Case Report

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A Case Report of Idiopathic Catastrophic Thrombotic Syndrome with Purpura Fulminans

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Abstract

Background: *Catastrophic thrombotic syndrome (CTS) is a rare life-threatening condition defined as rapid onset of multi-organ thrombosis affecting diverse vascular beds. Predisposing conditions include catastrophic antiphospholipid syndrome (APS), atypical thrombotic thrombocytopenic purpura (TTP), delayed heparin-induced thrombocytopenia and Trousseau syndrome. Patients who do not meet any of these criteria are diagnosed with idiopathic catastrophic thrombotic syndrome.*

Case description: *A 44-year-old Caucasian woman with type II diabetes and hypothyroidism presented with acute onset of myalgia and extensive bruising over a period of four days. Physical exam revealed hypotension, tachycardia, and extensive purpuric and bullous skin lesions. Laboratory evaluation demonstrated microangiopathic hemolysis, thrombocytopenia, elevated D-dimer and coagulopathy suggesting disseminated intravascular coagulation (DIC) along with acute kidney injury (AKI) and transaminitis. Aggressive transfusions including packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate were required to reverse her severe coagulopathy. Ultrasound showed occlusive thrombus in the left basilic vein and the greater saphenous veins bilaterally and heparin infusion was started. IV methylprednisolone, all-trans retinoic acid and doxycycline were empirically given.*

Workup was negative for any coagulation factor deficiency or hypercoagulable state although heterozygous factor V Leiden (FVL) mutation was found. Bone marrow biopsy was normal. Infectious and auto-immune workups were unremarkable. Skin biopsy showed diffuse intravascular thrombi but no evidence of vasculitis. Two weeks later, she developed Enterobacter bacteremia from infection of her bullous lesions. She was started on broad spectrum antibiotics and transferred to a burn unit. Eventually, her coagulopathy, bacteremia, AKI and transaminitis resolved, she was discharged with indefinite anticoagulation.

Discussion: *CTS presented in our patient with rapidly progressive thrombosis with consumptive coagulopathy. No obvious instigating source was found, her clinical presentation was out of proportion for the isolated heterozygous FVL mutation. Anticoagulation remained the main therapy in the acute setting and aggressive supportive care in multi-disciplinary setting to manage acute and late complications was required.*

Conclusion: *Through this report, we emphasize the need for early recognition of CTS with this constellation of clinical findings and advocate for urgent interventions to prevent untoward outcomes.*

Keywords: Catastrophic Thrombotic Syndrome, Anticoagulation; Purpura Fulminans

Introduction

Catastrophic thrombotic syndrome or "thrombotic storm" is a rare but serious, and life-threatening condition in which patients develop aggressively accelerated course of thromboembolic events involving multiple organs or vascular systems or unusual sites over days to weeks [1]. Thrombotic storm was first described by Kitchens in 1998 with the following key characteristics: an underlying hypercoagulable state, a provocative event such as pregnancy, infection, trauma or surgery, a sudden onset of thromboses, aggressive anticoagulant therapy as a prompt intervention, good long-term prognosis if successfully interrupting the cycle of thrombosis early [1-5]. Several hypercoagulable disorders such as catastrophic antiphospholipid syndrome (APS), atypical thrombocytopenic purpura (TTP), cancer-associated thrombosis and delayed heparin-induced thrombocytopenia (HIT) can present with this clinical syndrome [3]. However, a small group of patients presenting with catastrophic thrombotic syndrome do not have any known pro-thrombotic disorders. In this paper, we report a rare case of a 44-year-old Caucasian female with no known pro-thrombotic disorder who developed purpura fulminans as a result of catastrophic thrombotic syndrome of unknown etiology. Given the scarcity of literature describing the optimal intervention for patients with this disorder, we want to share our experience in the diagnostic and

therapeutic management of such an unusual scenario.

