Reversible Posterior Leukoencephalopathy Syndrome in a Case of Adult Onset Still’s Disease with Concurrent Thrombotic Thrombocytopenic Purpura: Response to High Dose Immunoglobulin Infusions


Abstract
Thrombotic thrombocytopenic purpura (TTP) is a multisystem disorder characterized by a pentad consisting of thrombocytopenic, microangiopathic hemolytic anemia, renal dysfunction, neurological signs and fever. Coexistence of thrombotic thrombocytopenic purpura and Adult Onset Still’s Disease (AOSD) is extremely rare. We report a case of 18 year old girl with AOSD who developed TTP. Neuroimaging of brain demonstrated white matter edema consistent with reversible posterior leukoencephalopathy syndrome (rPLS). Complete recovery occurred with prompt anti-hypertensive treatment and high dose immunoglobulin infusions (IVIg). Plasma exchange is the standard of care and the first line treatment for patient with TTP. We used IVIg alone in our case and this showed a gratifying response. Use of IVIG before considering plasmapheresis is justifiable or not requires randomized control clinical trials. This should determine the optimal therapeutic strategies for TTP.

Introduction
Adult Onset Still’s Disease (AOSD) is a systemic disorder characterized by spiking high fever, evanescent rash, myalgia, serositis, leucocytosis and the involvement of various organs. About 5% of patients with fever of unknown origin have (AOSD).1 Despite the constellation of characteristic clinical manifestations, this disease is difficult to diagnose in view of absence of specific pathological and serological findings. In addition, the clinical features show some overlap with other rheumatological or infectious diseases, and even malignancies.

We present a case of an 18 year old girl with AOSD who developed neurological symptoms. Based on neuroimaging and laboratory findings she was diagnosed to have Thrombotic thrombocytopenic purpura (TTP) and posterior leukoencephalopathy syndrome (rPLS). Previous twelve cases of TTP occurring in AOSD have been reported in literature so far.2,3 Our case is the first report of RPLS developing in the setting of AOSD with concurrent TTP.

Case Report
An 18 year old girl was admitted to our hospital because of high grade fever, throat pain, arthralgias and myalgia. She was apparently alright one year back. She then started having intermittent fever accompanied by headaches, anorexia and weight loss. There was no significant past medical history and the family history was non contributory. On examination, the patient was febrile (temperature 39° c) pulse 120/min, blood pressure 110/70 mmHg. She had pallor of the conjunctiva, no icterus, generalized lymphadenopathy (cervical, axillary and inguinal); and bilateral wrists and left elbow joint tenderness, without any restricted movement .There was hepatosplenomegaly. Breath sounds were normal bilaterally, the cardiovascular examination as well as neurological examination were normal.

Her initial laboratory findings showed: white blood cell count (WBC) of 23000/mm³ (normal 3900-9700/mm³); hemoglobin 6.0gm/DL (normal 11.7-17.1 g/dl); platelet 250000/mm³ (normal 134000-387000/mm³); erythrocyte sedimentation rate (ESR) 165 mm/hour by Westergreen method (normal < 20 mm/h); and C-reactive protein (CRP) 48 mg/DL (normal 0.02-0.80 mg/DL). Urine analysis showed no albumin, red blood cells, WBC or casts. Kidney function test and liver function tests were normal. Blood smear for malarial parasites were repeatedly negative. X-ray chest was normal. As the clinical picture was suggestive of bacterial sepsis, after three consecutive blood cultures, the patient was empirically started on injection Ceftriaxone. After one week no response to this treatment was noted, blood cultures were sterile and this drug was stopped. Mantoux test was negative and fine needle aspirate cytology from cervical lymph node did not show features of tuberculosis infection and culture of the same for mycobacterium tuberculosis was negative. Serological evaluation for hepatitis B, C; HIV, CMV, EBV and toxoplasmosis was negative. Computed tomography of chest and abdomen revealed multiple hiliar, peritoneal non necrotic lymph nodes and hepatosplenomegaly. Hence left axillary lymph node biopsy was done and this showed follicular hyperplasia. This was characterized by many follicles of variable sizes dispersed throughout the lymph node. Some of them showing hyperplastic germinal centre. Bone marrow aspiration did not show any features of hematological malignancies or features of hemophagocytic syndrome. Screening for auto antibodies including antinuclear antibodies (ANA), rheumatoid
Her fever, arthritis, responded to treatment within 2 weeks; partial regression of lymph nodes and spleen was observed with an improved sense of well being and appetite. However two weeks later, while she was still on high dose steroids and indomethacin she developed high grade fever (107°F requiring hypothermia blanket), worsening headaches, blurred vision, vomiting and altered behavior with progressive deterioration leading to binocular loss of vision, generalized tonic clonic seizures and altered mental status and hypertension (200/110 mm of Hg). On examination she was drowsy but localizing pain, pupils were bilaterally equal and sluggishly reacting to light with bilateral extensor plantar response. Her neck was supple. She required endotracheal intubation and mechanical ventilation for airway protection and control of seizures. At this time she had leucocytosis (WBC 35000/mm³), pan culture was negative and serum procalcitonin level was 0.5 (normal). She had hemoglobin of 7.8 gm/DL, platelets of 52000/mm³ and reticulocyte count of 3.1%. Her serum LDH was 1362.4 IU/L and serum haptoglobin level was decreased; peripheral smear showed schistocytes (fragmented red blood cells) 6-8/ HPF prompting a tentative diagnosis of TTP. Prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen levels were normal. She was discharged on anti-hypertensive; anticonvulsant and indomethacin. She was also given blood transfusions for anemia.

