

**TITLE:** Intravenous Immunoglobulin induced pulmonary embolism: It's time to act!

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**Abstract:**

Pulmonary Embolism (PE) is a common clinical problem affecting 600,000 patients per year in United States. Although the diagnosis can be easily confirmed by imaging techniques such as Computed Tomographic Angiography (CTA) of the chest, the identification of underlying mechanism leading to PE is important for appropriate duration of anti-coagulation and prevention of subsequent episodes. The differential diagnosis of underlying mechanism is broad and must include careful review of medication history. Drug-related thromboembolic disease can be easily missed and may have catastrophic consequences. Identification of the culprit drug is important for prevention of subsequent episodes and choosing appropriate duration of anti-coagulation. We report a case of a middle-aged male who developed pulmonary embolism after administration of Intravenous Immunoglobulin (IVIG).

Keywords: Pulmonary Embolism, Intravenous Immunoglobulin, Selective Immunoglobulin G deficiency, Anticoagulation.

**Introduction:**

IVIG is an immune modulating agent which is given as a plasma protein replacement therapy (IgG) for immune deficient patients to maintain adequate antibody levels by conferring passive immunity. FDA approved indications for IVIG use include allogeneic bone marrow transplant, chronic lymphocytic leukemia, common variable immunodeficiency, idiopathic immune thrombocytopenia purpura, pediatric HIV, primary immunodeficiency's, Kawasaki disease, chronic inflammatory demyelinating neuropathy, kidney transplant<sup>1,2</sup>. The list of off label indications is very extensive. IVIG is being tested in many ongoing clinical trials for treatment of various diseases including Alzheimer's<sup>3</sup> and Behcet's disease<sup>4</sup>.

The prevalence of common side effects such as fever, chills, myalgia, and headache is less than 10%<sup>5</sup>. However, it has also been associated with rare and serious side effects such as

thromboembolic events. IVIG related thrombotic complications were first reported by Woodruff et al. <sup>6</sup> in 1986. A steady increase in the incidence of these complications has been observed afterwards (Table 1), which is estimated to be between 3% and 5% <sup>5,7</sup>. We are reporting a case which unmasks this serious but uncommon side effect of IVIG.

### **Clinical presentation:**

A 57-year-old male with history of hypertension, hyperlipidemia, benign essential tremors, selective deficiency of immunoglobulin G (IgG) and Hodgkin's Lymphoma (in remission) presented with acute onset of dyspnea. He denied chest pain, palpitations, cough, hemoptysis, fever, night sweats and weight loss. He had no history of recent surgery, travel, trauma or immobilization. His medications included aspirin, amlodipine, lisinopril, atorvastatin and IVIG. His past surgical history is significant for splenectomy for treatment of Hodgkin lymphoma. On physical examination, temperature was 38.5 C, blood pressure 135/ 85 mmHg, pulse 106/min and respirations 25/min. Lungs were clear to auscultation and there was no calf tenderness or swelling. His complete blood count and chemistries were normal. Troponin-I was elevated (0.55) without ischemic changes on EKG. CTA of the chest revealed bilateral pulmonary emboli involving upper, middle and lower lobe on the right side and upper and lower lobe on the left side (Figure 1, 2). Doppler venous ultrasound revealed deep vein thrombosis in lower legs bilaterally. He received low-molecular-weight heparin acutely and was transitioned to warfarin anticoagulation prior to discharge. He was referred for outpatient hypercoagulability work up and recommendation for continued IVIG therapy by his immunologist in conjunction with hematology.

### **Discussion:**

This patient received IVIG for selective IgG deficiency which is an off-label indication for IVIG use. It is thought that IVIG related thromboembolic disease occurs within 30 days of administra-

tion of IVIG. It is unclear if length of therapy or the dose of IVIG accounts for any additional risk. This patient developed pulmonary embolism 3 days after administration of 40g of IVIG.

The pathogenesis is poorly understood but it is suggested that increased blood viscosity secondary to use of IVIG increases the risk of thrombosis. It is unclear if this effect is dose dependent<sup>8,9</sup>. It is likely that increased viscosity predisposes to thromboembolism particularly in the presence of vascular risk factors such as advanced age, history of cerebrovascular or cardiovascular disease, hypertension, and hypercoagulability from other causes such as splenectomy. Splenectomy increases thromboembolic complications which can be a potential risk factor in our patient in addition to his hypertension and dyslipidemia

Other proposed mechanisms leading to thromboembolism secondary to IVIG include platelet activation, increased fibrinogen levels and activation of the serum complement<sup>6</sup>. IVIG may induce localized production of vasoconstrictive cytokines and arterial vasospasm leading to thrombotic events<sup>10</sup>. In patients with hypertension and atherosclerotic disease, IVIG-induced arterial vasospasm may further disrupt atherosclerotic plaques, leading to intimal damage, in situ thrombosis and arterial vasospasm<sup>11</sup>. It is unclear if these mechanisms were operative in this patient.

We searched Medline (via Medline and Ovid SP) to identify the incidence and determinants of IVIG related thromboembolic disease. It was concluded that true incidence and determinants are not well established. Although sporadic cases of thromboembolism have been reported in patients receiving IVIG but it is known that factors such as age, sex, race, indication, dose or duration of IVIG therapy independently increase the thromboembolic risk<sup>12</sup>. The number of FDA approved indications as well as off label use for IVIG has increased tremendously in last two decades which has been accompanied by several IVIG related thromboembolic events.

## **Conclusions:**

The reports of IVIG-related thromboembolic events warrant that specific diagnostic criteria and risk factors should be defined. Evidence based recommendations are required for monitoring of IVIG therapy in high risk patients. In patients receiving IVIG, the risk for thromboembolism should be emphasized and steps should be taken for risk stratification and monitoring for thromboembolic complications. Measurement of serum viscosity can be helpful in selected cases. Threshold for diagnostic workup in regards to thrombotic events should be kept very low in these patients. The risk and benefits of IVIG should be carefully weighed prior to initiation of therapy in patients at high risk of thromboembolism, prophylactic anti-coagulation, at least for the duration of therapy, should be considered in these individuals.

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