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Case Report

Catastrophic Antiphospholipid Syndrome and Heparin Induced Thrombocytopenia after Pulmonary Vein Isolation Ablation

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Abstract

Introduction: Antiphospholipid syndrome can rarely present as catastrophic antiphospholipid syndrome. Main characteristics include small vessel thrombosis, microangiopathic hemolytic anemia and rapid onset of multisystem involvement. The underlying mechanism is believed to be proinflammatory and a prothrombotic milieu created by antiphospholipid antibodies directed against a heterogeneous group of phospholipid associated proteins. Heparin induced thrombocytopenia is similar to antiphospholipid syndrome in that both are mediated by prothrombotic autoantibodies.

Case Report: We present a case of a 53-year-old male with known antiphospholipid syndrome, hypertension and atrial fibrillation who developed catastrophic antiphospholipid syndrome after pulmonary vein isolation ablation.

He presented with acute renal failure, bilateral adrenal hemorrhage and multiple deep venous thrombosis (DVT). He was treated with intravenous heparin and developed heparin induced thrombocytopenia with positive platelet factor 4 and serotonin assay. Heparin therapy was replaced by Argatroban, until his clinical course was further complicated by diffuse alveolar hemorrhage and thrombotic cerebrovascular accidents. He was treated with high dose steroids and once clinically stable, he was on anticoagulation therapy with Argatroban which was then bridged to warfarin with good clinical response.

Discussion: Pulmonary vein isolation ablation is increasingly being used to treat atrial fibrillation. This procedure involves isolation of pulmonary veins and burning tissue around the veins to create scar tissue. The endothelial injury releases phospholipids that can lead to autoantibody mediated disseminated acute thrombotic microangiopathy leading to multiorgan failure as seen in our patient. This case not only helps to highlight that minimally invasive procedures that cause endothelial injury can lead to a significant "second hit" in patients with antiphospholipid syndrome leading to catastrophic events, but also documents the simultaneous occurrence of catastrophic antiphospholipid syndrome (CAPS) and heparin induced thrombocytopenia (HIT). Although around 65% of patients with CAPS will have thrombocytopenia it is important to have high suspicion for HIT not only as a differential diagnosis for multiple thrombi but also as a coexisting entity. Catastrophic antiphospholipid syndrome creates a systemic inflammatory response, which leads to platelet activation and can predispose these patients to heparin-induced thrombocytopenia.

Keywords: *Antiphospholipid Syndrome; Catastrophic Antiphospholipid Syndrome; Heparin Induced Thrombocytopenia*

Introduction

We present a patient with a past medical history of antiphospholipid syndrome who developed concurrent catastrophic antiphospholipid syndrome and heparin induced thrombocytopenia after pulmonary vein isolation ablation. Antiphospholipid syndrome (APS) is mediated

by autoantibodies that are pro-thrombotic, autoantibodies are generated to phospholipids or to phospholipid-binding proteins. The diagnosis of APS requires clinical manifestations such as venous, arterial or small vessel thrombosis, pregnancy related morbidity, and the presence of at least one of the phospholipid autoantibodies including IgG/IgM anticardiolipin, lupus anticoagulant or IgG/IgM β2 glycoprotein antibodies [1]. Patients who present with APS after a "second hit" can develop catastrophic antiphospholipid syndrome (CAPS), which is characterized by small vessel thrombosis, microangiopathic hemolytic anemia and rapid onset of multisystem involvement. The underlying mechanism is believed to be formation of a proinflammatory and prothrombotic state created by antiphospholipid antibodies directed against a heterogeneous group of phospholipid associated proteins. Heparin induced thrombocytopenia (HIT) is similar to antiphospholipid syndrome in that both are mediated by prothrombotic autoantibodies [2]. HIT is an adverse drug reaction which manifests as thrombosis and thrombocytopenia. Platelet factor 4 (PF4) and heparin form neo-antigens that are seen as foreign invaders by the immune system, leading to the formation of antibodies against the PF4/heparin complex resulting in platelet activation, aggregation and release of platelet granules and procoagulants [3].

