Unusual presentation of Thrombotic Thrombocytopenic Purpra in a newly diagnosed pediatric patient with Systemic Lupus Erythematosus in the setting of MIS-C

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Abstract

The understanding of Coronavirus disease 2019 (COVID-19) immune dysregulation is evolving. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with alternations in both innate and adaptive immunity, probably caused by a complex interplay of genetics and environmental exposure with various triggers. A rare hematological complication of SLE as well as recently reported in adult with COVID-19 is thrombotic thrombocytopenic purpura (TTP). We report a pediatric case with features suggestive of multisystem inflammatory syndrome in children (MIS-C) with coronary artery ectasia, TTP, autoimmune hemolytic anemia (AIHA) and thrombocytopenia with new onset SLE as well.

Introduction

In addition to the classic features of COVID-19, children may present with multisystem inflammatory syndrome in children (MIS-C) with prolonged fever, shock, mucocutaneous symptoms and cardiac dysfunction.[1] In adults, acute COVID-19 has been shown to be associated with hematological complications such as thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP). [2] We present a pediatric patient with features suggestive of MIS-C with coronary artery ectasia, AIHA and TTP. He also had immunological features consistent with new onset Systemic lupus erythematosus (SLE) and presence of antiphospholipid antibodies. Although thrombotic microangiopathy (TMA) due to complement activation has been reported in some children with COVID-19 across a spectrum of clinical manifestations,[3] our patient had unusual presentation of TTP which has hitherto not been described. As data on COVID-19 continues to evolve in children, our case adds to the body of literature defining the multitude of manifestations of this challenging disease.

Case Description

We present a previously healthy 11-year-old male presented with fevers, dizziness, loss of appetite and new onset petechial rash on his lower legs with prolonged epistaxis of one-week duration. The family history was notable for his mother having died due to lupus nephritis. Both his father and paternal grandfather were symptomatically positive for COVID-19 infection three weeks prior to his presentation. Initial laboratory tests were remarkable for anemia and thrombocytopenia. [Table 1] A review of the peripheral blood smear shown in Figure 1 A. He also exhibited marked abnormalities in hemolysis markers. [Table 1] Direct antiglobulin (DAT) was positive with normal immune globulins. [Table 1]

A nasopharyngeal swab showed he was COVID-19 positive by RT-PCR, with elevated SARS-COV-2 IgG antibodies. Inflammatory markers and cytokines were normal. [Table 1] His troponin I and Brain natrutic peptide were both highly elevated. [Table 1] A 2D-echocardiogram was obtained which was significant

for ectasia of left main coronary artery (LMCA) with uniform dilation with a moderately decreased left ventricular (LV) function.

We therefore suspected him to have MIS-C with likely TTP or Evan's syndrome. Due to the family history of SLE and hematuria and proteinuria on presentation, we investigated for an underlying rheumatologic disease. The resultant laboratory tests revealed strong positive SLE serology [Table 1]

Patient was given Intravenous immune globulin (IVIG) for the treatment of Evan's syndrome and followed by pulse methylprednisolone. After 48hrs following IVIG and methylprednisolone with no clinical or laboratory improvement and also with new neurological symptoms of drowsiness and headache as well as right upper quadrant (RUQ) pain, we increasingly considered TTP. Low ADAMTS13 activity and a high inhibitor titer confirmed the diagnosis. Thereafter patient was immediately started on plasma exchange (PE), and promptly exhibited an impressive clinical improvement in under 24 hours. Following 7 sessions of PE, his platelets count normalized and anemia gradually improved with complete resolution of hemolysis markers, proteinuria and hematuria. [Table 1] and [Figure 1B] A repeat DAT following PE was negative. His echocardiogram also showed normalization of his LV size and function, resolution of LMCA dilation and now dilation of the right coronary artery without evidence of aneurysm for which he was started on low dose aspirin. Patient was transitioned to prednisone and started on mycophenoloate mofetil and hydroxychloroquine sulfate for SLE control. Genetic testing was negative for inherited TTP.

