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Hemophagocytic Lymphohistiocytosis Secondary to Varicella Zoster with Acute Liver Failure

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life threatening syndrome of excessive immune activation. This condition can be inherited or secondary to other diseases. The therapeutic success is directly related to the rapid diagnosis with the patient who has high clinical suspicious index such as febrile illness with cytopenia, liver enzyme derangement, raised serum ferritin and low fibrinogen levels. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases. We report a 31 years old man who presented with diagnosis of severe varicella zoster infection with multiorgan involvement. The laboratory data showed thrombocytopenia, an elevated level of the liver transaminases and coagulopathy. Antiviral therapy along with supportive treatment initiated. However the general condition deteriorated and he eventually required mechanical ventilation with intensive care unit support. He had persistent high spiking temperature, acute liver failure and raised serum ferritin. With the history of steroid contained health supplements ingestion prior to current hospitalization leading to immunosuppressed state, HLH was diagnosed and treatment was directed towards suppressing the overt immune response. Dexamethasone is chosen here because it can cross the blood brain barrier and tapered over the eight week induction. He responded well to treatment and discharged home.

Subject Areas

Gastroenterology & Hepatology, Hematology, Infectious Diseases

Keywords

Hemophagocytic Lymphohistiocytosis, Varicella Zoster, Liver Failure

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a serious hematological disorder characterised by severe immune system dysregulation with cytokine storm, resulting cytopenias and histologic evidence of hemophagocytosis [1]. This condition can be inherited or secondary to other diseases. The diagnosis is often challenging to establish due to its variable presentation and association with other pathologies [2]. Acute liver failure can be due to numerous causes such as severe varicella zoster infection or HLH in this case and can result in high fatality rate or necessitate liver transplantation if left untreated [3]. Possible etiologies include infection, ischemia, toxins, venous obstruction, medications, and autoimmune hepatitis [4] [5]. Fulminant hepatic failure secondary to varicella zoster virus hepatitis is rare and deadly [6].

2. Case Report

31 year old man hospitalized after 7 days fever and rash noticed on the leg subsequently spreading to whole body. He also complained abdominal pain on day 4 of fever associated with multiple vomiting episode. The patient had no significant medical history prior to hospitalisation.

He had history of consuming dexamethasone contained health supplements for past 3 months. On physical examination upon arrival to hospital, he was in regular general state with normal vital signs. The examination showed diffuse maculo papular eruption with few vesicles over face, trunk and extremities (**Figure 1**). Cardiovascular and pulmonary system was unremarkable, chest X-ray (**Figure 2**) abdominal examination revealed minimal tenderness over right hypochondriac region. Laboratory investigation revealed transaminitis as follows:

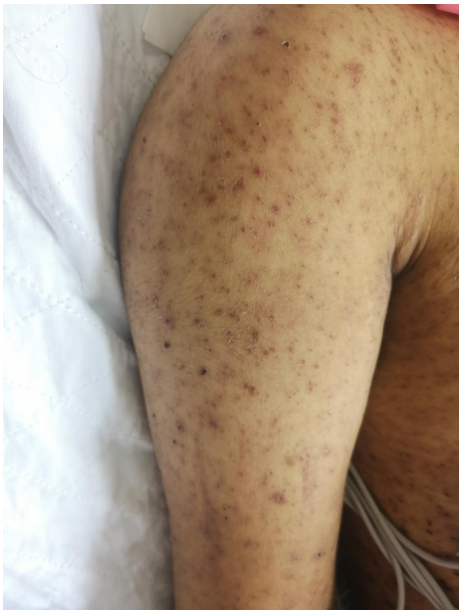

Figure 1. Diffuse maculo papular eruption with few vesicles over the extremities.

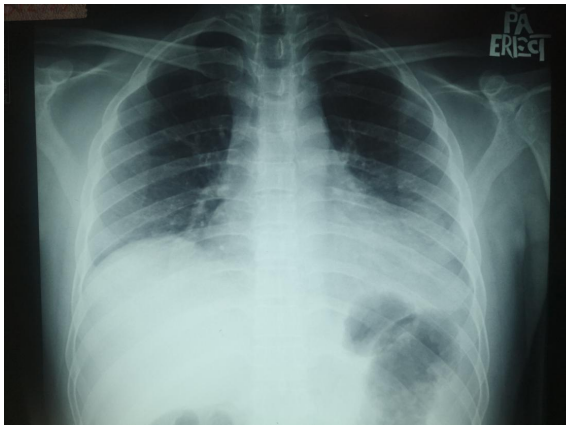

Figure 2. Chest X-Ray on arrival.