Fig. 1: MRI Flair images showing hyperintensities in bilateral occipital lobes and posterior temporal lobes.

Diagnosis of AOSD remains a clinical one and laboratory profile of the disease is a reflection of the systematic inflammation and cytokine cascade present. AOSD is a rare diagnosis and differential diagnoses must be excluded. The spectrum of differential diagnoses is wide including infectious, neoplastic and, autoimmune disorders. All these were excluded in our case by relevant investigations. Several sets of classification criteria have been published for AOSD. Yamaguchi’s criteria were shown to be the most sensitive (93.5%) and these were used for diagnosis in our case. In the definition proposed by Yamaguchi, 5 or more criteria including 2 or more major criteria need to be met and the other diseases need to be excluded. Major criteria met were (1) fever >39°C for one week or more, (2) arthralgia for one week or more, (3) leucocytosis > 10000cells/mm³ with more than 80% of granulocytes. Minor criteria were (1) Lymphadenopathy or splenomegaly, and (2) negative RF and negative ANA. Yamaguchi’s criteria mandate exclusion in order to diagnose AOSD.

Multiple lymphadenopathy develop in approximately 44-90% of patients with AOSD and were one of the prominent clinical findings in our case. In the past the lymph node pathology of AOSD was often described as merely normal or non-diagnostic lymphadenopathy. One recent report emphasizes that the lymph nodes in AOSD exhibit a wide spectrum of histopathological features, which can be classified into four patterns and that the pathology can change dynamically during the courses of the disease. These are 1) Paracortical hyperplasia with prominent vascular proliferation. 2) Paracortical hyperplasia accompanied by massive sinus histiocytosis. 3) Exuberant immunoblastic reaction and 4) Distinct follicular hyperplasia. Our patient showed the fourth pattern.

One of the important laboratory markers in this case was very high serum ferritin level of more than 14000ng/L. Besides AOSD, elevated ferritin level of more than 10000ng/L is observed in severe liver damage, multiple blood transfusions and hemophagocytic syndrome. Our patient did not have liver pathology or any evidence of hemophagocytic syndrome on bone marrow aspiration. However she did receive six units of blood transfusion for anemia before blood was collected for serum ferritin level estimation. Yamaguchi’s criteria do not include serum ferritin level as a diagnostic criterion for AOSD. A more specific diagnostic marker than ferritin is its glycosylated fraction. In healthy subjects, 50-80% of ferritin is glycosylated, a process that provides protection from proteolytic enzymes. In inflammatory diseases, saturation of glycosylation mechanisms causes the glycosylated fraction to drop to 20-50%. This phenomenon is particularly prevalent in AOSD, where the
glycosylation of ferritin is often < 20%. However glycosylated ferritin test was not available in our laboratory.

