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CASE REPORT

Incomplete Catastrophic Antiphospholipid Syndrome and Heparin-Induced Thrombocytopenia in Diffuse Systemic Sclerosis: A Case Report

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Abstract

Background. Catastrophic Antiphospholipid Syndrome (CAPS) and Heparin-Induced Thrombocytopenia (HIT) are rare, life-threatening thrombo-inflammatory conditions that may overlap in patients with systemic autoimmune disease.

Case Report. A 63-year old woman with diffuse cutaneous systemic sclerosis (dcSSc), relapsing polychondritis and established antiphospholipid syndrome developed multiorgan failure after a brief switch from vitamin K antagonist therapy to low molecular weight heparin and a confirmed infection with Clostridium. The hospital course was complicated by suspected HIT, fulminant cardiac dysfunction and widespread microthrombosis despite clean coronary angiography. Autopsy confirmed innumerable myocardial microthrombi, aortic cross mural thrombosis and left subclavian arterial thrombosis, fulfilling three of the four criteria and can be classified as incomplete CAPS.

Conclusions. Early recognition of CAPS and immediate cessation of all heparin products in suspected HIT are critical to improve survival in similar high risk patients.

Keywords: incomplete catastrophic antiphospholipid syndrome; heparin-induced thrombocytopenia; systemic sclerosis; microvascular thrombosis.

Abbreviations:
ANA - Antinuclear antibody
APS - Antiphospholipid syndrome
CAPS - Catastrophic Antiphospholipid Syndrome
CK-MB - Creatine Kinase-MB
CPAP - Continuous positive airway pressure
CRP - C-reactive protein
dcSSc - Diffuse cutaneous systemic sclerosis
DLCO - Diffusing Capacity of the Lungs for Carbon Monoxide
DOAC - Direct Oral Anticoagulants
ECG - Electrocardiography
HIT - Heparin-Induced Thrombocytopenia
HRCT - High-Resolution Computed Tomography
ICU - Intensive Care Unit
KDIGO - Kidney Disease Improving Global Outcomes
NSIP - Non-specific interstitial pneumonia
PF4 - platelet factor 4

Introduction

Thrombotic events remain a major cause of morbidity and mortality in systemic autoimmune diseases. Two rare but severe conditions that exemplify this are Catastrophic Antiphospholipid Syndrome (CAPS) and Heparin-Induced Thrombocytopenia (HIT). Although distinct in etiology, both syndromes are marked by a rapid and often fulminant course, requiring prompt recognition and intervention [1]. CAPS is a life-threatening variant of antiphospholipid syndrome (APS), characterized by widespread vessel thrombosis affecting multiple organ systems over a short period, usually days [2].

Two forms of heparin-induced thrombocytopenia (HIT) are recognized. Type 1 is a non-immune, transient drop in platelet count occurring within the first 1–3 days of heparin exposure, typically benign and self-limiting. Type 2 is an immune-mediated reaction developing 5–14 days after heparin initiation. It is caused by antibodies directed against complexes of platelet factor 4 (PF4) and heparin. This leads to platelet activation, thrombocytopenia, and a paradoxical hypercoagulable state requiring immediate treatment.

HIT can complicate anticoagulation strategies in patients with APS, increasing the risk of further thrombotic events and requiring a shift to non-heparin anticoagulants. These conditions, though individually rare, can coexist or sequentially trigger one another, particularly in vulnerable patients with autoimmune backgrounds, previous thromboses, or recent infections.

Case report

A non-smoking 63-year-old female patient with a known history of recurrent deep vein thromboses, chronically anticoagulated with acenocoumarol and stage 3b chronic kidney disease (KDIGO classification) was referred for 2 years history of arthralgias, Raynaud's phenomenon, and more recently, sclerodactyly, myalgias (upper and lower limbs). Other symptoms were exertional dyspnea, dysphagia, epigastric pain, and recurrent auricular and nasal chondritis. Physical exam revealed grade III obesity, facial and thoracic telangiectasias, reduced mouth opening, sclerodactyly, Rodnan skin score of 8. Laboratory showed: mildly elevated CRP, leukocytosis, ANA 1:2560, strongly positive anti-Scl-70, and significantly elevated anti-β2-glycoprotein I antibodies. Nailfold capillaroscopy revealed late scleroderma pattern. HRCT chest showed early NSIP pattern, and the patient had a decreased DLCO of 72%. Echocardiography was done with no pulmonary hypertension. The diagnosis of large esophageal ulcer and chronic gastritis, H. pylori negative, was established during gastroscopy. Additional investigations were performed to determine the cause of kidney disease and angio-CT showed near-complete obstruction of the left renal artery accompanied by significant atrophy of the left kidney. The following diagnoses were established - Diffuse cutaneous systemic sclerosis overlapping with relapsing polychondritis and APS.