Discussion

COVID-19 has been associated with a significant dysregulation of the immune system, the ramifications of which are still being investigated. A number of maladaptive immune responses involving innate and adaptive immunity with abnormal cytokine/chemokine profiles have been described across the various clinical spectrum of COVID-19. Acute COVID-19 is often accompanied by a cytokine storm akin to macrophage activation syndrome, with the accompanying hallmark of elevated IL-6.[4] Diorio *et al*has found evidence of TMA in MIS-C[3] and an autopsy of a child who died from MIS-C revealed significant viral particles in several tissues, that could be an emerging suggestion of a "second-hit" virus-mediated pathology.[5]

COVID-19 has been associated with several hematological manifestations, AIHA has been reported in children.[6] New onset SLE associated with TTP in the setting of COVID19/MIS-C has not been previously reported in pediatrics. Patients with COVID-19 infection may develop a severe inflammatory response leading to cytokine release which can present similar to autoimmune diseases.[7] Furthermore, it is well known that environmental triggers, such as viral infections, can trigger the activation of immune response with increased synthesis of cytokines, mainly TNF-α, IL-6 and IL-1β, IL-17, IL-18, in genetically predisposed patients.[7,8]Therefore, genetically predisposed patients, such as in the case presented (given the family history), who develop cytokine storm syndrome in COVID19/ MIS-C can theoretically be at risk of developing other autoimmune syndromes.[9] The chain of events is not fully clear in this case, but most likely the patient encountered COVID-19 infection around the time his father had which followed by immune dysregulation and led to SLE onset.

It's unclear whether or not COVID-19 triggered TTP directly or triggered the onset of SLE which led to his TTP. The role of his positive DAT in his cytopenias not yet explained. In TTP, loss of ADAMTS-13 leads to microangiopathic hemolytic anemia, thrombocytopenia, and organ injury.[10] This hemolytic process is mechanical intravascular with increased schistocytes seen on a peripheral blood film; as opposed to Evan's syndrome which is extravascular and usually DAT testing is negative.[10] Thrombocytopenia and immune-mediated hemolysis based on DAT positivity in the setting of COVID19 led to the initial diagnosis of Evans Syndrome in our case.[6,11]However, the diagnosis of TTP was clinched by the worsening of schistocytes and the lack of clinical and other laboratory improvement despite received IVIG and methylprednisolone, coupled with new onset neurological symptoms. Furthermore, the results of a reduced ADAMTS-13 confirmed TTP diagnosis.

Overall, TTP is very rare in children with an estimated incidence of 0.09 children per million.[12] However, Burnner*et al* [13]reviewed all the cases of childhood onset TTP from 1975 to 1998 and 5 patients was diagnosed

with idiopathic TTP; concluded that childhood TTP is commonly associated with SLE few years after initial diagnosis. But, none reported any pediatric case presented with TTP and SLE simultaneously at diagnosis as it has been reported in adults so far.[5]

To our knowledge this is the only reported case with COVID-19 associated with a positive DAT TTP in the setting of new onset SLE. Zenno *et al* [9] reported an adolescent case with DAT positive TTP initially diagnosed with Evans but failed outpatient steroid management. His SLE screening markers were negative and no concomitant infection.

In children, the MIS-C syndrome has been associated with cardiogenic findings similar to Kawasaki disease.[14] Our patient presented with coronary. Coronary artery disease is rare but a known manifestation in SLE and TTP patients. However, usually it is a thrombotic event rather than ectasia.[15]

In conclusion, we believe that COVID-19/MIS-C can be a possible trigger in developing new onset SLE in genetically predisposed patients. Furthermore, TTP should strongly be considered in pediatric patients who presents with thrombocytopenia and immune mediated anemia with worsening schistocytosis who are refractory to steroids; this will allow early intervention with lifesaving plasma exchange and avoiding contraindicated platelets transfusion.

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Figures and tables legends Figure 1 A Peripheral blood smear at presentation: Red blood cells (RBC) with numerous schistocytes and spherocytes with rare basophilic stippling and significant polychromasia. The platelets were markedly decreased in number with few large in size. White blood cells (WBC) were morphologically normal with activation**Figure 1 B** Peripheral blood smear following treatment: RBC with mild polychromachia and occasional schistocytes averaged 2-3 per high power field, but otherwise normal morphology. Platets and WBC are number and morphologically normal.**Table 1.** Summary of laboratory finding comparing presentation and following treatment

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