



Hemophagocytic Lympho-Histiocytosis HLH Triggered by Acute Hepatitis A Virus Infection: Lessons for COVID-19

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Summary

We report a case of Acute Hepatitis A virus infection that triggered HLH. The result over several weeks was fulminant, acute hepatitis followed by renal failure requiring hemodialysis, severe eosinophilic gastroenteritis, dermatitis, Bell's Palsy and Guillaume-Barre syndrome. Treatment with high dose steroids, initiated early, resulted in amelioration of symptoms, with exacerbation when the drugs were transiently stopped.

HLH is frequently triggered by a viral infection that is not effectively terminated. This sets off a cytokine storm leading to multiorgan failure. The similarities with the severe multiorgan damage spectrum of Covid-19 are striking. Lessons to be learnt include immune-suppressive treatment with steroids, etoposide and other therapies that may prove as effective in the treatment of severe Covid-19, as for HLH.

Introduction

Hemophagocytic Lympho-histiocytosis HLH is an under-recognized, potentially lethal, severe systemic inflammatory syndrome, characterized by continued activation of macrophages and cytotoxic T cells with resulting hypercytokinemia with hyperinflammation and damage to host tissues. It can occur as a primary, genetic condition due to specific mutations in genes that induce apoptosis in target cells. It can also occur secondary to an infection or cancer, which triggers an excessive activation of the immune system. In both instances, the defective termination or downregulation of the immune response is the likely, underlying cause. Clinically, HLH presents as a febrile illness in association with multiple organ involvement [1-6].

Clinical Case

The patient is a 40-year old male, who had suffered from an episode of Kawasaki syndrome at the age of five years. He initially presented to an Urgent care facility with intermittent fever and generalized weakness. He was diagnosed with influenza and sent home on a therapeutic dose of Tylenol. Ultrasound showed borderline splenomegaly, 13 cm. He continued to feel unwell, and presented to the ER of an OSH with worsening symptoms. LFTs were elevated (AST 1909, ALT 2281) and IgM HAV was positive. He admitted to consuming Yak meat three weeks prior

to admission. He was discharged home with a diagnosis of acute HAV infection.

Two days later, he was admitted via the ER at our hospital with generalized weakness, fevers up to 104°F and severe acute liver failure. LFTs were grossly abnormal: AST 6900; ALT 8080; AP 224 and TBil >27 mg/dl. INR was > 3.0. Hepatic encephalopathy developed 48 hours after admission. There was also evidence of acute kidney failure, due to a combination of possible HRS, AIN, ATN and CIN from contrast nephropathy. A CT study had been performed on admission. Renal failure progressed and dialysis was initiated. The patient was listed for liver transplantation.

The fever persisted. Blood culture was positive for *S. mitis* in one of two sets. This was treated initially with vancomycin and later changed to Ancef. The fever persisted and eosinophilia developed. Drug fever was suspected. Ancef was stopped and vancomycin substituted, but the fever persisted (Figure1) and a diagnosis of HLH was considered. Six out of eight of the 2004-HLH trial defined criteria viz [7]: Cytopenia involving more than two cell lines (Hb <9g/dL, platelets <100,000/ul or ANC <100 /ul); Splenomegaly; Elevated ferritin >500 g/L; Elevated Triglycerides (fasting triglycerides > 2.0 mmol/L or hypofibrinogenemia (< 1.5 g/L); Hemophagocytosis (Bone marrow, spleen or lymph node biopsy); Fever (peak temperature of > 38.5 C for > 7 days). Facilities for the estimation of NK cell activity or soluble IL-2

receptor alpha were not available. Otherwise, all six other criteria were present.

The HScore generates a probability for the presence of secondary HLH and HScores greater than 169 are 93% sensitive and 86 % specific for HLH [8]. Based on the available clinical parameters, an HScore of 274 was calculated for this patient.

Peripheral blood smear suggested hemolysis. On testing, G6PD levels during the acute phase of the hemolysis was normal as expected due to the large numbers of new red cells. However, G6PD levels were low, when tested several weeks after recovery.



