LETTER TO THE EDITOR

Title: Histiocytosis-lymphadenopathy plus syndrome on follow-up of a child with secondary hemophagocytic lymphohistiocytosis

To the editor,

We report the follow-up of an immunocompetent child who was diagnosed with histiocytosis-lymphadenopathy plus syndrome with an earlier report of hemophagocytic lymphohistiocytosis, secondary to Parvovirus infection[1].

The patient first presented in 2019 at three-years of age with complaints of fever and a non-itchy maculopapular rash. She was first in birth order borne out of a non-consanguineous marriage. She presented with fever, hepatosplenomegaly and pancytopenia. Her bone marrow biopsy revealed presence of macro-ovalocytes and histiocytes, and subsequently myelofibrosis and CD71 positivity. The serum anti-parvoviral immunoglobulins were raised. A diagnosis of secondary HLH post-parvoviral infection was made which was atypical as she had HLH instead of transient pure red cell aplasia. She was discharged after the fever and pancytopenia subsided on conservative treatment. Six weeks later, she presented with multiple, sub-cutaneous swellings, on her face, neck, and trunk, which consisted of chronic inflammatory dermal deposits. The swellings resolved on their own. On follow-up, her counts were found to be within normal limits, and she remained asymptomatic in the intervening 2-year period[1].

She then presented in June 2021, with two months history of intermittent, high-grade fever, which was associated with chills and rigors.The patient had tested positive for SARS-CoV2 on the nasal swab sample on PCR in May 2021 which was treated with oral steroids for five-seven days. She improved subsequently and didn't require any further medical treatment or testing. She developed fever 3 weeks later and was tested as positive for SARS-CoV2 on PCR (persistent positivity in the absence of a negative report). She maintained saturation on room

air but was hospitalized elsewhere for persistent fever and COVID positivity with a suspicion of post-COVID multisystem inflammatory syndrome in children (MIS-C), which was treated with intravenous immunoglobulins (IVIg) as per the documents. However, fever persisted, and she was referred to our hospital for further management. She did not have any other systemic complaints. There was no significant family history.

At presentation, she had pallor, excessive hair on forehead and face, poor oral hygiene, enlarged Group I and II cervical lymph nodes (maximum diameter 2.5 cm) and hepatosplenomegaly. Her weight was 16kgs (-0.9 SDS), height 104cm (-1.14 SDS) and head circumference 48cm (-1.35 SDS). There was no rash or arthropathy. Rest of the systemic examination was unremarkable. Repeat SARS-CoV2 RT-PCR was negative. Baseline investigations revealed bi-cytopenia with hemoglobin of 6g/dL, total leucocyte count 1,780 cells/mm3 (Neutrophils 25%, Lymphocytes 75%), absolute neutrophil count of 445 cells/mm^3 and platelets 150,000/mm^3. The peripheral blood smear showed normochromic normocytic anemia without any atypical lymphocytes. Serum transaminases were raised (alanine aminotransferase 111 units/L aspartate aminotransferase 64 units/L), blood urea 24 mg/dL, serum creatinine 0.3mg/dL and qualitative COVID antibody (IgG) were raised. Further investigations showed raised inflammatory markers – D-dimer (>5000 ng/mL), interleukin-6 (127.2pg/ml), ferritin (1300 ng/mL) and C-reactive protein (225.66 mg/L). She was started on antibiotics and workup for other inflammatory conditions was planned. The workup for tuberculosis, blood culture, urine culture, bone marrow culture, WIDAL test for salmonellosis, HIV by ELISA, IgM ELISA for dengue virus, parvovirus, scrub typhus and anti-viral capsid antibody for Epstein Barr virus were found negative. Serum antinuclear-antibodies was negative. A chest radiograph, electrocardiograph and echocardiography were normal. Contrast enhanced computed tomography of neck, chest, abdomen revealed hepatosplenomegaly and fibro-atelactatic opacities in right upper zone, middle zone and left lingular segment. Cervical

and bilateral axillary lymphadenopathy with mild cardiomegaly were also reported. A fine-needle aspiration from cervical lymph nodes showed reactive hyperplasia.