Case Report

A 53-year-old Caucasian male with a history of hypertension, atrial fibrillation and antiphospholipid syndrome presented two days after pulmonary vein isolation ablation with shortness of breath. He was diagnosed with antiphospholipid syndrome 12 years prior to this presentation after an unprovoked DVT of the right lower limb. He was anticoagulated with warfarin, however this medication was discontinued after he developed a traumatic subdural hematoma due to a fall. He was off anticoagulation for ten years, during this time frame he did not have any pro-thrombotic events. However, he was diagnosed with atrial fibrillation and was treated with apixaban for 12 months, ultimately it was decided he was an appropriate candidate for pulmonary vein ablation.

Two days after the procedure he presented to hospital with shortness of breath associated with chills, fever and productive cough with pink sputum. He was initially treated with antibiotics because aspiration pneumonia was suspected.

Anticoagulation with intravenous heparin was started and hematocrit dropped within 24 hours from 36% to 27%. He began to complain of vague abdominal pain, an abdominal CT scan demonstrated bilateral adrenal hematomas (Figure 1). Treatment with high dose steroids was started, however, he developed acute renal failure, and acute hypoxic respiratory failure requiring intubation and mechanical ventilation. His platelet count decreased from 230 x 10E3/uL on admission to 70 x 10E3/uL in 24 hours. Enzyme-linked immunosorbent assay (ELISA) was performed to detect heparin associated platelet antibodies (HAPA) and antiphospholipid antibodies (APLA). HAPA was strongly positive: 1.817 and his serotonin release assay was positive with 86% (normal, ≥ 20%), serotonin release with low-dose heparin (0.1 U/mL) and 2% (normal, =20%) serotonin release with high-dose heparin (100 U/mL). Antiphospholipid antibody profile demonstrated elevated anti-β2 glycoprotein 1, anticardiolipin, and positive lupus anticoagulant, heparin was then discontinued.

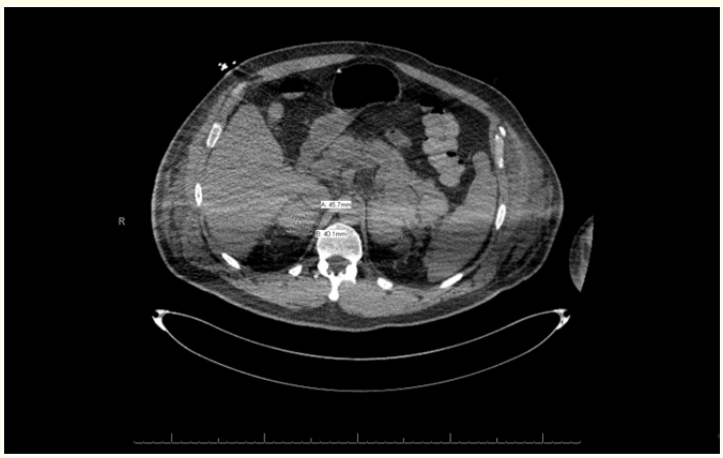

Figure 1: *CT abdomen and pelvis demonstrating bilateral large adrenal hemorrhage.*

Five days later, he developed occlusive DVT in the left jugular, left posterior tibial, and left peroneal veins for which anticoagulation with argatroban was started.

He developed altered mental status which necessitated a brain MRI, which showed "watershed" strokes (Figure 2). After clinical stabilization, warfarin was bridged with argatroban until the INR reached therapeutic levels. Treatment with high dose steroids was continued, and the patient was discharged to a rehabilitative facility where he continued to do well. Three months after the initial hospital admission, antiphospholipid antibodies levels were still high, confirming the diagnosis of antiphospholipid syndrome (Table 1).

