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A Feather in Your CAPS: Probable CAPS treated with rituximab

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INTRODUCTION: Catastrophic antiphospholipid syndrome (CAPS) is a rare complication occurring in 1% of patients with Antiphospholipid Syndrome (APS). [4] It presents with widespread intravascular thrombosis leading to the failure of multiple organs (commonly the kidneys, lungs, brain, heart, and others. These thromboses are caused by antiphospholipid antibodies which are thought to induce a hypercoagulable and prothrombotic state by acting on endothelial cells, platelets, and fibrinolysis. Furthermore, the autoantibodies act to activate the complement system and ramp up the immune system creating a hyper-inflammatory state which explains why most patients with CAPS will also meet criteria for SIRS. [1]

Diagnosis of CAPS remains challenging due to its clinical overlap with other thrombotic microangiopathies. [2] However, diagnostic criteria include but are not limited to the involvement of three or more organs, development of the signs and symptoms contemporaneously within one week, biopsy demonstrating microangiopathy, and two separate serological findings of antiphospholipid antibodies separated by six weeks. Generally, a diagnosis of Definite CAPS is made if all the criteria are met but if only three are met the diagnosis is Probable CAPS. [1,2,3] Serology can reveal anticardiolipin, Lupus Anticoagulant, anti-β2-glycoprotein I, and antinuclear antibodies. [1]

Management with anticoagulation, corticosteroids, plasmapheresis, IVIg, and aspirin resulted in a decline in the mortality rate from a half to a third of patients. Cyclophosphamide produces greater survival benefit in patients with SLE. Refractory cases can be treated with rituximab or eculizumab [4]. Rituximab is thought to be a possible alternative treatment due to its ability to reduce the detrimental autoantibodies and cytokines speculated to be involved in CAPS. [5] Here, we report a case of Probable CAPS, in the setting of SLE, treated with rituximab in addition to most of the standard treatments (plasmapheresis, IVIg, glucocorticoids).

CASE REPORT: Previously healthy 18 year old African female college student initially presented to an outside hospital with 2 week history of low grade fevers, erythematous rash with blisters on her hands, feet, and face, diarrhea (15 bowel movements a day), decreased appetite with weight loss, shortness of breath, and worsening fatigue and weakness. She was diagnosed with Hand Foot Mouth disease and discharged 3 days later. Three weeks later, her condition worsened and she was admitted to the same hospital. Labs at the OSH were significant for: hgb 10.5, plt 114, PT 16.75, INR 1.58, Na 130, tbili 10, dir bili 8.4, ALP 312, AST 1263, ALT 187, lactate 1.7, HIV neg, CRP < 0.29, RF < 10. The patient experienced a tonic-clonic seizure 4 days after admission and was given Ativan and Keppra. She is up to date on her immunizations and had no

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recent sick contacts. She was born in Nigeria and moved to the US two and a half years ago for college and has not left the US since then. After the seizure at the OSH, the patient was taken by family to our ED. She was lethargic and unresponsive in her car and was brought in by ED staff, patient was tachycardic up to 131, tachypneic up to 50, and hypotensive 80/50. She was given 3 liters of IVF with transient improvement in BP. Due to patient's worsening mental status and desaturation, she was intubated and required vasopressors for hypotension. Labs were significant for hgb 7, plt 78, INR 4.3, Na 134, K 3.4, Cl 112, HCO3 8, BUN 31, Cr 1.7, alb 1.4, AST 1102, ALT 156, alk phos 267, tbili 6.7, CRP 9.3, lactate 5.4, procal 73, UA with 74 WBC, 259 RBC, 5 granular casts on sediment, and UPC of 8338 mg/g. CXR showed diffuse bilateral interstitial and alveolar opacities. CT chest showed patchy bilateral consolidation, pleural effusion and axillary/supraclavicular LAD. CT head had minimal prominence of the temporal horns and third ventricle. CT abdomen showed hepatomegaly, inguinal LAD, and small amount of free fluid in the abd/pelvis.