Prednisone 80 mg daily was started with improvement in fever. However, leucopenia worsened and hypothermia developed. The patient was transferred to the University Hospital, after 31 days at our Institution for further management. His weight at transfer was 85.1 Kg. At the tertiary care facility, a liver biopsy showed marked bile duct injury and cholestasis consistent with acute hepatitis. It did not show hemophagocytosis. However, review of bone marrow slides from our hospital confirmed activated macrophages with occasional hemophagocytosis. Histiocytes/macrophages with hemophagocytic activity, highlighted by CD68 and CD 163 staining were present.

An MRCP showed ascites and bilateral pleural effusion. A PET scan showed increased FDG uptake in the bone marrow as well as moderate volume ascites, hepatosplenomegaly and anasarca. RUQ ultrasound confirmed both liver and spleen enlargement, 18.7 and 15.1 cm respectively. Soluble IL-2 receptor was normal, 993 (normal <1033 pg/ml). However, this was after several days on steroids. Genetic markers for Familial HLH were sent and later found to be absent. Prednisone was tapered over six days and discontinued as the diagnosis of HLH was said to have been “Quickly removed from consideration based on the liver biopsy and normal soluble IL-2 receptor.”

Serum bilirubin on admission at the University Hospital was 33.4 mg/dL, AST 114, ALT 265 and AlkP 364. Bilirubin remained elevated, but stable at 27.8. AKI was still present with a serum creatinine of 5.23. The patient was discharged home on

outpatient dialysis after seven days of hospitalization. Two weeks after discharge and still off prednisone, his weight had dropped to 70.9 Kg. Serum bilirubin had dropped spontaneously to 24. He complained of daily fevers up to 101.5°F, with negative blood cultures on several. He remained on dialysis three days a week. The patient associated the fevers with stopping prednisone. Serum bilirubin dropped further to 19.3, AP 585 ALT 94, AST 81 and serum albumen dropped to 2.4, two weeks later.

Three weeks later, he was self-referred back to the ER at our hospital with a four-day history of severe diarrhea, weight loss, moderate abdominal pain and a flaky skin rash. Renal function had improved and hemodialysis had been discontinued. On physical examination, he was noted to be cachectic, jaundiced and dehydrated. His skin was flaky and he had glossitis and stomatitis. His body weight had dropped to 56.7 Kg (125 lbs). His BP was low 87/69 and he had a sinus tachycardia to 147bpm. Pertinent labs included WBC 21.3, Ca 6.6, venous lactate 7.8, lipase 4688; LFTs were ALT 68, AP 375, bilirubin 10.5, total protein 4.8 and Alb 1.1; ferritin 1624, zinc 65 (N 60-120) and serum Cr 3.38.

Blood, urine and stool cultures were all negative. Duodenal aspirate and small bowel biopsy showed no evidence of infection or celiac sprue. However, there was histological evidence of severe eosinophilic gastroenteritis. There was no evidence of Graft-versus-host-disease and hemophagocytosis was not detected. Naso-jejunal feeding was started He was placed back on steroid treatment. Following fluid resuscitation and addition of steroids, WBC, lactate, lipase, abdominal discomfort and creatinine levels gradually resolved to normal. Diarrhea, glossitis, flaky skin and appetite improved rapidly during the first week.

Five months after the initial admission, he presented with left sided facial weakness that had developed over three to four days. He had continued on low dose prednisone with azathioprine. Physical examination confirmed left sided Bell’s palsy. Vital signs were normal. Weight was 65.9 Kg (145 lbs). Liver function tests were as follows: AST 53, ALT 124, AP 217; total Bili 0.8 and serum albumin 4.2. CBC was normal, with a Hb of 13.4. The Bell’s palsy improved spontaneously.

Later, he noted parasthesiae and numbness of his fingers. Serum B12 and folate were normal. The peripheral neuropathy progressed to involve his lower extremities bilaterally. Two weeks after the onset of the Bell’s palsy, he was admitted with Guillaume-Barre syndrome (GBS). Plasmapheresis was started. After five sessions of plasmapheresis, symptoms of GBS improved. He was discharged home and continued out-patient follow up. Twenty-four months after his initial presentation, symptoms had completely resolved. Steroids had been tapered off and he was on azathioprine 50 mg daily. His weight was 79 Kg (173.8 lbs.), his approximate pre-morbid weight. Vital signs were normal. CBC was normal: WBC 4.9; Hgb 12.2 and Platelets 239. LFTs were also normal:

Bilirubin 0.3, AST 27, ALT 34, AP 122 and Albumin 4.9.

