Case Report

A rare case of streptococcal pharyngitis in an adult male causing hemophagocytic lymphohistiocytosis

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ABSTRACT

Hyperinflammatory responses due to cytokine storms involve multiple systems in hemophagocytic lymphohistiocytosis (HLH) leading to morbidities. Multiple bacterial etiologies have been suggested as a cause of secondary HLH but streptococcal infection has only been reported in pediatric cases. *Streptococcus* has been considered a notorious pathogen due to its ability to interfere with host immunity through the phenomenon of molecular mimicry. This case report shows the sequence of events post-streptococcal pharyngitis in a 28-year-old male, which lead to HLH and fatality to life, and how a timely intervention of steroids salvaged the patient.

Key words: Hemophagocytosis lymphohistiocytosis, Steroids, *Streptococcus* pharyngitis

Hemophagocytic lymphohistiocytosis (HLH) syndrome is the hyperimmune response caused either due to the abnormalities of the primary genetic immune system or secondary causes such as infection. HLH caused by bacterial infection is relatively rare [1]. It includes a myriad of presentations of fever, rash, and multiorgan dysfunctions. Due to a wide spectrum of presentation and a rapid life-threatening course of illness, it warrants urgent diagnosis and treatment with antimicrobials and immunosuppressives.

We report the case of a 28-year-old patient with a long-standing history of fever and sore throat, developed HLH, and a hyperimmune cascade of organ system failures.

CASE REPORT

A 28-year-old male presented with an 1-month history of fever with chills up to 103°F, throat pain of acute onset for 1 month which was associated with pain while swallowing both liquids and solids, and a generalized erythematous, non-pruritic rash that appeared on 4th day of the onset of fever, began on the neck and face followed by the involvement of the trunk, both upper limbs and lower limbs and subsided in 2–3 days. He was taken to an outside hospital where he received multiple antibiotics but the fever still persisted.

He presented to the emergency department and on examination, the patient was conscious, oriented, febrile with a temperature of 100.4 F, tachypneic, and had tachycardia. He had an erythematous rash present in the sternal region measuring 3 × 4 cm, scaly, non-pruritic, and erythematous blanching rash present over the back (Fig. 1). Systemic examination revealed a palpable liver 5 cm below the costal margin, soft, and smooth with a liver span of 14cm present in the mid-clavicular line and palpable spleen by classical method 3 cm below the left costal margin.

Laboratory investigations revealed hemoglobin – 9.5 g/dL, white blood cells – 5.93 thous/uL, and platelets – 20 thous/uL. Blood urea nitrogen was 48.38 mg/dL, serum creatinine was 7.01 mg/dL, sodium was 134 meq/l, and potassium was 3.6 meq/l. Total bilirubin was 0.67 mg/dL, direct bilirubin was 0.48 mg/dL, serum glutamic-pyruvic transaminase was 153IU/l, serum glutamic-oxaloacetic transaminase was 118 IU/l, alkaline phosphatase was 348 IU/l, and gamma glutamyl transferase was 288 IU/l.

Two cycles of dialysis were done for the patient in view of acute kidney injury and anuria. Chest X-ray showed cardiomegaly. Throat swab cultures revealed *Streptococcus*. Blood cultures were sterile. HIV, Hepatitis B, Hepatitis C, and malaria were negative. Serological tests for dengue, scrub, *Leptospira*, *Brucella*, and typhoid were negative. Anti-nuclear antibody profile was negative. Urine routine revealed +1 protein, numerous red blood cells (RBC), and 10–15/hpf pus cells. Urine cultures were sterile. Urine for dysmorphic RBC was negative.

High-resolution computed tomography chest revealed minimal consolidative changes with air bronchogram in the posterior-basal segment of bilateral lower lobes (left>right) and minimal bilateral pleural thickening with fibrotic strands in bilateral lower lobes.

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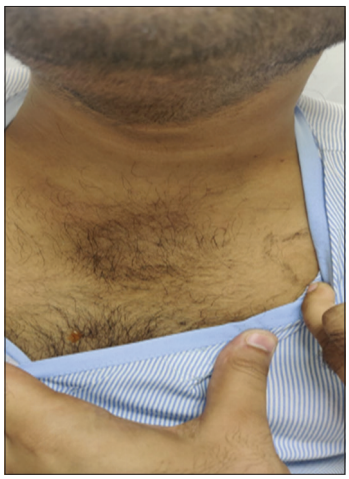

Figure 1: An erythematous rash present in the sternal region – measuring 3 × 4 cm

FERRITIN ng/ml	Day 1 81437	Day 2 32537	Day 3 16130	Day 4 8772	Day 5 5359	Day 6 3764	Day 7 2826

Ultrasound whole abdomen revealed mild hepatosplenomegaly and Grade 1 fatty liver. 2D Echocardiography showed trace tricuspid regurgitation, pulmonary artery systolic pressure of 33 mmHg, and left ventricular ejection fraction of 55%, with trace pericardial effusion.