Due to worsening respiratory status, patient required intubation and mechanical ventilation. Her pulmonary edema, elevated cardiac enzymes, and renal function (urine output and creatinine) worsened even with gentle diuresis so she required dialysis. Her hospital course was complicated by MSSA bacteremia (on HD 8), MSSE bacteremia (on HD 32), C. krusei candidemia (on HD 37), and CMV Colitis (on HD 46). TEE was negative for any other structural or valvular abnormalities. She was treated with vancomycin, pip-tazo, cefepime, cefazolin, ciprofloxacin, metronidazole, fluconazole, voriconazole, micafungin, valganciclovir, and acyclovir during admission. Autoimmune work-up was positive for ANA+ (homogeneous 1:640 titer), dsDNA 96, Chromatin >8, Smith 1.9, Sm RNP 2.5, RNP 6.6, Lupus Anticoagulant, Beta-2-glycoprotein IgA, decreased C3/C4 levels, and elevated ESR/CRP. PBS showed 6-9 schistocytes/hpf. Additional lab work showed consistent elevation of PT/PTT, LD (1494), normal fibrinogen, haptoglobin, and slight decreased ADAMST13 activity (36%). On HD6, MRI Brain that showed interval development of several significant intraparenchymal hematomas with mild mass effect (largest in left frontal lobe is 26cc with 3 mm midline shift) and intraventricular extension suggestive of severe coagulopathy. Pt was transfused with platelets and pRBC's and started on hypertonic saline boluses. Patient was treated for Probable CAPS, in the setting of SLE, with daily hydroxychloroquine, daily methylprednisolone 80 mg, 5 cycles of plasmapheresis, and 3 cycles of rituximab (beginning on HD 16; 375mg/m2 each dose). Anticoagulation was held in the setting of the patient’s intracerebral hemorrhage and frequent bleeding from tracheostomy site. Renal biopsy was not performed since the patient had thrombocytopenia and leukocytosis. Given her positive anti-dsDNA antibody, microscopic hematuria, nephrotic range proteinuria on UA, and poor renal function, patient was treated with mycophenolate mofetil for Lupus Nephritis.

On HD 19, pt had a seizure-like episode and Keppra was started. vEEG showed diffuse background changes and no evidence of seizure. Contrast CT Head was negative for abscesses or masses. The patient gradually began showing signs of improvement with the ability to follow simple commands and improvement of laboratory values. Repeat CT head demonstrated improving edema and resolved midline shift. On HD 52, patient was taken off of hemodialysis with good renal function and only required hemodialysis on HD 58 due to hyperkalemia.

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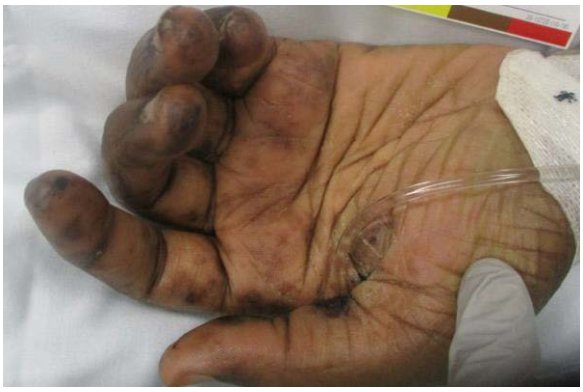
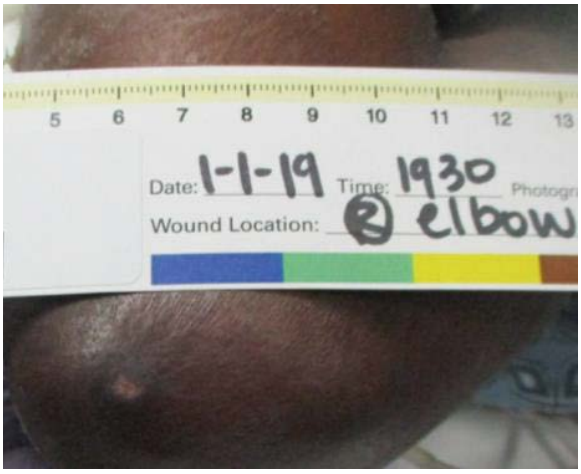
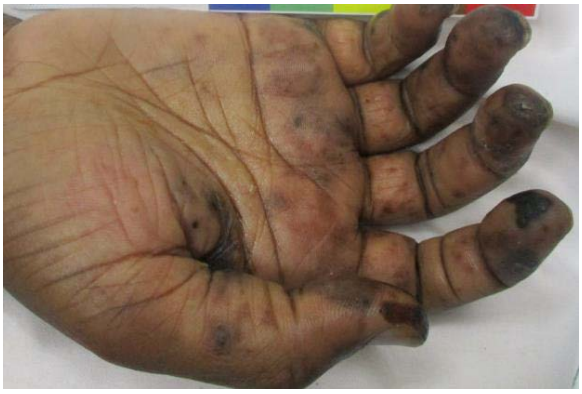
R hand rash