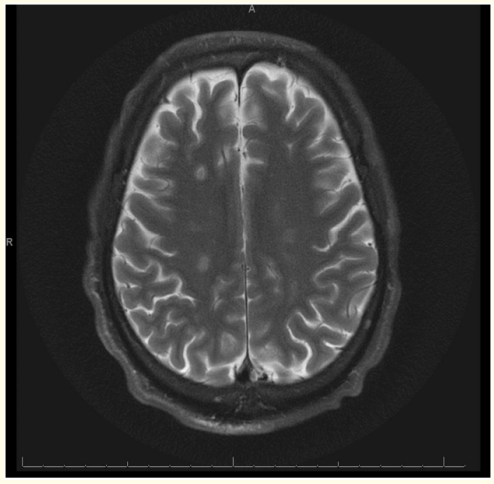

Figure 2: *MRA T2 Flair showing multiple, bilateral, predominantly subcentimeter foci of increased T2 signal involving the cerebral hemispheres.*

Tests	2013 at Initial Diagnosis	At Presentation	3 Months after
Anticardiolipin IgG (0-14 DRVVTGPLU/ml)	124	78	10
Confirmation (0.8-1 Anticardiolipin.2 ratio)	2.1	1.8	2.0
IgM (0-12 MPL U/ml)	49	35	20
Anti- 2 glycoprotein 1 IgG (0-20 GPI IgG units)	> 150	35	
Anti- 2 glycoprotein 1 IgM (0-32 GPI IgM units)	67	59	
aPTT, lupus sensitive (0.0 - 51.9 sec)	88	41	72
DRVVT screen (0.0 - 47.0 sec)	76.8	60.4	59.8

Table 1: *Antiphospholipid profile at the time of presentation and at twelve-week follow-up.*

Discussion

Pulmonary vein isolation ablation is increasingly being used to treat atrial fibrillation. This procedure involves isolation of pulmonary veins and burning tissue around the veins to create scar tissue. The endothelial injury releases phospholipids which can lead to autoantibody-mediated disseminated acute thrombotic microangiopathy, leading to multi-organ failure as seen in our patient. This case demonstrates the impact of minimally invasive procedures causing endothelial injury, which can lead to a significant "second hit" in patients with antiphospholipid syndrome leading to catastrophic events. Interestingly, it also documents the simultaneous occurrence of CAPS and clinical heparin induced thrombocytopenia. Although around 65% of patients with CAPS will have thrombocytopenia, it is important to remember HIT not only as a differential diagnosis for multiple thrombi, but also as a coexisting entity with CAPS. Catastrophic antiphospholipid syndrome creates a systemic inflammatory response, which leads to platelet activation and can predispose these patients to heparin-induced thrombocytopenia.

Catastrophic anti-phospholipid syndrome (CAPS) is a life-threatening form of anti-phospholipid syndrome (APS) characterized by the presence of multiorgan involvement developing over a short period of time, histopathologic evidence of multiple small vessel occlusions and laboratory confirmation of antiphospholipid (APL) antibodies, typically, in high titers [1]. CAPS is an uncommon complication that occurs in less than 1% of APS patients however its mortality rate of ~50% emphasizes the importance of early recognition and appropriate treatment [1,3].

Infection is the most common precipitating factor, although the syndrome has also been described following the withdrawal of anticoagulant therapy, low international normalized ratio (INR), angiographical procedures, surgical interventions, obstetric complications, systemic lupus erythematosus (SLE) flares, trauma, and certain medications such as oral contraceptives [1-3]. In the case presented here we suspected the inciting event was the pulmonary vein isolation procedure causing endothelial activation and release of phospholipids.

The pathogenesis of CAPS is incompletely understood; Mechanisms proposed include molecular mimicry and endothelial activation in the setting of microvascular and macrovascular occlusion [3]. Antiphospholipids have demonstrated the ability to activate endothelial cells, up-regulate adhesion molecules, and promote the release of tissue factor to activate the coagulation cascade. Molecules such as pro- inflammatory cytokines, products of the activated complement cascade and anti-phospholipid antibodies can act on leukocytes and platelets to increase their adhesion to vascular endothelium, thereby promoting micro-thrombosis resulting in the diffuse microvasculopathy, characteristic of CAPS [3,5].