Case presentation

A 44 year-old Caucasian female with a history significant for type II diabetes, hypothyroidism and irritable bowel syndrome presented with progressive myalgia, arthralgia and random bruising. She developed an acute onset of diffuse purpura on all extremities and then spreading to her trunk over a four-day period. She denied any history of clots, recent travel or infection, exposure to ticks, or new drug use. Family history was remarkable for leukemia and breast cancer in her maternal side. Laboratory findings revealed prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), severe thrombocytopenia, low plasma fibrinogen, elevated INR and plasma D-dimer concerning for acute disseminated intravascular coagulation (DIC) (Table 1). Peripheral blood smear showed rare schistocytes and no dysplasia. Labs were otherwise remarkable for transaminitis and elevated serum creatinine (Table 1). A computed tomography (CT) scan of thorax, abdomen and pelvis with contrast was negative for pulmonary embolism or acute abnormalities. Ultrasound of all extremities revealed occlusive thrombus in the left basilic vein and the greater saphenous veins bilaterally. Patient was admitted to the intensive care unit; Hematology-Oncology, Vascular Surgery and Nephrology team were consulted.

Physical exam was remarkable for hypotension (blood pressure 95/57mmHg), tachycardia (heart rate 99), and extensive purpuric and bullous skin lesions from ankles to just below groin creases bilaterally. Purpura was non-blanching and had clear demarcation. She had edema in all extremities, the forearm and thigh compartments were tight but compressible (Figure 1). She had good extremity movement with Dopplerable pulses bilaterally.

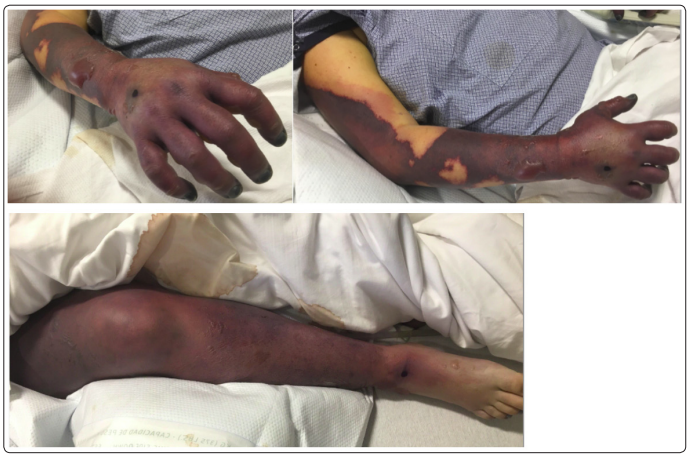

Figure 1: Extensive purpuric skin lesion with demarcation in all extremities with bullous skin lesions

She was given aggressive intravenous (IV) fluid resuscitation due to signs of hemodynamic instability. Further, with concern for purpura fulminans and thrombosis in multiple sites, heparin drip was started. One day after admission, her hematocrit dropped and she received platelets, fresh frozen plasma (FFP), cryoprecipitate and packed-red blood cells to reverse her thrombocytopenia, coagulopathy and anemia. She received intravenous methylprednisolone 125 mg every 8 hours for any possible auto-immune causes. All-trans retinoic acid was started empirically before ruling out acute promyelocytic leukemia given her purpura fulminans and DIC manifestation. Empiric Doxycycline was started for possible tick bite infection. She was given patient-controlled analgesia pump with morphine for pain control.

Table 1: Laboratory data at admission and discharge

	Reference Range	Values at admission	Values at discharge
Hematology			
WBC	4.2-10.2 thou/mL	13.1 H	6.9
hemoglobin	11.5-14.5 g/dL	5.5 L	7.5
hematocrit	34.6-43.8%	15.3 H	21.2
platelet	150-240 thou/mL	46 L	261
MCV	81.4-97.7 fL	90.3	86.6
Haptoglobin	30-200 mg/dL	14.5 L	110
Fibrinogen	208-475 mg/dL	15 L	539 H
aPTT	23.2-34.1 second	61.3 H	96.2 H
INR	0.8-1	3.3 H	1.3 H
PT	11.7- 14.5 second	32.4	15.5
D-dimer	0 – 0.44 mcg/mL	>20 H	Not checked
Retic count	30-90 thou/mcL	57.2	Not checked
Antithrombin III	84-125%	71 L	Not checked
Lactate dehydrogenase	84-246 units/L	304 H	Not checked
Chemistry			
Blood urea nitrogen	7-18 mg/dL	41	10
Serum creatinine	0.52-1.21 mg/dL	1.8 H	0.46
Total bilirubin	0.2-1.0 mg/dL	1.6 H	0.8
Total protein	6.5-8.2 g/dL	6.6	6.4
Albumin	3.4-5 g/dL	3.2	2
Alkaline phosphatase	45-117 units/L	138	141
AST	15-37 units/L	232 H	29
ALT	13-56 units/L	247 H	60
Creatinine kinase	26-192 units/L	482	Not checked

Abbreviations

WBC: White Blood Count
MCV: Mean Corpuscular Volume
aPTT: Partial Thromboplastin Time
INR: International Normalized Ratio
PT: Prothrombin Time
AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase.

