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Thromboembolic events as an emerging adverse effect during high-dose intravenous immunoglobulin therapy in elderly patients: a case report and discussion of the relevant literature

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Introduction

The therapeutic indications for intravenous immunoglobulin (IVIg) have increased significantly in the last years. It is currently FDA approved for the treatment of primary humoral immunodeficiency syndromes, idiopathic thrombocytopenic purpura (ITP), preventively after bone marrow transplantation, in B-cell chronic lymphocytic leukemia, in pediatric HIV infection and Kawasaki syndrome [1]. However, it is also being used in at least 53 off-label conditions [2], with various strengths of evidence supporting its use. The listed adverse reactions include anaphylactic reactions (especially in patients with selective IgA deficiency), aseptic meningitis syndrome, acute renal failure, headaches, fatigue, chills, backache, leg cramps, lightheadedness, fever, urticaria, flushing, slight elevation of blood pressure, nausea and vomiting, and local pain and irritation at the infusion site [1]. Reviews on the topic of possible adverse effects

also mention liver enzyme abnormalities, immune complex arthritis, hypersensitivity myocarditis, neutropenia, hypotension, encephalopathy, alopecia, uveitis, hypothermia [3], as well as acute hemolytic reactions [4], and the hyperviscosity syndrome [5]. Furthermore, there is a low but definitive risk that the final product can be virally contaminated with HIV, HBV, or HCV [2]. A case of transmission of parvovirus B19 has been reported [6].

There have been several cases of thromboembolic events reported in the world literature that occurred either during or in short temporal relation to IVIg infusion. Some reviews [3, 4, 7–9] mention this serious side effect; others [5, 10] do not. Our recent experience with a patient suffering a large anterior wall myocardial infarction while receiving IVIg therapy prompted us to review the current literature and to discuss possible causes and treatment options.

Case presentation

An 82-year-old man with a past medical history significant for hypertension, benign prostatic hyperplasia, and chronic myelogenous leukemia diagnosed 4 months earlier and complicated by refractory immune thrombocytopenia was admitted to our institution for active bleeding and thrombocytopenia. During the admission he received platelet and blood transfusions as well as a trial of IVIg therapy. He had had two significant episodes of spontaneous bleeding within the last 4 months—one episode of spontaneous gross hematuria requiring transfusions and one episode of a spontaneous subdural hemorrhage which required neurosurgical drainage. He also had had an episode of paroxysmal atrial fibrillation 1 month earlier, which was attributed to a trial of interleukin 11. He was taking prednisone 20 mg daily, metoprolol 50 mg daily, imatinib mesylate 400 mg daily, and doxazosin 2 mg daily. The physical exam on admission was significant for numerous chronic ecchymoses on the trunk, and both arms and legs, as well as a left subconjunctival hemorrhage and a right periorbital hematoma which had developed 2 days prior to admission. He also had a palpable spleen, and his liver was palpable 2 cm below the costal

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margin. His laboratory values on admission were significant for a BUN of 55, creatinine of 1.4, glucose of 184, and a calcium of 8.2. His white count was 24,200 (differential 49% neutrophils, 13% lymphocytes, 15% monocytes, 8% bands, 6% metamyelocytes, 7% myelocytes, and 2% atypical lymphocytes), hemoglobin 8.7, hematocrit 25.4%, and platelet count 21,000. His electrocardiogram on admission showed a normal sinus rhythm at 62 beats per minute, axis and intervals were within normal limits and there were no ST-segment or T-wave changes.

He received a total of 37.5 g of IVIg (10% Venoglobulin, Alpha Therapeutic, at a rate of 1 mg/kg/min) as well as one platelet transfusion on the 1st hospital day. A total of 65 g of IVIg (10% Venoglobulin, Alpha Therapeutic, at a rate of 1 mg/kg/min) was given on the 2nd hospital day prior to a transfusion of packed red blood cells.

