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SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A CHILD WITH CONCOMITANT EBSTEIN BARR VIRUS AND SCRUB TYPHUS INFECTION – A RARE ENTITY

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ABSTRACT Scrub typhus is a life threatening zoonosis caused by Orientia tsutsugamushi organisms that are transmitted by the larvae of trombiculid mites. It is endemic to a geographically distinct region, the so called Tsutsugamushi triangle, which includes Japan, China and South Korea. The disease is more prevalent in southern and northern India.It is characterised by focal or disseminated vasculitis and perivasculitis involving the lungs, liver, spleen and central nervous system.

We report our experience with pediatric scrub typhus at a hospital in eastern India with EBV positive and secondary HLH.

An 8 year old boy with fever, maculopapular rash, hepatosplenomegaly and lymphadenopathy was admitted in our institution and diagnosed with Scrub typhus. Physical and laboratory data showed hepatosplenomegaly, bicytopenia, hyperferritinemia, and hypofibrinogenemia. Secondary HLH was diagnosed and the child was managed with IVIG and steroids. In view of rash followed by lymphadenopathy and hepatosplenomegaly EBV serology was also sent as a cause of HLH. Surprisingly, EBV panel was also positive.

We therefore concluded that the most probable explanation was EBV triggered HPS following scrub typhus infection.

Another possible explanation is EBV can be reactivated in critically ill patients.

To our knowledge this is the first such case in the pediatric population reported till date.

KEYWORDS : Epstein-Barr virus infections,Scrub typhus,hemophagocytic lymphohistiocytosis

INTRODUCTION

Scrub typhus is a life threatening zoonosis caused by Orientia tsutsugamushi organisms that are transmitted by the larvae of trombiculid mites. It is endemic to a geographically distinct region, the so called Tsutsugamushi triangle, which includes Japan, China and South Korea. The disease is more prevalent in southern and northern India.

It is characterised by focal or disseminated vasculitis and perivasculitis involving the lungs, liver, spleen and central nervous system.

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome resulting from dysregulated activation and proliferation of lymphocytes. Infections like cytomegalo virus (CMV) and Epstein-Barr virus (EBV) are important triggers for hemophagocytosis.

We report our experience with pediatric scrub typhus at a hospital in eastern India with EBV positive and secondary HLH.

CASE

A 8 year old male child presented in the emergency room (ER) with high grade fever for 12 days along with slurring of speech, decreased level of consciousness and decreased urine output for the last one day. There was an additional history of generalized rash 7 days back. The child was treated with oral antibiotics (amoxicillin clavulanic acid) for 5 days.

On examination, the child was afebrile, irritable and had slurred speech. He also had positive meningeal signs and maculopapular rash over his body along with facial puffiness, subconjuctival hemorrhage and red coated tongue. These were associated with hepatosplenomegaly and generalised painful lymphadenopathy.

CT brain was normal. Echocardiography revealed dilated LAD and RCA with perivascular brightness. A provisional diagnosis of MISC/scrub typhus was considered.

On admission in PICU, child was tachycardic and tachypnoeic. His mean blood pressure was low with wide pulse pressure. Normal saline bolus was administered followed by empirical antibiotics (meropenem and doxycycline) in strong clinical suspicion of scrub typhus. Acyclovir was also added in view of altered consciousness.

Due to fluid refractory shock, infusion noradrenaline was started and later infusion adrenaline was also added. In view of persistent shock and encephalopathy the child was intubated and put under PRVC mode ventilation.

Based on echocardiography reports (in suspicion of MISC), infusion IVIG @2gm/kg was started and injection methylprednisolone 2mg/kg was added. Blood tests revealed raised CRP, deranged coagulation, raised LDH, ferritin, NT PRO BNP. Scrub typhus IGM was positive. Inj. vitamin K, cryoprecipitate and platelets were transfused for correction of abnormal coagulation.

Hb (gm/dl)	PLATELET (cu/mm)	FIBRINOGEN (mg/dl)			FERRITIN (ng/ml)	NT PRO BNP (pg/ml)	TRIGLYCERIDE (mg/dl)	COVID SEROLOGY	BLOOD C/S	URINE C/S	SCRUB TYPHUS IgM
7.3	20,000	Day1 168	Day2 80	Day3 40	19,800	>25,000	278	positive	No growth	No growth	positive

Covid serology turned out to be positive,but the case could not be classified as MISC as all criteria were not fulfilled (no other obvious cause of inflammation other than COVID infection for diagnosis). In view of clinical parameters (fever and splenomegaly), hematological parameters (bicytopenia, decreased fibrinogen, hypertriglyceridemia and hyperferritinemia) secondary HLH was suspected. Bone marrow examination could not be done as child was not stable hemodynamically. As there was history of rash followed by lymphadenopathy and hepatosplenomegaly EBV serology was also sent as a cause of HLH. Surprisingly, EBV panel was positive (EBV IgM, EBV IgG, EBCA, EBEA, EBNA)

The child was showing improvement hemodynamically and hematological parameters were also gradually improving but neurologically wasn't showing any improvement. In view of encephalopathy, MRI brain was done which showed leptomeningeal enhancement. Inj. methyprednisone was thus increased to 30 mg/kg(pulse dose). Following this the child showed dramatic improvement neurologically. The child was extubated on day 8 of admission and discharged on day 13.