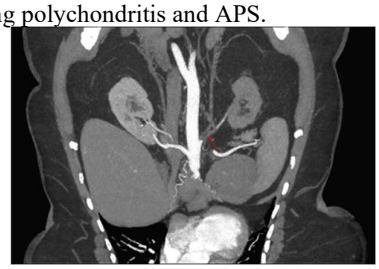

Figure 1. *Abdominal angio-CT showing near-complete occlusion of the left renal artery (indicated by the red arrow) with associated atrophy of the left kidney*

The patient had been previously treated with DOACs but developed recurrent thrombotic events, leading to reinstatement of vitamin K antagonist therapy. During hospitalization, anticoagulation was briefly switched to enoxaparin in preparation for endoscopy, which resulted in a 60% drop in platelet count meeting the 4T score criteria for probable HIT (score 7/8). She was switched to fondaparinux and after a few days returned to acenocoumarol. She subsequently developed diffuse abdominal pain, chest pain, fever, leukocytosis, and thrombocytopenia. Empiric antibiotic therapy (Ceftriaxone + Metronidazole) was initiated. It was stopped after negative results of blood cultures and abdominal ultrasound which ruled out cholecystitis. The patient's course was complicated by Clostridium difficile infection, which was successfully treated with oral Vancomycin. Despite resolution of infection, chest pain worsened. Cardiac reevaluation was unremarkable initially. Two days later, the patient developed acute respiratory failure, hypotension, a new left bundle branch block on ECG, markedly elevated troponin (>25,000), and CK-MB levels. She was transferred to the ICU requiring CPAP and vasopressor support. Urgent coronary angiography showed no significant coronary artery lesions, though echocardiography revealed severely reduced left ventricular function. Despite maximal supportive therapy, the patient suffered cardiac arrest and resuscitation was unsuccessful. An autopsy was conducted with no myocarditis, no significant coronary artery disease but there were multiple cardiac microthrombi of varying age (Figure 2).

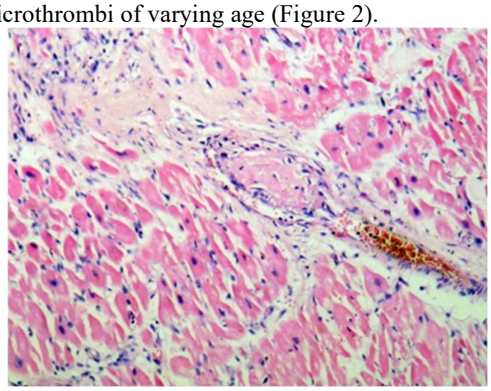

Figure 2. *Histopathology (H&E ×20) showing fresh fibrin thrombus adherent to endothelium and organizing thrombus with perithrombotic fibrosis*

Discussions

This case underscores the deadly synergy between systemic autoimmunity, CAPS and HIT. Small vessel vasculopathy is central to systemic sclerosis and may facilitate CAPS by exposing neoepitopes and activating complement. CAPS occurs in less than 1% of APS patients and is often triggered by infection, trauma, surgery, or changes in anticoagulation. Diagnostic criteria include evidence of thrombosis in at least three organs, laboratory confirmation of

antiphospholipid antibodies, and histopathologic evidence of small-vessel occlusion [3]. Our patient fulfilled three of the four established CAPS criteria—(1) an abrupt, ≤ 7-day clinical evolution; (2) histopathological confirmation of small-vessel occlusion and (3) persistent positivity for antiphospholipid antibodies, but she did not satisfy the requirement for thromboses involving three or more distinct organs, systems or tissues.

Although the patient had a left renal thrombosis, this was considered chronic —evidenced by ipsilateral renal atrophy on CT angiography — so it could not be counted as a new, rapidly progressive event and therefore does not fulfill the organ-involvement criterion required for a diagnosis of definite CAPS in the current episode.

The autopsy revealed thrombotic lesions confined to the cardiovascular system— widespread myocardial microthrombi together with an aortic mural thrombus and a left-subclavian arterial thrombus—which, despite their multiplicity, collectively represent only one organ-system. According to the International CAPS Registry, cardiac involvement is relatively frequent in patients with CAPS (up to 50%), making the heart the fourth most commonly affected organ system [3]. Recent evidence indicates that myocardial ischemia may be the predominant form of cardiac involvement, with troponin and NT-proBNP elevated in 93% and 100% of patients, respectively [4].

