upper extremity deep venous thrombosis (DVT) after receiving IVIg.4 We now report a case of thrombosis in the setting of IVIg therapy, only the fourth such case, to our knowledge, in the dermatology literature. We also review some less commonly known clinical presentations of thrombotic events associated with this therapy.

Case Report

We were treating a 43-year-old black man who had an 18-month history of oral pemphigus vulgaris. His disease, which had been limited to the oral mucosa, had been refractory to numerous therapies including prednisone alone or with mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, and oral cyclophosphamide. His trial of cyclosporine was complicated by the development of hypertension, which necessitated oral antihypertensive medication.

After much consideration and investigation into the literature supporting the use of IVIg in refractory pemphigus vulgaris,5,6 we decided to proceed with this therapy. In the first treatment session, the patient received IVIg 40 g daily for 5 consecutive days. He experienced mild chills but otherwise tolerated the therapy well. However, no clinical benefit was observed. After further evaluation of the literature on the benefit of repeated doses of IVIg, we elected to repeat the therapy, this time using a regimen advocated by Ahmed’s group.7 In the second course, which was begun 3 months after the first course, the patient received IVIg 70 g daily for 3 consecutive days, for a total dose of 2 g/kg. A complete blood count and metabolic panel on the last day of the infusion were within reference range. The patient had no notable clinical benefit after the second course of IVIg therapy.

Sixteen days after his last IVIg treatment, the patient underwent elective surgery at a local hospital for an anal fissure. The patient noted that he was particularly lethargic for the 3 days of his hospital stay, but he resumed his normal active daily routine immediately after discharge. Twenty-six days after his last IVIg treatment and 10 days after his anal surgery, he noted significant swelling and pain in his left calf that progressed over the course of several days. Thirty days after his last therapy, he was admitted to the hospital for workup of his leg swelling. A Doppler study demonstrated thrombus in the superficial femoral vein, common femoral vein, and popliteal vein. A diagnosis of DVT was made, and the patient was discharged on a therapeutic regimen of warfarin.

Comment

To our knowledge, there are only 3 reports in the dermatologic literature regarding thrombotic complications in the setting of IVIg therapy. Katz et al4 described one patient with pemphigus vulgaris who developed an upper extremity DVT after receiving IVIg.6 We now report a case of thrombosis in the setting of IVIg therapy, only the fourth such case, to our knowledge, in the dermatology literature. We also review some less commonly known clinical presentations of thrombotic events associated with this therapy.

A review of the literature regarding thrombotic complications with IVIg also revealed several other clinical scenarios of which dermatologists should be made aware. Evangelou et al8 reported a case of transverse sinus thrombosis presenting as an acute, sudden, severe headache in a 54-year-old woman who had recently received IVIg replacement therapy. Of note, the woman was known to have thrombocytosis prior to the therapy.8 In addition, Klaesson et al9 reported fatal venoocclusive disease of the liver in 11% of patients who had bone marrow transplants and were treated with IVIg; none of the transplant patients who served as controls experienced fatal venoocclusive disease of the liver. The difference was statistically significant (P = .02).9 Finally, Steinberger and Coleman10 reported a case of Anton syndrome in a patient with Guillain-Barre syndrome who was treated with IVIg. Anton syndrome is a form of cortical blindness in which the patient denies the visual impairment and may even attempt to ambulate, bumping into surrounding objects. This syndrome arises from damage to the occipital lobes, and the authors speculated that it arose in the setting of hyperviscosity, a known consequence of treatment with IVIg.10

Serial measurements of serum viscosity in patients with amyotrophic lateral sclerosis and
polyneuropathy associated with IgM paraproteinemia before and after treatment with IVIg demonstrated an increase in serum viscosity, with the majority of patients having values above the upper limit of the reference range.\textsuperscript{11} In addition to the hyperviscosity created by IVIg, other possible ways IVIg can predispose patients to thrombotic complications are through vasoactive effects and generation of platelet-activating factor.\textsuperscript{12} Specifically, IVIg has been shown to cause hypotension in a rat model, and in vitro incubation of human neutrophils with IVIg has elicited generation of platelet-activating factor.\textsuperscript{12}

There are many known risk factors for thrombosis including immobility, obesity, surgery, trauma, pregnancy, oral contraceptive use, malignancy, and coagulation disorders. We believe our patient's DVT can be attributed at least in part to his IVIg therapy, though certainly his 3-day period of immobility after his anal fissure surgery, along with hypertension, could have been contributing factors. Other authors have noted that periods of immobility may have predisposed their patients to thrombosis after treatment with IVIg.\textsuperscript{13}

Estimates regarding the absolute risk for thrombotic complications with IVIg therapy have ranged from 3% to 5%, although this has not been well-studied.\textsuperscript{11,14} At our institution, approximately 200 individuals received a total dose of 18,000 g of IVIg in 2003. Unfortunately, no mechanism is in place to record the frequency of complications. Certainly, more information is required to ascertain the overall frequency of clotting complications after IVIg.

Given the preponderance of evidence (including one controlled study) supporting a role for IVIg in causing thrombotic events, we believe physicians should consider traditional risk factors for thrombosis, particularly surgery and immobility, as possible contraindications to treatment with IVIg. There may be some benefit in performing a workup for more subtle predispositions for thrombosis such as factor V Leiden, protein C deficiency, or protein S deficiency. Additionally, if a patient has had a thrombotic complication while being treated with IVIg, caution should be exercised before reinstating therapy.

Emerson et al\textsuperscript{15} recently reported a case involving a 33-year-old woman who had DVT while being treated with IVIg for autoimmune thrombocytopenia and Coombs-positive hemolytic anemia. Five months after the DVT, IVIg therapy was reinstated, and the patient died from a pulmonary embolism. Further studies may be needed to determine if prophylactic anticoagulation with heparin or warfarin may be needed when IVIg is used in the setting of risk factors for thrombosis.

**Conclusion**

We report the fourth case of thrombotic complications occurring with IVIg in the treatment of dermatologic diseases, and we maintain that caution should be exercised in employing this treatment modality in patients who have underlying risk factors for thrombotic events. In particular, caution should be used with immobile patients and with those who need to undergo surgery or other procedures that may render them susceptible to DVT. We reported this case to the US Food and Drug Administration Adverse Event Reporting System, and we encourage others to do the same if thrombotic complications with IVIg are encountered.

**REFERENCES**


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