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Case Report

A case of concomitant connective tissue disorder and thrombotic thrombocytopenic purpura in an Indian middle aged female

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ABSTRACT

Thrombotic thrombocytopenia (TTP) is a rare disease which is rarely present in adults. Adults usually have an acquired version of disease, associated with some underlying autoimmune disease. There has been paucity of literature about reports which shows the coexistence of connective tissue disorder in patients of acquired TTP. This is a case report of a female who presented with vague symptoms of breathlessness, abdominal pain and petechial rashes and was diagnosed as TTP, developed neurological complications but was stabilized by timely management through plasma exchanges and steroids.

Keywords: Connective tissue disease, Seizures, Thrombotic thrombocytopenic purpura, Rituximab

INTRODUCTION

Connective tissue disorders with concomitant TTP has a higher mortality. TTP is a disease which involves development of hemolytic anemia in micro vasculature leading to formation of schistocytes, low platelets and several systemic dysfunctions.[1] TTP results from decrease activity of ADAMTS13 enzyme which can be due to congenital or acquired causes. This is a case of a 42-year-old who was diagnosed with both connective tissue disease and TTP and that presence of related autoantibodies might have triggered development of immune-TTP in this patient.

CASE REPORT

A 42 year old female with no known comorbidities, came with complaints of difficulty in breathing exertion with moderate exercise for 15 to 20 days, abdominal pain in the epigastric region, dull aching, non-radiating, non-migratory, not associated with meals for 1 day and rash petechial, erythematous, non-itchy present on bilateral feet distally, started from great toe and then involved all small toes (Figure 1). On examination she was afebrile and hemodynamically stable, and maintaining saturation, she had pallor and sublingual icterus, no cyanosis, clubbing or lymphadenopathy. Patient had epigastric tenderness but other systemic examinations were within normal limits.

Figure 1: Petechial, non-itchy, erythematous rash with irregular outlines present over bilateral toes.

On routine workup, the laboratory investigations revealed anemia hemoglobin-6.5 g/dl, thrombocytopenia-13 thous/ul with a normal leukocyte count. Renal function test was within normal limits. Liver function test revealed unconjugated hyperbilirubinemia with a hypo-proteinemia 6.48 mg/dl. Elevated inflammatory markers-erythrocyte sedimentation rate-93 mm and C reactive protein-9.4 mm, serum procalcitonin was negative 0.05 ng/ml. Peripheral blood smear revealed-red cells moderate aniso-poikilocytosis with predominantly normocytic normochromic cells, along with frequent poly-chromatophils, few microcytic hypochromic cells, occasional schistocytes and micro-spherocytes were seen. Schistocyte index-1.4%, corrected reticulocytes-2.6%, WBC- Marginal lymphocytosis, platelets-markedly reduced, immature platelet fraction 6.9%.

Anemia profile revealed vitamin B12 deficiency 149 pg/ml, elevated LDH and ferritin levels 915 U/L and 308.6ng/ml respectively. Stool occult blood negative. PT/INR/aPTT 12.08/1.5/30 sec. Viral markers including antibodies to HIV1 and HIV 2, Hepatitis B surface antigen, antibodies to HCV negative. D dimer was slightly elevated 0.7 ug/ml. Direct Coombs test was +3 positive. Indirect Coombs ' test was sterile. Blood and Urine cultures were sterile. USG whole abdomen and pelvis within normal limits. 2D Echo revealed an ejection fraction of 65%. In view of bi-cytopenia, bone marrow aspiration and biopsy were done. Aspiration revealed trilineage hematopoiesis with no abnormal cells/cell cluster and biopsy revealed cellular reactive marrow with erythroid hyperplasia.

Patient was transfused 1U packed RBC, platelet products were arranged. Complete blood count monitoring was done daily and vitamin B12 supplementation was given to the patient.

Patient was diagnosed to have microangiopathic hemolytic anemia and to investigate the cause further extensive workup was done, autoimmune workup was sent. ANA was sent titres 1:80 which revealed +3 speckled pattern. ANA profile showed +1 anti SSA. Serum C3 and C4 were normal. C ANCA and P ANCA were negative. Anti dsDNA was negative. Antibodies for antiphospholipid antibody syndrome were negative. 24 urinary proteins raised. In view of breathlessness with underlying connective tissue disorder, CT thorax and abdomen was done which revealed, mild emphysematous changes in bilateral lungs and, minimal bilateral pleural effusion, subcentimetric lymph nodes in mediastinum and retroperitoneum (Figure 2).

Plasmic score was calculated for the patient which came out to be 7 (High risk), ADAMTS13 levels were sent which were low (0.3%). A diagnosis of immune thrombotic thrombocytopenic purpura was made and Intravenous Solumedrol (Methylprednisolone sodium succinate) 125 milligram once a day was started.

Five cycles of plasma exchange (PLEX) were done for the patient. PLEX volume exchange of at least 3 L was done with 8 units of fresh frozen plasma. She developed acute onset generalized tonic clonic seizures after the 1st cycle of PLEX. She was given intravenous levetiracetam 1 gm stat followed by levetiracetam 500 milligram intravenous twice daily. The seizures were evaluated and a non contrast CT imaging of the brain was normal and an electroencephalogram of the brain was normal. Patient was given intravenous rituximab 1 gram, the condition of the patient improved and she was discharged, with advice to follow up with reports of complete blood count to monitor platelets and therapy response.