A meticulous post-mortem examination found no additional macro- or micro-thromboses in other organs (lungs, kidneys, adrenals, central nervous system, skin, or gastrointestinal tract). Consequently, the case cannot be classified as definite CAPS and is best designated as incomplete CAPS, a category that nevertheless warrants the same aggressive "triple" therapy because of its comparable pathophysiologic mechanism and high mortality risk [2].

Distinguishing CAPS from severe myocarditis or septic cardiomyopathy is challenging; however, normal coronary angiography, absent myocarditis on histology and widespread myocardial microthrombi support CAPS as the dominant mechanism of acute heart failure. During hospitalization, imaging evaluation of the large vessels did not reveal any signs of thrombosis. The coronary angiography showed no abnormalities of the cardiac vessels. There were no signs of thromboembolism or potentially biopsiable skin lesions. Renal function deterioration occurred two days before death and was interpreted as secondary to cardiac dysfunction. In the absence of any new signs of thrombosis—with renal artery stenosis and a sclerotic-appearing kidney suggesting an old thrombotic pathology—the most plausible diagnosis at that time was myocarditis.

Despite the patient having known APS and acute cardiac deterioration, there was no clear evidence of simultaneous involvement of multiple organ systems at the time. This highlights a key limitation in real-time CAPS diagnosis—when microvascular involvement is clinically silent or attributed to pre-existing pathology, the syndrome may go unrecognized. The postmortem histopathological result identified the exact cause of death as heart failure due to the presence of intracardiac microthrombi. The patient's clinical condition deteriorated rapidly, with death occurring one day after coronary angiography.

Treatment guidelines advocate early triple therapy (anticoagulation, high dose corticosteroids and plasma exchange and/or intravenous immunoglobulin) plus targeted complement inhibition in refractory disease [5]. In our case treatment for CAPS was not initiated due to the absence of clinical data suggesting this condition.

HIT, on the other hand, is an immune-mediated adverse reaction to heparin exposure, marked by thrombocytopenia and a paradoxical prothrombotic state. Anti-PF4 antibodies performed with ELISA technique and platelet serotonin release assay are diagnostic markers of HIT. Absolute contraindications are represented by the use of another type of heparin, platelet mass and warfarin. DOACs and Fondaparinux can be used. Their overlapping prothrombotic mechanisms can rapidly evolve into critical illness, posing significant diagnostic and therapeutic challenges [6]. Although testing for anti-PF4/heparin antibodies was not available during hospitalization, the clinical probability of type 2 HIT was high, supported by a 4T score of 7/8, a 60% drop in platelet count shortly after exposure to low molecular weight heparin, and the subsequent development of cardiac microthrombosis. In the absence of other plausible causes for thrombocytopenia and in the presence of a high thrombotic burden, the diagnosis of immune-mediated HIT remains strongly supported by validated clinical criteria. This is consistent with data from Girolami et al., where HIT, although infrequent, was associated with a 60% thrombotic complication rate, highlighting the importance of early recognition even in the absence of antibody confirmation [7].

Fewer than 30 cases of combined CAPS and HIT have been described [8]. Reported survivors uniformly received early non-heparin anticoagulation and immunomodulation. Registry data suggest mortality for CAPS has fallen from 50 % to ≈35 % with adoption of triple therapy. Although the simultaneous occurrence of CAPS and HIT is rare, case reports such as Holahan et al. support that both syndromes can coexist, compounding thrombotic risk and worsening prognosis. In that report, a patient with APS and CAPS developed HIT after heparin re-initiation, leading to devastating multi-organ thrombosis and death [9]. Similarly, in our case—marked by APS positive serology, recent heparin exposure, and thrombocytopenia —a clinical course consistent with type 2 HIT emerged, followed by fatal cardiac microthrombosis. This overlap highlights the need for heightened vigilance in APS patients who exhibit new thrombocytopenia under heparin, as concurrent CAPS-HIT may go unrecognized and contribute to rapid deterioration.

Conclusions

In patients with systemic sclerosis and antiphospholipid antibodies, sudden multiorgan dysfunction should prompt aggressive screening for CAPS. Overlap of HIT and CAPS is rare but devastating. The case emphasizes the importance of high vigilance, immediate discontinuation of heparin products in suspected HIT, and consideration of non-heparin anticoagulants such as fondaparinux or direct oral anticoagulants. Earlier recognition of the thrombotic pattern and empirical initiation of CAPS-directed therapy, despite the absence of full diagnostic criteria, might have altered the outcome.

Conflicts of Interest: The authors declare no conflicts of interest.

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