The patient was started on Injection Cefepime and Sulbactum 1.5 g twice daily and injection Doxycycline 100 mg once daily. Despite antibiotic coverage for 5 days, the fever still persisted. In view of persistent fever, inflammatory markers were sent which showed ferritin – 81437.63 ng/mL, lactate dehydrogenase – 1069 IU/l, fibrinogen – 2.12 g/dL, and triglycerides – 350 mg/dL. Bone marrow aspiration and biopsy were done in view of bicytopenia and elevated inflammatory markers. Bone marrow aspiration and biopsy revealed a significant increase in histiocytes, showing hemophagocytosis. Epstein Barr Virus (EBV) and cytomegalovirus reverse transcriptase-polymerase chain reaction were negative. A diagnosis of secondary HLH was made based on modified HLH 2009 criteria, a H score was also calculated which was 262, conferring a probability of 99% of HLH. The patient was started on Injection Dexamethasone 6 mg twice daily.

The patient's laboratory parameters improved significantly within a week after starting the treatment (Fig. 2). The patient became afebrile, symptomatically better, and was discharged with tapering dosages of steroids. The patient did well on follow-up after stopping steroids.

DISCUSSION

Pharyngitis is more common in children. In adults, bacterial pharyngitis becomes less frequent with age, and bacterial cases are limited to age groups of <40 [2,3]. Most common causal agent of pharyngitis in adults is viral. *Streptococcus pyogenes* accounts for about 5–30% of total cases [4].

HLH is characterized by fever not resolved by antibiotics, bicytopenia, splenomegaly, hemophagocytosis in bone marrow,

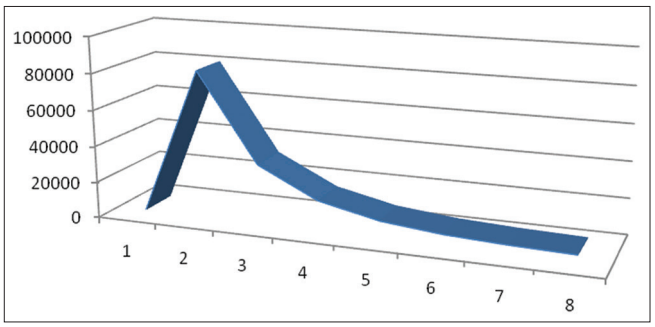

Figure 2: Trend of Ferritin after giving steroids (Y axis – Value of Ferritin in ng/mL; X axis – Consecutive number of days)

and elevated inflammatory markers. HLH is a syndrome of persistent immune activation leading to multiorgan damage in patients [5]. It can be primary or secondary. The primary form is due to mutations in immune pathways, whereas, the secondary form is triggered by infections, autoimmune diseases, and malignancies [6]. The reported incidence of HLH is 1.2 cases per million per year, EBV being the most common cause of infection-associated HLH. Among bacterial infections associated with HLH, there were many organisms found, *Streptococcus* being very rare [7].

In our case, a diagnosis of HLH was made based on the modified HLH 2009 criteria which had six out of eight criteria fulfilled and an H score of 262. Fardet *et al*. in their study calculated an optimal cutoff value of 169 for the H Score to predict the probability of HLH [8]. Our patient had no evidence of the presence of any autoimmune disease and so infection from *Streptococcus* isolated from a throat swab was the most likely etiology of secondary HLH.

The phenomenon of molecular mimicry due to structural similarities between host antigens and *Streptococcus* causes risk of development of non-infectious complications such as scarlet fever, post-infectious sequelae, such as acute rheumatic fever, and post-streptococcal glomerulonephritis. Multiple complications of streptococcal pharyngitis occur due to host defense against the pathogen and release of chemokines, soluble inflammatory mediators, such as antimicrobial peptides, prostaglandins, leukotriene B4, and pro-inflammatory cytokines, causing atypical hyperinflammatory responses against various organs which might have triggered HLH in our patient [9].

There is a paucity of literature on *Streptococcus* causing HLH in adults. The majority of the reported cases so far are from the pediatric age group. In a case report, describing a 12-year-old girl who had a fever, rash, hepatosplenomegaly, *Streptococcal suis* septicemia, and pneumonia had hemophagocytosis in the marrow. She had a good clinical outcome and improved with antibiotics and immunoglobulins [10]. Another reported case was of a 5-year-old girl who had unfortunately succumbed to HLH due to Group B *Streptococcus* in her bloodstream [11]. A similar pathogenic etiology of HLH was described in an 11-year-old male diagnosed as a case of brain abscess due to *Streptococcus intermedius*, he was administered penicillin and vancomycin. This pediatric male developed fever and features of Kawasaki disease after 1 week of antibiotic treatment. Laboratory parameters showed bicytopenia

with bone marrow biopsy showing florid histiocytes and he showed excellent recovery after initiation of methylprednisolone [12]. Complications due to *Streptococcus pneumoniae* bacteremia were also seen in a 46-year-old Filipino male, who had come with complaints of unresolved fever and multiple joint pains and was investigated to have elevated inflammatory markers and HLH. He responded well to a 2-week course of ceftriaxone and a 5-week course of dexamethasone [13]. This case is unique due to *Streptococcus* pharyngitis which appears rarely in an adult and rarely can cause a life-threatening syndrome like HLH.

CONCLUSION

HLH continues to be a diagnostic challenge to treat, due to the lack of specific clinical settings and rapid progression of disease. Therefore, a high index of clinical suspicion is required by physicians in cases of fever with cytopenias for prompt identification and intervention.

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