Case study

COVID-19 Induced Secondary Hemophagocytic Lymphohsitocytosis: A Case Series

Abstract:

Background:

Hemophagocytic lymphohistiocytosis (HLH) is a lethal and rapidly progressive hyper-inflammatory state that lead to development of fulminant multi-organ failure. HLH is divided into primary or familial HLH (FHL) and secondary HLH (sHLH). It can be triggered by a variety of agent that affect the immune system, infection is a common triggering agent. Recently, Coronavirus disease (COVID-19) has spread all over the world and was declared a pandemic. COVID-19 infection in children can induce serious hyper-inflammatory syndrome termed multisystem inflammatory syndrome (MIS-C). Clinically MIS-C patients present with features that resemble Kawasaki's disease or toxic shock syndrome and the clinical and laboratory manifestations may also similar to that of secondary hemophagocytic lymphohistiocytosis, or macrophage activation syndrome (MAS).

The reported HLH syndrome in children with COVID-19 increased during 2020-2021. In this case series we present two pediatric patient diagnosed as sHLH post-COVID-19 infection with a brief literature review of similar pediatric patients.

Key words: Hemophagocytic lymphohistiocytosis (HLH), Macrophage activation syndrome (MAS), COVID-19 , children

Introduction :

Hemophagocytic lymphohistiocytosis (HLH) is a lethal and rapidly progressive hyperinflammatory state due to highly stimulated, unregulated and mostly ineffective immune reaction characterized by development of fulminant multi-organ failure.

HLH is divided into primary or familial HLH (FHL) and secondary HLH (sHLH). It can be triggered by a variety of stimuli that affect the immune system, infection is a common triggering factor.[1]

Recently, Coronavirus disease (COVID-19) has spread all over the world and was declared a pandemic by the World Health Organization (WHO).[2]

Generally, most children aged <18 years with COVID-19 present with mild symptom or asymptomatic, but some children have had severe illness requiring hospitalization and some children develop life- threatening complication.[3.4]

COVID-19 induce serious hyper-inflammatory syndrome termed multisystem inflammatory syndrome in children (MIS-C). Clinically MIS-C patients present with features of Kawasaki's disease or toxic shock syndrome. The clinical and laboratory manifestations may also similar to that of secondary hemophagocytic lymphohistiocytosis, or macrophage activation syndrome (MAS). [5]

Affected patients with secondary hemophagocytic lymphohistiocytosis (sHLH) present clinicallywith acute onset of persistent high grade fever, lymphadenopathy, organomegaly associate with pancytopenia, hyperferritinemia, coagulopathy, hypertriglyceridemia and multi-organ dysfunction.[6]

The diagnosis of sHLH is based on the revised HLH-2004 guideline (presence of five criteria of out of eight diagnostic criteria) fever, bicytopenias (affecting two or more of three lineages in the peripheral blood), splenomegaly, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, hemophagocytosis in bone marrow/spleen/lymph nodes, low or absent natural killer (NK)-cell activity, or elevated soluble CD25 (interleukin [IL]-2 receptor). [7.8.9]

HHL is a severe, life-threatening disease with a fatal outcome, but a timely diagnosis and prompt treatment is critical since early and efficient management may improve survival

Treatment consists mainly of glucocorticoids, intravenous immunoglobulin (IVIG), and chemotherapy.[8.10] Biological treatments, anti-TNF drugs, anti-interleukin-1, anti-interleukin-6 , and B-cell depleting drugs have shown variable degrees of clinical efficiency in HLH subtypes in adult population.[11.12.13]

Case 1 presentation:

A ten-year-old male child with juvenile rheumatoid arthritis on methotrexate admitted to pediatric ICU with history of persistent high grade fever for ten days, diarrhea and vomiting for 3days . There was a household contacts of confirmed cases of COVID-19.On admission he was sick looking, meningeal signs were negative, ears and throat examination were normal and systemic examination was unremarkable, Sepsis was suspected for that investigation withdrawn including COVID-19 PCR and serology. Intravenous fluid and antibiotics started . On 2nd day of admission his consciousness was altered and developed recurrent attacks of convulsion, his blood pressure was 88/40 mmHg, body temperature was 39.5 °C , oxygen saturation was 94% . intravenous inotropes and antiepileptic medication started. His investigation showed

D1 D2 D4 D6

TLC:	9.5 (lymphopeina)	3.4	1.8	0.5
HB:	8.4	8	7.9	7
Platelets:	174	128	88	32

Nasopharyngeal swab for SARS-Cov-2 polymerase chain reaction (PCR) was negative, but Anti-SARS-CoV-2 S IgG was weakly positive and IgM negative

Triglycerides level : 563mg/dl (N 40-200)

LDH : 929 U/L result of second sample was 1000U/L

S. ferritin level > 1500 ng/ml (N 13 – 150)

S. Fibrinogen level 1.1g/l (N 1.7 -4.2)

D-dimer: >20.0mg/l

CRP: 120

Blood culture showed no growth

	D1	D6
Urea:	156 mg/dl	205
Creatinine:	4.6	5.7
AST:	1727U/L	5273
ALT:	700U/L	980
Bilirubin:	2.8g/dl	4.9

Bone marrow aspiration couldn't be performed

Patient met five of HLH-2004 criteria. He received Methylprednisolone in dose of 15mg/kg/day for w3 days along blood transfusion antibiotics but, he rapidly deteriorated died on day seven of the admission.