L hand rash

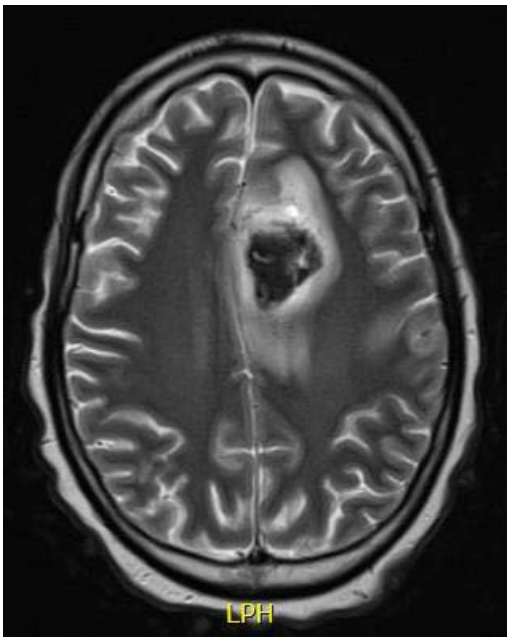


R elbow discoid rash

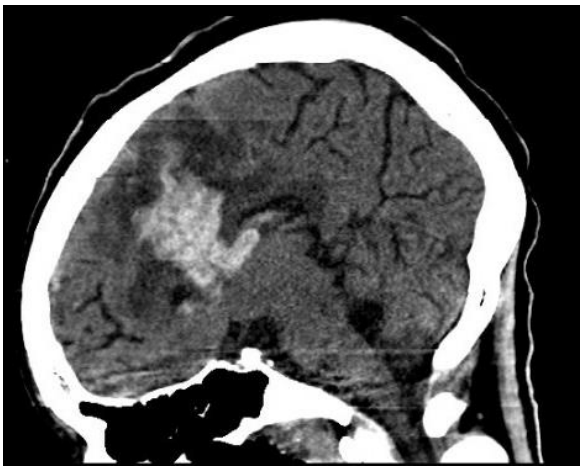


R hand rash

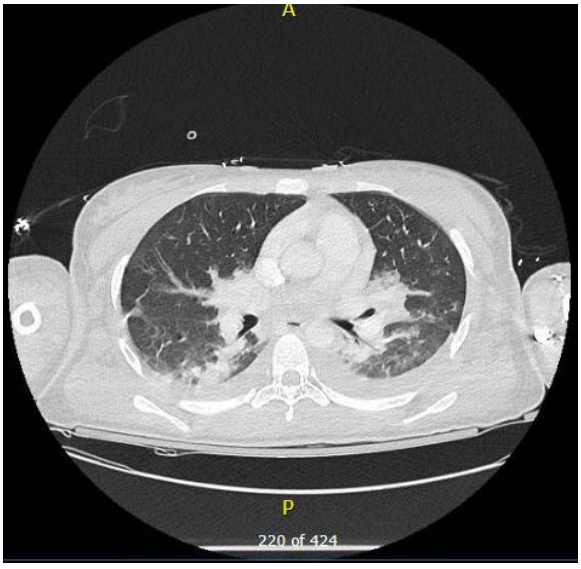
R lower lip mucosal erosion



T2 AX MRI Brain



Noncon CTH



CT Chest on admission with patchy opacities and bilateral pleural effusions noted

DISCUSSION: CAPS is a devastating syndrome that disproportionately affects women at higher rates than men (72% of CAPS occur in women). Most cases are precipitated by infection, operations, stopping anticoagulants, complications of pregnancy, and malignancy. Approximately half of patients with CAPS have an autoimmune disorder and 40% have SLE which is a poor prognostic factor. [6] Since there was no tissue biopsy demonstrating MAHA, the diagnosis was Probable CAPS.

The kidneys are the most commonly involved organ (greater than two thirds of CAPS cases) leading to acute kidney failure, proteinuria, hematuria, hypertension. Other frequently involved organs are the lungs (64%), CNS (62%), heart (51%), and skin (50%). [1] Our patient exhibited involvement of all these organs and the liver on initial presentation; furthermore, all of her signs and symptoms appeared within the same timeframe. The most common laboratory findings are antiphospholipid antibodies (especially Anticardiolipin IgG and Lupus anticoagulant), ANA, and thrombocytopenia. Because CAPS causes microangiopathy, schistocytes and hemolytic anemia can also be seen. All of these laboratory findings, except anticardiolipin IgG, were seen in this case. [1,2] CAPS is commonly treated with anticoagulation, antiplatelet agents, corticosteroids, plasmapheresis, and IVIg. Plasmapheresis and IVIg remove the antiphospholipid antibodies which are thought to be the causative agents of CAPS. Anticoagulation and antiplatelet agents counteract the hypercoagulable and prothrombotic state. Corticosteroids relieve the ongoing inflammatory processes caused by the activation of the complement pathways. Additionally, biologic therapies have been recommended for the treatment of refractory CAPS. Rituximab, an antibody against CD20, is thought to reduce B cells leading to decreased antiphospholipid antibody and cytokine levels. Eculizumab is an antibody that inhibits the terminal complement pathway thereby decreasing the amount of tissue injury and inflammation. Case reports and CAPS registry have shown resolution of CAPS refractory to standard management after use of eculizumab or rituximab. [5] Herein, we report the improvement of Probable CAPS upon adding rituximab to the therapeutic regimen.

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CONCLUSIONS: This is a life-threatening syndrome and as such a high index of suspicion and early diagnosis are required in order to reduce patient morbidity and mortality. [1-3] Standard treatments with proven survival benefit are anticoagulation, antiplatelet agents, corticosteroids, plasmapheresis, and IVIg. [4] SLE is a worse prognostic factor for CAPS but these patients can be treated with cyclophosphamide with improved survival. [6] Case reports have shown a role for additional biologic therapies like eculizumab and rituximab. [4,5,7]

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