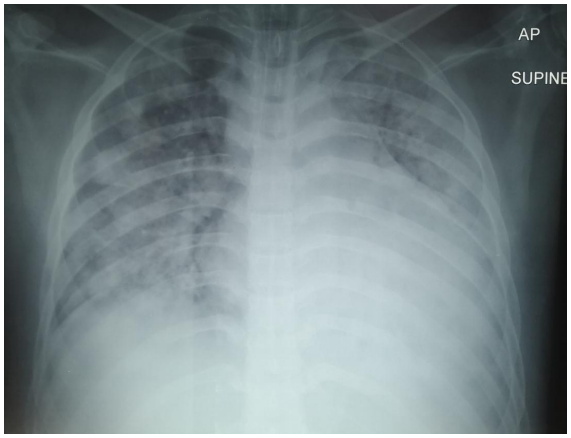

Figure 3. Chest X-Ray on day 2 of admission.

AST 727 U/L (0 - 35 U/L), ALT 621 U/L (0 - 33 U/L), ALP 63 U/L (35 - 105 U/L), INR: 1.39 ratio and APTT 49 (25.1 - 35.7). Ultrasound of hepatobiliary system demonstrated normal liver margin with thickened edematous gallbladder wall, no biliary ductal dilatation and wall of intrahepatic and portal vein appears thickened. The patient was initiated on IV acyclovir and referred to gastroenterology team in view of acute liver failure with MELD score less than 10. He was then planned for conservative management and for close monitoring of liver function. However on day 2 of admission the patient required mechanical ventilation for worsening hypoxic respiratory failure with multi organ involvement warranting transfer to medical intensive care unit. (**Figure 3** chest X-ray) The patient was started with broad spectrum antibiotic covered for secondary bacterial infection. Test for hepatitis B, C and human immunodeficiency virus (HIV) was negative. His condition continues to deteriorate despite on appropriate choice of antibiotic and antiviral. He also had multiple spikes of temperatures up to 40 degree Celsius. No positive cultures obtained from multiple septic workout. The diagnosis of HLH was made and investigation revealed a ferritin level of 40,368 ng/ml and LDH 4122 U/L, low Fibrinogen and high triglyceride level. HScore demonstrated 254 points (>99%) of probability. The patient was started

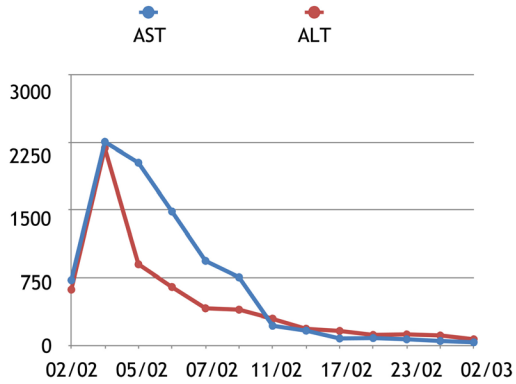

Figure 4. Illustrate trend of liver function which peaked at its worse on day 3 of admission but gradually returned back to baseline over a month.

immediately on dexamethasone. Bone marrow biopsy revealing hemophagocytic histiocytes activities. Unfortunately he was infected with multidrug resistant organism during intensive care unit stay leading to prolonged hospital stay. He responded well and treatment and discharge home after days of admission. (**Figure 4**) illustrates the trend of AST and ALT.

3. Discussion

Severe varicella zoster virus (VZV) infection may be life threatening in patient with immunocompromised state due to prolonged steroid usage in this case [7]. Here we discussed regarding the severity of the disease involving multi organ involvement and immunocompromised state. In the setting of VZV hepatitis, definitive diagnosis is made by liver biopsy, histopathology, culture and VZV PCR. Due to limited resources in district hospital, there was no liver biopsy done.

In this case, by imaging venous obstruction and ischemia cause is unlikely with no hypotensive event recorded. Likewise, the AST to ALT ratio was not in favour of classic alcoholic hepatitis. HLH is classified as either primary or familial HLH and secondary or acquired HLH. Primary HLH often results from defects in the perforin, munc 13-4, and syntaxin 11 genes and rarely occurs in adults. Secondary HLH arises from infectious, rheumatologic, malignant, or metabolic disorders [8]. The elevation of ALT and AST only mild to moderate level in most HLH patients. Nonspecific changes including sinusoidal dilatation, hepatocellular necrosis, endothelialitis and steatosis are common histopathological findings [9]. A bone marrow puncture is mandatory, not only to look for haemophagocytosis, but also to exclude leukaemia as trigger of HLH. Haemophagocytosis in the bone marrow is neither very sensitive nor specific [10].

In this case early acyclovir therapy and corticosteroid were started and full recovery was observed. This suggests that acyclovir if administered early, could be useful in some immunocompromised patient with severe visceral involvement including varicella hepatitis, coagulopathy and appropriate corticosteroids

therapy for Hemophagocytic Lymphohistiocytosis. [11], however the success rate of the treatment is still debatable and the physician must have a high degree of suspicion in patients in view of mortality rate [12].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Consent

Above photograph and informed consent obtained from the patient to report the case.

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