Case 2 presentation:

An-eight year old female child known to have Crohn's disease since 2 years back, she was on Azathioprine and Mesalamine tablets and she was on remission. She has presented with palpitation and dyspnea 6 weeks before admission. Echocardiography showed dilated cardiomyopathy, poor cardiac function with tricuspid and mitral regurgitation and also she had records of high blood pressure treated with captopril (Angiotensin – converting enzyme inhibitor), L-carnitine and furosemide. She was admitted to the hospital 3 weeks back with persistent high grade fever and lethargy for the last 4 weeks. On admission She was unwell, lethargic, febrile, meningeal signs

were negative, throat and ears examination were normal, no skin rash, no conjunctivitis, she has high temperature with records of hypotension, chest was clear and abdominal examination revealed mild hepatomegaly and significant splenomegaly

Nasopharyngeal swab for SARS-Cov-2 polymerase chain reaction (PCR) was negative, but Anti-SARS-CoV-2 S IgG was positive and IgM was weakely positive

CBP :WBC	3.7	1.5	2.4
HB	8.3	6.3	7
Platelet	150	58	17

Peripheral blood film shows neutropenia with relative lymphopenia, normal reticulocytes count and there was no blast cells.

ESR 100 mm/hr

CRP 52.9 mg/l

Blood and urine culture showed no growth of organisms

Bone marrow aspiration showed increase macrophages showing hemophagocytosis (suggesting macrophage activation syndrome MAS) and there was no blast cells.

S. Ferritine >2000 ng/ml (N 13 – 150)

LDH 1172U/L (313 – 618)

D.dimer 7.2 μgFEU/ml (0 – 0.5)

Uric acid 9.1mg/dl (2.5 – 6.2)

Triglyceride 399mg/dl (< 150mg/dl)

Fibrinogen 1.82g/l (N 1.7 -4.2) INR 1.2 (N 0.89 – 1.13)

C.T scan chest showed bilateral basal curvilinear and linear fibrotic bands and significant cardiomegaly

C T abdomen showed enlarged bulky spleen , hepatomegaly and mild ascites

Based on previous clinical symptoms, signs and laboratory finding sh was diagnosed as Post –COVD 19 secondary Hemophagocytic lymphohistiocytosis according to HLH 2004 criteria and the treatment was based on HLH protocols. The main treatment was immunosuppressive therapy (glucocorticoid as methylprednisolone 30 mg/kg/dose for 3 days) and intravenous immunoglobulin (2g/kg/day for two days) and chemotherapy (cyclosporine). She improved clinically with improvement in

laboratory investigation specially pancytopenia and discharged from hospital after one month duration.

Consent was obtained from the parents.

Discussion and conclusion:

COVID-19 infection in children has a variable clinical presentation ranging from asymptomatic to mild or severe life threatening disease. COVID-19 induce serious hyper-inflammatory syndrome termed multisystem inflammatory syndrome in children (MIS-C). A subset of children with severe COVID-19 develop intense inflammation and multi-organ dysfunction consistent with a lethal and rare clinical condition called sHLH.[14]

We reported two pediatric patients with chronic diseases and both of them on immunosuppressive therapy. **Akturk et al.** [15] Reported a 10-year-old boy with juvenile idiopathic arthritis (JIA) was diagnosed as MAS/sHLH post-SARS-CoV-2 infection without involvement of gastrointestinal, cutaneous and cardiovascular system. He had received Favipiravir, intravenous immunoglobulin and dexamethasone .The patient improved and all abnormal laboratory parameters returned to normal levels. In Contrary to our patient **Mostafavi et al.** [16] presented a young aged child, an 18-month-old a previously healthy child who presented with a high fever, conjunctivitis, drowsiness, respiratory distress, and hypoxemia. He was deteriorated rapidly and met five out of eight criteria of sHLH and successfully treated with high-dose dexamethasone, IVIG, interferon β-1a in addition to antiviral agents. Similarly **Kalita et al**.[17] reported a two years old child who presented with fever and convulsion and was diagnosed as a Post-COVID-19 Secondary Hemophagocytic Lymphohistiocytosis based on The H-score-2014. This child admitted to PICU and received steroid, antiepileptic medication and antibiotics.

Sever COVID-19 infection inducing hyper-inflammatory illness share a number of clinical signs and laboratory finding with sHLH .Therefore, all patient with severe COVID-19 infection should be suspected and screened for sHLH as survival is dependent on prompt diagnosis, and appropriate and early initiation of treatment. A multidisciplinary team of rheumatologist, hemato-oncologists, immunologists and intensivists are needed to treat this condition.

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