At the end of the first week of hospitalization, the child's fever, organomegaly and lymphadenopathy had not improved. The bi-cytopenia worsened into pancytopenia (hemoglobin – 5.9g/dL, total leucocyte count- 1,470 cells/mm^3, (Neutrophils 24%, Lymphocytes 75%, Monocytes 1%) and platelet count- 50,000/mm^3. Bone marrow aspirate and biopsy revealed bi-cytopenia with diluted marrow and decreased cellularity, suggestive of WHO grade -1 myelofibrosis. There were no blast cells or any other evidence of malignancy. The repeat blood parameters were suggestive of HLH (ferritin- >2000ng/mL, triglyceride- 310 mg/dL, fibrinogen -138 mg/dL).After excluding likely possible infections and malignancy, a possibility of SARS-CoV2 induced HLH with persistent MIS-C was kept in view of persistent fever associated with rash, pancytopenia, SARS-CoV2 antibody positivity and raised inflammatory markers. Intravenous methylprednisolone pulse therapy at 30mg/kg/day was initiated.

Keeping a possibility of exaggerated post-viral immune mediated bone marrow suppression in this immunocompetent child who previously manifested as parvovirus induced HLH and now with SARS-CoV2 induced HLH, a possibility of disorders of immune dysregulation was considered[2]. Genetic testing with whole exome sequencing was performed (outsourced) which detected a homozygous 5'splice variation in intron 2 of the SLC29A3 gene, affecting the invariant GT donor splice site of exon 2, a finding consistent with the diagnosis of histiocytosis-lymphadenopathy plus syndrome (**Figure 1**).

The child completed 5 days of methylprednisolone pulse therapy for 5 days followed by oral steroids over two weeks considering histiocytosis-lymphadenopathy plus syndrome as a possible diagnosis. She became afebrile after third dose of methylprednisolone with decrease in lymphadenopathy and hepatosplenomegaly and, was discharged home after three weeks of

hospitalization. Last laboratory parameters showed declining trend in inflammatory markers. Her last hearing screen was normal before discharge.

Histiocytosis-lymphadenopathy plus syndrome, also known as "*SLC29A3* spectrum disorder"[3], is a group of conditions characterized by mutations in the *SLC29A3* gene, present on chromosome 10q23 that codes for a nucleoside transporter (ENT3 transporter)[4]. The variable expressivity of this gene results in varied phenotypic presentations like H syndrome (cardiac anomalies, camptodactyly, endocrinal disorders, hepatosplenomegaly), pigmented hypertrichosis with insulin-dependent diabetes mellitus (PHID), Faisalabad histiocytosis, and familial Rosai-Dorfman disease. All these conditions have an autosomal recessive mode of inheritance and are characterised by presence of histiocytosis.Accumulation of histiocytes in different organs and tissues is responsible for the clinical manifestations associated with disorders of this spectrum[3].

Patients with histiocytosis-lymphadenopathy plus syndrome typically have cutaneous hyperpigmentation, hypertrichosis (as seen in this patient), short stature refractory to GH therapy, cardiac anomalies, hypogonadism, hyperglycemia/IDDM, hepatosplenomegaly, lymphadenopathy (also present in this patient), and various musculo-skeletal pathologies[4,5]. The skin rash in index case during the earlier hospitalization[1], was probably a spectrum of H-syndrome. An understanding of the transcriptome profile in H syndrome links *SLC29A3* mutations with mitochondrial dysfunction and oxidative stress which causes immune dysregulation, as was seen in the index patient[6]. The persistent SARS-CoV 2 antigenemia and elevated inflammatory markers in the index case were contributory to development of MIS-C, with the predisposition of the underlying genetic profile. The neutrophilic signatures in MIS-C were clearly seen to be different from those with acute COVID or in healthy controls, though testing for any underlying genetic signatures was not performed[7]. Type 1 diabetes and seronegative arthritis are however, commoner manifestations reported in this

spectrum[8].Rheumatological, endocrinal manifestations and camptodactyly may evolve with age in affected patients, necessitating the need for a continued follow-up[9].

The management of this condition has essentially been symptomatic. However, auto-inflammatory manifestations like rheumatological manifestations require immunosuppressant drugs. A case series of five patients reported partial response to oral steroids with need to use other immunosuppressive agents[8]. Monocloncal antibodies like adalimumab[8] and tocilizumab have been used in cases with persistent arthritis and autoinflammation refractory to steroids and immunosuppression[10]. The index patient responded to steroids in this admission but may need further drugs with evolution of disease phenotype in the future.

In hindsight, our patient, presented with immune dysregulation with H syndrome after mild viral exposures where an ominous genetic basis could be established. This highlights the need to suspect children with atypical manifestations of infectious diseases early and offer genetic diagnosis for better disease prognosis and management.

KEYWORDS:

HLH

Histiocytocis-Lymphadenopathy plus syndrome

H syndrome

Steroid therapy

MIS-c

Post-viral immune dysregulation

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LEGEND: Whole exome sequencing confirming pathogenic mutation in *SLC29A3* gene

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