Discussion

HLH is a life-threatening syndrome, characterized by abnormal immune activation [3]. Most often, it is triggered by a viral infection, the commonest being the Epstein-Barr virus (EBV) [9]. The liver is commonly involved as a bystander organ and the majority of patients have evidence of hepatitis. LFTs are elevated and there is often evidence of hepatic dysfunction. The extent of liver damage ranges from mild to severe hepatic failure [10]. Our case is unusual in having been triggered by a primary infection of the liver with HAV. The patient developed severe liver damage, leading to acute fulminant hepatitis requiring listing as a status 1 for liver transplantation. Over 80 percent of patients have cytopenia, especially anemia and thrombocytopenia at presentation [11-14]. Anemia was first noted two months into the illness in our case, associated in part with hemolysis due to G6PD deficiency.

A ferritin level greater than 10,000 mcg/L has been shown to be 90 percent sensitive and 96 percent specific for the diagnosis of HLH [15]. The diagnosis of HLH in our patient was first prompted by the finding of a ferritin level of greater than 40,000 mcg/L. In children, very high levels of ferritin are highly specific for the diagnosis of HLH. Macrophages are a primary source of ferritin, which is secreted via a nonclassical secretory pathway. In children with HLH, growth-differentiation factor 15, which enhances ferroportin-mediated iron efflux is markedly upregulated and is responsible for the hyperferritinemia [16]. Neurologic involvement has been observed in about one third of patients [17]. Our patient developed Bell's palsy and Guillaume-Barre. It is not clear whether these were incidental or directly related to the HLH. In a small series of 10 patients, seven had neurological abnormalities, including encephalopathy and seizures [18].

Diarrhea is not uncommon in HLH. In reported cases, it has been associated with *Clostridium difficile* infection [20] and enteropathy associated T-cell lymphoma [20]. Small bowel histology in our patient showed severe eosinophilic enteritis. Elevated Triglycerides (fasting triglycerides > 2.0 mmol/L) or hypofibrinogenemia (fibrinogen levels < 1.5 g/L) are common in HLH and recognized as one of the eight diagnostic criteria. Both are usually the result of severe liver involvement due to impaired hepatic synthetic function. Acute HAV infection appears to have been the triggering event for HLH in our patient. Thus, the elevated triglycerides and low fibrinogen levels may have been incidental to the liver disease.

Covid-19 runs a heterogenous disease course, varying from asymptomatic or with only mild symptoms in the majority of cases to a significant minority of patients with severe immunological complications reminiscent of HLH. These complications include macrophage activation syndrome MAS or secondary HLH,

resulting in cytokine storm syndrome and acute respiratory distress syndrome, ARDS [6]. In a number of instances, there is ferritin overexpression [21] and lymphopenia [22]. Neurological complications, including Guillaume-Barre syndrome as in our patient, has been described [23]. Liver abnormalities or hepatopathy are also not uncommon [24-26].

Corticosteroids have not been routinely recommended for the treatment of Covid-19 for fear of exacerbation of the associated lung injury [27]. However, the data suggest that in a subgroup of patients with Covid-19 with severe hyperinflammation and high HScore consistent with HLH, immune modulation could improve mortality. Therefore, several therapeutic options that have proved beneficial in HLH might be suggested for the treatment of the severe immunological complications of Covid-19 [28-32]. High dose steroids appears to have been particularly effective in our patient. Alternative suggestions include intravenous immunoglobulin, selective cytokine blockade (anakinra or tocilizumab) and JAK inhibition [32]. Etoposide, a topoisomerase II inhibitor is the mainstay of treatment for HLH. It appears to act as an immune modulator by selectively eliminating pathologically activated T cells [6]. Continuous intravenous anakinra (recombinant IL-1r antagonist) has shown efficacy in adults with MAS [33]. This drug has also shown promise in Covid-19 patients [34].

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