About 20 min after starting the blood transfusion and about 3 h after finishing the infusion of IVIg, he began complaining about sudden onset substernal chest pressure in an intensity of 5/10 with radiation to the back. The transfusion was stopped and an initial electrocardiogram showed hyperacute T waves in V3, V4, and V5. Serial electrocardiograms then showed further peaking and ST-segment elevations in V2–V5. An initial troponin was 0.2 with a total CPK of less than 20; however, a second troponin obtained 4 h later showed a troponin of 14.8 and a total CPK of 163. He was started on 2 l oxygen via nasal cannula, and one sublingual nitroglycerin and 2 mg of morphine i.v. were given. The patient was free of chest pressure after the above treatments. No aspirin, heparin, or lytic agents were administered, and also primary PTCA was not attempted because of concern for bleeding complications.

An electrocardiogram obtained 6 h after the onset of chest pressure showed complete resolution of the ischemic changes with no more evidence of peaked T waves or ST-segment elevations, consistent with spontaneous reperfusion of the infarct-related artery. An echocardiographic exam the next day showed a normal ejection fraction and no abnormalities except a dilated left atrium. The patient was discharged home 2 days after the event and has had no further episodes of myocardial infarction or ischemia. He underwent one more course of IVIg 4 weeks later, which was uneventful but did not improve his platelet count. The patient remained thrombocytopenic and was requiring episodic platelet transfusions. He died 9 months after the above event from a spontaneous intracerebral hemorrhage.

Discussion

After a careful search of the world literature we found a total of 29 reported cases in which thromboembolic events occurred in a close temporal relationship to IVIg therapy (Table 1).

There are four more reports of thromboembolic events in patients with ITP treated with IVIg; however, a clear-cut temporary association to the IVIg treatment cannot be established from the report [11–14]. An abstract on a retrospective study [15] found a total of 16 thromboembolic events in 295 patients who received IVIg, however the com-

plete data has never been published. Most studies evaluating the side effects of IVIg have studied younger populations, with an inherent lower risk of developing thromboembolic complications, and therefore this side effect might not have been observed [16, 17]. Studies focusing on the use of IVIg in older patients generally do not have enough patients to show the true incidence of these serious side effects [18–21]. Two larger studies focusing on the use of IVIg in older patients reported one thromboembolic event in 81 patients [22] and one in 56 patients [23]. Several reviews about the use of IVIg mention thromboembolic side effects but most cite only a few cases and list these as rare [7–9].

Several mechanisms have been proposed for the prothrombotic effect of IVIg:

- IVIg could have platelet agonist activity as it enhances ATP release in vitro [24].
- The plasma and blood viscosity both in vitro and in vivo are increased by IVIg, and this is demonstrated in the short term [25] as well as in the long term [26]. Elevated plasma viscosity was reported in one case of a thromboembolic event [27].
- Treatment with IVIg may lead to alterations in the cytokine profile with a localized production of vasoconstrictive cytokines leading to thrombotic events [28].
- IVIg may induce arterial vasospasm [29, 30].
- It has been shown that IVIg may be contaminated with activated coagulation factor XI [31].
- An immunologic immunoglobulin-induced cerebral vasculitis has been suspected in some cases of cerebral infarction related to IVIg therapy [29, 30].

There have been very few reports focusing on the treatment of thromboembolic events associated with IVIg therapy, and these have mostly implicated standard therapeutic interventions with platelet inhibitory drugs, anticoagulation, and thrombolysis. In our reported case we opted for an extremely conservative approach in fear of the high bleeding risk of our patient, and the patient eventually spontaneously reperused the infarct-related artery. If the underlying pathophysiologic event in thromboembolic events associated with IVIg therapy is rather a transient hyperviscosity syndrome and not a true thrombotic event, therapy should be rather aimed at reversing hyperviscosity and not using standard treatment approaches for thromboembolism. However, further basic and clinical research will be necessary to find the optimal therapeutic approach.