Coagulopathy workup including factor assays and mixing study were ordered (Table 2). Unfortunately, results were indeterminate because patient received FFP and cryoprecipitate prior to lab draw. Mixing studies were negative for any factor inhibitors. Patient was heterozygous for factor V Leiden mutation, but this presentation was drastically out of proportion for this condition. Her initial coagulopathy, thrombocytopenia and elevated D-dimer suggested DIC. A bone marrow biopsy revealed normocellular marrow with erythroid predominant trilineage and no blasts present. Serum protein electrophoresis was unremarkable. Flow cytometry for Paroxysmal Nocturnal hemoglobinuria and ADAMTS 13 testing for TTP were negative as well.

Table 2: Laboratory data for Coagulopathy workup

Coagulopathy	References	Values at admission
Factor IX assay	64-170 %	254 H
Factor V assay	83-146 %	90
Factor VIII assay	67-164 %	159
Factor X assay	64-153%	73
Heparin anti XA assay	Unit/mL	0.8
Von willebrand factor antigen	50-160%	420% H
Von willebrand cofactor	42-200%	>600% H
Activated protein C resistance	>2.1	2 L
Protein C functional	74-161 %	12%
Protein S function	47-134%	54%
Russel Viper venom	28.3-43.1 second	26.6 L
Factor V Leiden mutation	N/A	heterozygous
Prothrombin mutation/factor II PCR	N/A	negative
Cryofibrinogen	N/A	negative
Lupus Anticoagulant Panel	NA	Negative
Anti-cardiolipin IgG	0-9.9 unit/mL	0
Anti-cardiolipin IgM	0-9.9 unit/mL	0
Beta 2-glycoprotein antibody	0-9.9 unit/mL	1.6
FISH t(15,17) mutation	N/A	negative
Fibrinogen antigen	180-350mg/dL	155

Abbreviations

PCR: Polymerase Chain Reaction
FISH: Fluorescence in Situ Hybridization

Infectious workup including blood and urine cultures, meningococcal infection, HIV, hepatitis A, B and C, Rickettsiae was negative. An extensive auto-immune work up was undertaken and was negative a (Table 3). A skin biopsy showed diffuse intravascular thrombi consistent with a hypercoagulable state but no evidence of vasculitis.

Table 3: Laboratory data for autoimmune disease workup

Immunochemistry		
Anti-Scl 100 antibody	180-350 mg/dL	155
Anti-nuclear antibody		negative
ANA index	0-0.89	0.2
DNA double stranded antibody	0-24.9 units/mL	4.1
C-reactive protein	<3mg/L	102 H
C3 (serum complement)	90-180 mg/dL	62.1 L
C4 serum complement	10-40 mg/dL	8.4 L
Anti-smith	0-15.9 EU/dL	0.8
Anti- RNP	0-15.9 EU/dL	1.0
Anti- SSA	0-15.9 EU/dL	4.1
Anti-SSB	<0.1 EU/dL	<0.1
Rheumatoid factor	0-15 units/mL	<10
Homocysteine	4-15.5mcmol/L	6.9
Anti-PR3 (c-ANCA)	0-0.79 index	0.11
M protein	0	0
Cryoglobulin screen		negative

Abbreviations

Anti-Scl: Anti-Scleroderma Antibody
Anti-RNP: Anti-Ribonucleoprotein
ANA: Antinuclear Antibody
Anti-SSA: Anti-Sjögren's-syndrome-related antigen A
Anti-SSB: Anti-Sjögren's-syndrome-related antigen B
Anti-PR3: Anti-Proteinase 3
C-ANCA: Cytoplasmic Anti-neutrophil Cytoplasmic Antibodies

She was treated with supportive care including as needed transfusion with the goal to keep her hemoglobin level above 7 g/dL, platelet above 50,000 counts and fibrinogen above 150mg/dL. After aggressive transfusions her acute coagulopathy state, anemia and severe thrombocytopenia had resolved. The transaminitis and AKI also resolved in 3 days. Heparin drip was continued during the entire hospital stay. Patient was weaned down on her intravenous corticosteroid slowly.