In the clinical course of this case, the symptoms were exacerbated two weeks after starting systemic steroids for AOSD. On the basis of thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, and fever she was diagnosed to have TTP. TTP is a rare disease (5-10 case per million persons per year) characterized by the massive formation of platelet-rich thrombi in the microcirculation of multiple organs. TTP is associated with an ever-growing list of bacterial and viral infections, inflammatory and immunologic disorders, neoplasm, transplantation, pregnancy and drugs (mainly chemotherapeutic agents). These were reasonably excluded in our patient. Also the normal level of fibrinogen, PT and aPTT ruled out the presence of disseminated intravascular (DIC) cugulation which has to be distinguished from TTP. DIC is associated with different disorders from TTP such as sepsis, shock or obstetrical complications including preeclampsia.

Coexistence of TTP with exacerbation of AOSD might suggest a common pathophysiological pathway in the pathogenesis for both of these diseases. The association of TTP and AOSD is rare2,3 and our case is a thirteenth report of such an association. In the previous reports five patients had renal thrombotic microangiopathy which was absent in our case.

TTP pathogenesis has been associated with deficiencies in the metalloproteinase, ADAMTS13. The principal function of ADAMTS13 involves the cleavage of unusually large forms of von Willebrand factor (ULvWF), thereby preventing ULVWF multimers from accumulating in the circulation; platelet aggregation in TTP is thought to be the consequence of the binding of the platelets from ULVWF remaining in the circulation. Immunoglobulin G (IgG) autoantibodies that block the activities of ADAMTS13 have been detected in patient suffering from TTP; this may account for the impairment of ADAMTS13 characteristically observed in case with TTP. In this case, we could not study these parameters due to technical insufficiency.

RPLS is a clinico-radiological entity, associated with reversible white matter edema involving most commonly the posterior central nervous system circulation; the etiology of RPLS is believed to be due to a failure of cerebral autoregulation in the setting of severe hypertension, along with possible additive endothelial injury secondary to uremia, cytotoxic drugs, and microthrombosis. This results in the breakdown of the blood/brain barrier with transudation of fluid and protein into the extra vascular space, resulting in cerebral edema. MRI brain demonstrates hyperintensity on T2 weighted images with normal or slightly weakly positively signal intensity on diffusion weighted images (DWI) in the areas of vasogenic edema12. RPLS has been associated with hypertensive encephalopathy, eclampsia, immunosuppressive drugs, cytotoxic chemotherapy for hematologic malignancies, TTP, acute intermittent porphyria, connective tissue diseases.12 Most of the TTP-associated RPLS patients have difficulty- to control hypertension and/or renal failure indicating a connection between RPLS and hypertensive tissue encephalopathy. TTP-induced RPLS infrequently results from cerebral reversible segment vasoconstriction syndrome.14 Our patient developed severe hypertension, altered mental status, seizures and cortical blindness with MRI brain features suggestive of RPLS. She did not have renal failure and/or fluid overload. In our case, accelerated hypertension and vascular injury secondary to TTP were likely contributing factors in the development of RPLS. Our patient had high signal intensity on T2 weighted images predominantly in bilateral posterior parietal and occipital lobes with normal DWI and her CSF exam was normal. Although reversibility of clinical and neuroimaging abnormalities is one of the hallmarks of the syndrome, neurologic sequel has been reported. In our case, repeat MRI one and a half months after the initial MRI study showed near total recovery and patient also did not have any residual neurologic deficit.

The use of IVIG in AOSD has been described in the treatment of flares and disease refractory to NSAIDs, with responses seen at doses ranging from 0.4 to 2 g/kg/day and remission lasting for 2-53 months. The rationale for use of IVIG in TTP is based on the fact that IVIG is capable of neutralizing IgG autoantibodies against ADAMTS13 and case reports have noted the efficacy of IVIG in the management of TTP refractory to plasma exchange. Our patient had AOSD that only partially responded to NSAIDs and high dose steroid therapy, and later developed flare with coincident TTP and RPLS. This led us to use IVIG and pulse methyl prednisolone that resulted in complete recovery of clinical, hematological and radiological features. Plasma exchange is the standard of care and the first line treatment for patient with TTP. We used IVIG alone in our case and this showed a gratifying response. Use of IVIG before considering plasmapheresis is justifiable or not, requires randomized control clinical trials. This should determine the optimal therapeutic strategies for TTP.

References