Conclusion

- In the face of 30 (including our case) reported patients—10 of whom died—with serious thromboembolic complications while receiving IVIg therapy, we consider it necessary that physicians and manufacturers alike are aware of this rare but potentially fatal adverse effect and that they inform patients about it. From the known data, the risk seems to be especially high in elderly patients with previous thromboembolic events

Table 1 Characteristics of 29 reported cases of thromboembolic events occurring at or near time of IVIg therapy. *CAD* coronary artery disease, *CIDP* chronic inflammatory demyelinating poly-neuropathy, *DM* diabetes mellitus, *DVT* deep vein thrombosis, *HTN* hypertension, *ITP* idiopathic thrombocytopenic purpura, *MI* myocardial infarction, *ND* not disclosed, *PE* pulmonary embolism

Reference	Age (years)	Indication	Complication	Treatment	Risk factors	Previous events
[24]	73	ITP	MI and stroke-fatal	ND	HTN	No
	72	ITP	MI-fatal	ND	HTN	No
	62	ITP	Stroke-fatal	ND	No	Stroke
	83	ITP	Stroke	ND	No	Stroke
[35]	84	Guillain-Barré syndrome	Stroke-fatal	ND	Ex-smoker	TIA
[25]	70	Posttransfusion purpura	MI-fatal	ND	ND	No
[36]	61	Guillain-Barré syndrome	MI-fatal	Streptokinase	ND	Unstable angina, s.p. CABG
[26]	62	Amyotrophic lateral sclerosis	PE-fatal	ND	ND	No
	52	CIDP	Spinal cord ischemia	ND	ND	Nerve infarcts
[37]	27	Myasthenia gravis	Stroke	Heparin	ND	No
[38]	ND	CIDP	Leg DVT	Coumadin	Immobility	ND
[39]	76	Uveitis	MI	ND	Smoker, family history of CAD, hypercholesterolemia	ND
[32]	76	CIDP	MI-fatal	Aspirin, heparin, PTCA (failed)	HTN, Angina	MI×2
[27]	17	Allogenic bone marrow transplant	Bilateral central retinal vein occlusion	Decreased dose and increased intervals of immunoglobulin administration	ND	ND
[33]	52	Immune thrombocytopenia	Arm DVT	Heparin, Urokinase, PTA	ND	No
[40]	78	ITP	MI	Aspirin, heparin	HTN, angina	No
[41]	60	Relapsing polychondritis	MI	Aspirin, heparin, thrombolytics	HTN	Stroke
	41	Polymyositis	MI	ND	HTN, DM, family history of CAD	DVT×2
	67	CIDP	MI	ND	Hypercholesterolemia	No
	67	Systemic castleman disease	MI and stroke	ND	ND	TIA
[29]	60	Guillain-Barré syndrome	Stroke	ND	ND	ND
[28]	40	CIDP	Central retinal vein occlusion	Immunoglobulin held, aspirin	ND	ND
[42]	65	Guillain-Barré syndrome	Stroke	ND	ND	ND
[43]	63	ITP	Leg DVT and PE	Heparin, Fluindione	HTN	DVT×1
[44]	70	Guillain-Barré syndrome	Stroke-fatal	ND	Polycythemia vera	No
[45]	75	ITP	MI	Aspirin	CAD, DM, HTN, Hypercholesterolemia	MI, Stable Angina
[34]	54	ITP	Stroke and Leg DVT	Low molecular weight heparin	Obesity, immobility	ND
	33	Evans' syndrome	Leg DVT and PE-fatal	Heparin, Coumadin	Obesity	ND
[46]	54	Isolated IgG1 deficiency	Bilateral transverse and saggital sinus thrombosis	Heparin, Coumadin	Thrombocythaemia	Migraine headaches after IVIg infusion

or cerebrovascular risk factors and also may be higher in patients with paraproteinemias.

2. It has been suggested that when IVIg therapy is administered to a patient with a high risk of thromboembolic events, this should be done in a well-monitored setting with careful attention to the development of any symptoms of thromboembolism [32], a baseline serum viscosity should be obtained if the patient has a concomitant paraproteinemia [26], the infusion rate should be slowed down, high-dose infusions should be avoided, and blood products should not be given concomitantly [33]. There is, however, currently no clinical evidence to indicate that the above measures are of any benefit. Some authors suggest lowering the dose in obese patients to prevent high intravascular concentrations, because of their relatively smaller intravascular volume [34].
3. The optimal treatment for acute myocardial infarction associated with IVIg therapy is not known. However, if the indication for IVIg therapy is immune thrombocytopenia, it may be safe to withhold antiplatelet therapy to avoid bleeding complications as spontaneous reperfusion can occur and also because platelet activation may not play the same role as in classic acute coronary syndromes.

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