At presentation 45 percent of her body surface area was affected by purpura fulminans. One week later, she developed dry gangrene at the tips of all fingers and all toes. Plastic surgery and wound care were involved and antimicrobial silver-coated dressing was applied. Two weeks after admission, patient developed sepsis with Enterobacter asburiae bacteremia, from superimposed infection from her diffuse rupturing bullae. She was started on broad spectrum antibiotics with vancomycin and piperacillin/tazobactam. She was later transferred to a burn intensive care unit in a different facility for extensive skin care. She was discharged home one month later with indefinite anticoagulant therapy.

Discussion

CTS or thrombotic storm is a life-threatening condition in which multiple thromboembolic events affecting diverse vascular beds develop rapidly over days to weeks. The rapid progression of thrombosis often occurs in multiple locations and sometimes in unusual sites such as dural sinus, hepatic veins and inferior vena cava [4]. While the pathogenesis of thrombotic storm is unclear, it is believed to be triggered by several existing conditions including injury, infection, malignancy or pregnancy [1]. Hypercoagulable state is an underlying risk factor that triggers clot formation. Several distinct disorders can present with this extreme manifestation, including catastrophic antiphospholipid syndrome (APS), heparin-

induced thrombocytopenia (HIT), Trousseau syndrome and atypical presentations of TTP [3] . However, there is a small group of patients with no known triggers or any personal history of coagulation disorders.

Diagnostic workup is important to determine if any of these hypercoagulable conditions are present as treatment is tailored by the underlying disorder [3]. Initial evaluations include a thorough history and physical exam and laboratory workup including lupus anticoagulant panel, peripheral blood smear, ADAMTS 13 level to identify any underlying disorders [3]. Imaging studies are needed to identify the location of thrombosis. At presentation, our patient had thrombosis in the left basilic vein and the greater saphenous vein bilaterally. She denied any precipitating events such as recent illnesses, surgery, trauma, medication changes and heparin exposure. She was heterozygous for factor V Leiden mutation; however, this mutation would not predispose her to such an extreme state of thrombosis. Her fulminant coagulopathy was best described as idiopathic catastrophic thromboembolism.

The primary treatment for most of the catastrophic thromboembolic disorders is prompt initiation of anticoagulation [3]. Even though diagnostic workup is important, initial anticoagulant therapy is critical and must not wait on these results. Unfractionated heparin is the most common use anticoagulant due to its ability to titrate dose and the availability of a reversal agent when hemorrhagic complications occur [1]. In those patients with atypical TTP or lupus attack, treatment would involve plasma exchange, corticosteroids and immunomodulatory agents respectively [5, 6]. However, acute onset of thrombotic storm can be extremely difficult to treat as anticoagulants can increase risk of bleeding. To date, there have been very few studies in the medical literature to guide its therapy. In this case, the patient was started promptly on heparin drip with good response. Although her hematocrit dropped, no new bleeding was identified and no further thrombotic or bleeding events occurred after the initiation of anticoagulation. After the acute onset of thrombotic events has been controlled, indefinite anticoagulant therapy should be considered to prevent recurrent of further events [3].

CTS can be associated with microangiopathic process leading to microvascular occlusions affecting internal organs and purpura fulminans [3]. In this patient, AKI was thought result from ischemic acute tubular necrosis (ATN) Her extensive non-blanching purpuric skin lesion with clear demarcation, and a skin biopsy revealing diffuse intravascular thrombi suggested purpura fulminans. This is typically seen in infants with inherited protein C deficiency or adults with severe meningococcal infections, both causes were excluded in our patient. The mechanism of purpura fulminans is poorly understood, but it is believed to be a result of a massive generation of thrombin which triggers acute onset of extensive intra-microvascular thrombosis leading to cutaneous hemorrhage and necrosis [7-9]. Purpura fulminans is a dermatological emergency, treatment involves supportive care including hydration, transfusion to correct acquired deficiencies and anticoagulation should be considered to prevent further skin necrosis [10]. Additionally, early surgical debridement of necrotic areas has proven to decrease mortality [9]. This patient developed skin breakdown and infections, managed by plastic surgery and eventually requiring care in a burn unit.

Conclusion

In summary this case highlights the need for high index of suspicion and early recognition of catastrophic thrombotic syndrome. Prompt initiation and continuation of anticoagulation with aggressive supportive care in a multi- disciplinary setting is imperative. This case report adds to the literature on the diagnosis and management of this rare and life threatening entity.

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