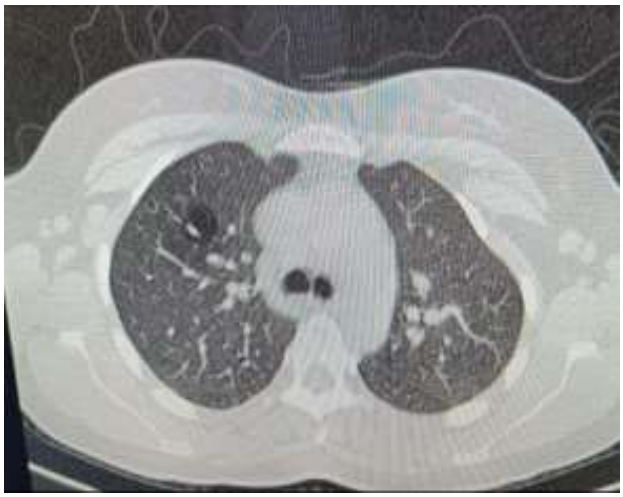

Figure 2: Emphysematous bullae in the right lung.

DISCUSSION

Thrombotic microangiopathy has a myriad of presentations, which include development of haemolytic anemia, thrombocytopenia and thrombus formation causing perfusion defects of organs and tissues and is associated with ischemia related mortality.[2] Thrombotic microangiopathy can primarily be due to TTP, Shiga toxin induced or complement dysfunction and secondary TTP can be due to various other causes such as drugs, immune mediated like in SLE, pregnancy related, or miscellaneous including transplant, HIV infection.[3] In our patients, presence of schistocytes and decreased ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, 13) levels were found to be confirmatory of TTP. There are two types of TTP, first being hereditary one in which there is a biallelic mutation of ADAMTS13 enzyme gene, which leads to deficiency of enzyme and inadequate clearing of von-Willebrand factor .The second one being immune thrombocytopenic purpura in which there is formation of autoantibodies that bind to ADAMTS13 and enhance their elimination from the body and collection of massive molecules of von Willebrand factors which leads to increased activation and binding of platelets, following which microvascular thrombus formation occurs, causing obstruction of capillaries and end-organ damages. [4]

This patient had immune TTP because of coexistence with CTD and an autoimmune state which had probably led to depletion of ADAMTS13. The existence of CTD and TTP together is rare and is more commonly seen in children than adults. In this case direct anti coomb's result was positive with presence of schistocytes. According to literature both these findings can be there in patients of lupus due to vasculitis or autoantibodies.[5] Although our patient had significant numbers of schistocytes in the peripheral smear which suggested a microangiopathy and with reduced ADAMTS13 it was more in favor of TTP leading to thrombus formation rather than vasculitis. Certain studies done in patients having both TTP-CTD pointed out to a mechanism of autoimmunity in development of both the diseases due to presence of antibodies against capillary endothelium and platelets, and anti-ADAMTS13 antibodies in these patients.[6]

Most common signs and symptoms of the disease process includes fatigue, dyspnea, petechiae, or bleeding, followed by development of neurological abnormalities like stroke, seizure or coma followed by development of kidney function abnormalities like acute kidney failure with fever present only in 10% of patients. [7]A patient is labeled presumptively as TTP is made by findings of microangiopathic hemolytic anemia and thrombocytopenia after ruling out other causes in clinical settings. TTP is confirmed through ADAMTS13 levels (activity ≤10 percent of normal, sometimes higher) and presence of an ADAMTS13 inhibitor.[8]

TTP is a hematological threat that can lead to mortality if not treated in a timely manner. Diagnosis remains challenging but with scores like PLASMIC score, it becomes helpful to guide diagnosis and initiate management on an early basis.[9] Treatment strategies include therapeutic plasma exchange which refills the deficient ADAMTS13 and clears up the antibodies, steroids and monoclonal including rituximab, which suppresses production of antibodies. A newer drug caplacizumab which is a monoclonal antibody that binds to von-willebrand factor and blocks its action and by preventing activation and binding of platelets to endothelial surface and adjacent platelets is now being used.[10]

The coexistence of CTD and TTP has been seen more frequently to be present in black women who are young.[11] CTD, renal tubular inflammatory states and low leukocytes are shown to be risk factors for TTP in cases of SLE.[12]

In a case series mortality rates were seen to be 46-50% in TTP associated CTD, and also increased in infections and a later starting of plasmapheresis.[13] Identification of TTP with underlying CTD is difficult due to the super-imposed clinical features like hemolysis, falling platelets, renal system failure, seizures and pyrexia- can also be seen with CTD, and may be misdiagnosed as CTD flare.[14] Anti-SSA antibodies was associated with an increased risk of getting TTP and other autoimmune diseases in follow-up in certain studies.[15]

CONCLUSION

With cases of CTD and TTP occurring in association, although rare, should be diagnosed early and managed as an emergency with plasma exchanges and by suppressing immunity, multi disciplinary specialists should be involved to plan and ensure better management of the patient.

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