The majority of clinical features seen in CAPS occur as a consequence of thrombotic microangiopathy. Cevera., *et al.* [4] reviewed 280 patients with CAPS from a large web-based international registry and reported that the first clinical manifestation was pulmonary complication in 24% of cases, neurologic findings in 18%, and renal failure in 18% [3,4]. Adrenal hemorrhage is a recognized, not infrequent complication of this syndrome [4,5]. The most common laboratory findings are thrombocytopenia, hemolytic anemia and disseminated intravascular coagulation. Presence of APL is necessary for the diagnosis, specifically anticardiolipin (aCL), lupus anticoagulant (LA), or anti- β2-glycoprotein I.

The mainstay of treatment involves the combination of high dose steroids, intravenous (IV) heparin, IV immunoglobulin (IVIG), and plasma exchange [2,3]. The patient we present was successfully treated with high dose steroids, IV heparin which was replaced by Argatroban due to the concomitant diagnosis of heparin-induced thrombocytopenia and was bridged to warfarin. Heparin induced thrombocytopenia is a complication of heparin therapy in which heparin forms complexes with platelet factor 4 resulting in neoantigens that results in the formation of autoantibodies [6]. HIT should be suspected if the platelet count decreases by 30-50% after five days of treatment with heparin. The predominant clinical feature is thrombosis, and not bleeding despite thrombocytopenia [7].

The concurrent diagnosis of both CAPS and HIT as presented in this case is rare. Adedrian and Agostino [6] reported a less severe case in which a 37-year-old woman developed recurrent DVT and PE and was found to be positive for both heparin associated antibodies and APL antibodies, with the Serotonin release assay being positive.

There are many similarities in HIT and APS immune mechanisms (Table 2). In both disorders there is an antibody that targets a protein-antigen complex. In APS, the complex is a phospholipid bound to beta-2 glycoprotein (β2-GPI) and in HIT it is heparin bound to platelet factor 4 (PF4). This results in formation of a neoepitope that induces antibody formation, which binds to and activates FcγIIa receptors on platelets and endothelial cells, resulting in platelet activation and damage to vascular endothelial cells. It has been suggested that APS and HIT can trigger one another. In APS, platelet activation results in the release of PF4, which can bind to heparin sulfate on endothelial cells. This complex could provoke the generation of HIT antibodies. Additionally, the distortion of vascular endothelium occurring in APS results in the exposure of glycosaminoglycans that then complex with platelet factor 4 producing neoantigens and causing HIT [1,6]. Conversely, HIT antibodies can cause vascular damage that could result in configurational changes in the membrane phospholipids of endothelial cells, thereby leading to the generation of APL antibodies [1]. In the clinical case we present here, we suspect the pulmonary vein isolation procedure resulted in endothelial injury resulting in the release of phospholipids and generation of APL antibodies. The patient then developed CAPS that resulted in platelet activation and the release of PF4 ultimately leading to the simultaneous development of HIT.

	HIT	APS
Protein-Antigen Complex	Heparin + PF4	β2-GPI+phospholipid
Autoimmune response	+	+
Pro-coagulant state	+	+
Platelet activation	+	+
Thrombocytopenia	+	+
Hemolytic anemia	_	+
Prolonged aPTT (activated partial thromboplastin time)	_	+ If lupus anticoagulant present
Obstetric complications	-	+
Leukocyte activation	+	+
Endothelial cell remodeling	+	+
Up regulation of cytokines	+	+
Up regulation inflammatory mediators	+	+
Therapy	Discontinuation of heparin, anticoagulation with direct thrombin inhibitor (Argatroban)	Unfractionated or lower-molecular-weight heparin followed by warfarin (target INR 2-3)
Associated disorders	Infection, malignancy, trauma	SLE, HIV, malignancy, connective tissue disorders, autoimmune disorders, drug reactions, infection, trauma

Table 2: *Clinical similarities and differences between HIT and APS.*

Conclusion

CAPS is the most severe form of APS and is characterized by hematological manifestations such as micro thrombosis accompanied by multiple organ thromboses. The clinical manifestations usually overlap with other thrombotic microangiopathies. The diagnosis requires a high index of clinical suspicion and it is imperative to diagnose and treat early. We hope our case report will help practitioners better assess aPL-positive patients with multiple organ involvement, ultimately leading to a timely diagnosis and treatment.

Disclaimer

Patient gave informed consent to publish this case report.

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