So our case was finally diagnosed as scrub typhus positive with secondary HLH along with EBV positive serology.

DISCUSSION

Secondary HLH is diagnosed by the following:

any five out of the following eight criteria –

1. prolonged fever
2. unexplained progressive cytopenias involving at least 2 cell lines (hemoglobin ≤ 90 g/L, platelet count ≤ 100 × 10^9/L, absolute neutrophil count < 1 × 10^9/L)
3. splenomegaly
4. hyperferritinemia (≥ 500ng/mL)
5. fasting hypertriglyceridemia (≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 1.5 g/L)
6. histiocytic hemophagocytosis in bone marrow, liver, spleen, or lymph nodes without evidence of malignancy
7. low or absent NK cell cytotoxicity and
8. elevated soluble CD25 levels (≥ 2400 IU/mL of interleukin-2Rα chain).

It is associated with viral infections including EBV, autoimmune diseases, malignant diseases, and acquired immune deficiency conditions. EBV is the most common infectious agent in patients with the viral-associated HLH and is particularly notorious for its severe morbidity and mortality. Therefore, the early diagnosis and treatment of EBV-associated Hemophagocytic syndrome (EBV-HPS) is essential for a good outcome. The pathogenesis of EBV-HPS is that EBV-infected B cells stimulate cytotoxic T lymphocytes which leads to hypercytokinemia and the stimulation of histolytic cells. EBV causes the stimulation, generation, and uncontrolled secretion of T and NK cells as well as the generation of IL-2, INF-α, and IL-6 which are responsible for HPS.

In a study of thirty children with scrub typhus from Thailand, most children presented with lymphadenopathy (93%), hepatomegaly (73%), eschar (68%), conjunctival hyperemia (33%), maculopapular rash (30%), and splenomegaly (23%) were the commonest signs. Eleven patients had interstitial pneumonitis and one patient had meningitis.[1]

In our study the child had hepatosplenomegaly, lymphadenopathy, maculopapular rash and leptomeningitis (on MRI brain)

A study done with 58 children with scrub typhus infection showed HLH in 18 patients. The mean age of patients with HLH was 3 years and 61% were male. Hypertriglyceridemia, hypofibrinogenemia, coagulopathy were noted in 78%, 56% and 44% patients. All the patients were treated with intravenous doxycycline for an average duration of 9.5 days. Intravenous immunoglobulin and methylprednisolone were given in 33% and 22% of cases.[2]

In our case the child received intravenous doxycycline for 10 days, IVIG and methylprednisolone for 10 days.

Few studies showed occurrence of secondary HLH in rickettsial infection in children.[3,4] Understanding this drove us to find other causes of HLH.

In a study by Rouphel et al, Epstein Bar Virus infection alone was found to be associated with secondary HLH in a pediatric patient.[5]

A study done by pediatric hematooncology team in a hospital in Korea showed a 7-year-old boy with pancytopenia, cervical lymphadenopathy, interstitial pneumonia and hepatosplenomegaly was diagnosed with Epstein-Barr Virus (EBV)-associated hemophagocytic lymphohistiocytosis. His clinical course was characterized by hepatorenal syndrome and myocarditis. Based on his serological markers for EBV and an immunochromatography test for scrub typhus, this case was inferred as an EBV infection that was reactivated during tsutsugamushi infection.[6]

In addition, previous case reports showed that viruses such as EBV, CMV and parvovirus can trigger HPS after scrub typhus infection(studies comparing pediatric vs adult population)[6,7,8,9] . Therefore, we regarded that EBV triggered HPS after a scrub typhus infection in the current case.

In an adult study, we found a case of Epstein-Barr virus (EBV)-associated HPS after scrub typhus infection that did not improve using antirickettsial treatment. A 73-year-old male who had been diagnosed with scrub typhus didn't improve despite 7-day doxycycline therapy. Physical and laboratory data showed secondary HLH.[11] EBV was detected in BM aspirates using polymerase chain reaction. After a diagnosis of HPS was made, the patient was treated successfully using high-dose steroids.

CONCLUSION

We therefore concluded that the most probable explanation was EBV triggered HPS following scrub typhus infection.We have discussed previously that EBV,CMV,parvovirus can trigger HPS after scrub typhus infection.

Another possible explanation is EBV can be reactivated in critically ill patients. Larger dynamic prospective studies are needed to correlate viral reactivation with immune system evolution during PICU stay and to determine the role of polyviral reactivations.

To the best of our knowledge this the first such case in the pediatric population reported in the English literature.

Our case suggests that secondary HPS should be considered as a differential diagnosis when there is no improvement after treating scrub typhus using adequate antirickettsial therapy.

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