

Case Report

Hemophagocytic lymphohistiocytosis associated with visceral Leishmaniasis in a patient with cirrhosis of HCV: diagnostic challenge

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ABSTRACT

Leishmania infection associated hemophagocytic syndrome is very rare. Moreover, visceral leishmaniasis related hemophagocytic lymphohistiocytosis in a patient with liver cirrhosis will be very difficult to recognize because of the overlapping clinical features and negative marrow evaluation at onset. In this report, we present a 53-year-old

male patient diagnosed with visceral leishmaniasis related hemophagocytic lymphohistiocytosis who had referred to our clinic for further evaluation of decompensated cirrhosis due to hepatitis C virus. Although the correct diagnosis was made, the patient did not improve due to co-morbidities.

KEYWORDS: cirrhosis, HCV, hemophagocytic, leishmaniasis, lymphohistiocytosis

INTRODUCTION

Visceral leishmaniasis (VL) is a systemic disease caused by dissemination of protozoan parasite *Leishmania* throughout the reticuloendothelial system. It may mimic or lead to several types of hematological disorders including hemophagocytosis. Infection associated hemophagocytic syndrome implicating *Leishmania* is very rare and often difficult to diagnose^[1].

Clinical features lacked discriminating value to recognize VL as the inciting etiology. Bone marrow aspiration establishes the diagnosis in about 80% of cases but is often negative at onset of the syndrome due to the pauci-microbial nature of the disease and patchy involvement. Repeated marrow aspiration, liver biopsy, blood cultures and serology may be required to establish the diagnosis.

VL related hemophagocytic lymphohistiocytosis (HLH) in a patient with liver cirrhosis is often under-recognized because of the overlapping clinical features and negative marrow evaluation at onset, leading to high mortality rates^[2].

In this study, we report a patient with hepatitis C virus (HCV)-associated liver cirrhosis who suffered complications of HLH secondary to VL.

CASE REPORT

A 53-year-old male patient referred to our clinic for the treatment of decompensated cirrhosis due to HCV. In his past medical history, he had partial gastrectomy due to upper gastrointestinal bleeding. Apart from these, he had no remarkable past medical history. His complaints were fever and night sweat lasting for four months. He had referred to a local hospital, and was hospitalized because of pancytopenia. At that time, bone marrow aspiration was obtained which had revealed dysmyelopoiesis, dysmegakaryopoiesis and dyserythropoiesis. Neither hematologic nor any other malign infiltration was detected. In abdominal ultrasonography, hepatomegaly and splenomegaly had been reported. Anti-HCV antibody and HCV-RNA was positive. The patient was diagnosed with chronic HCV infection while no proper explanation was suggested regarding the origin of the fever. Meanwhile, the

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Table 1: Laboratory data of the patient

| Variable | Reference Range* | On presentation | 3 rd day of treatment |
|---|------------------|-----------------|----------------------------------|
| Hemoglobin (g/dl) | 13.6–17.2 | 8.7 | 8.9 |
| Hematocrit (%) | 39.5–50.3 | 26.5 | 26.9 |
| White-cell count (per mm ³) | 4300–10300 | 700 | 2900 |
| Platelet count (per mm ³) | 156000–373000 | 33000 | 56000 |
| Neutrophils (per mm ³) | 2100–6100 | 450 | 1770 |
| Sodium (mmol/liter) | 135–145 | 126 | 124 |
| Potassium (mmol/liter) | 3.5–5.5 | 3.4 | 3.87 |
| Urea nitrogen (mg/dl) | 8–22 | 18 | 42 |
| Creatinine (mg/dl) | 0.81–1.40 | 0.69 | 1.03 |
| Glucose (mg/dl) | 70–110 | 99 | 57 |
| Calcium (mg/dl) | 8.5–10.5 | 7.94 | 8.04 |
| Albumin (g/dl) | 3.3–5.0 | 2.12 | 2.47 |
| Lactate dehydrogenase (U/liter) | 220–450 | 1373 | 3676 |
| Amylase (U/liter) | 25–100 | 30 | 49 |
| Alanine aminotransferase (U/liter) | 10–40 | 16 | 102 |
| Aspartate aminotransferase (U/liter) | 10–40 | 74 | 425 |
| Alkaline phosphatase (U/liter) | 38–155 | 331 | 452 |
| Gamma glutamyl transferase (U/liter) | 10–55 | 72 | 90 |
| Total bilirubin (mg/dl) | 0.2–1.0 | 1.18 | 8.12 |
| Direct bilirubin (mg/dl) | <0.2 | 0.47 | 5.08 |
| Ferritin (ng/ml) | 22–322 | 12096 | |
| Fibrinogen (mg/dl) | 200–500 | 68 | |
| Leishmania rK-39 dipstick | negative | positive | |
| Leishmania IFA&ELISA Ig G | negative | positive | |

* Reference ranges are Gulhane hospital's values. These ranges are affected by the patient population and the laboratory methods used. They may therefore not be appropriate for all patients.

patient experienced upper gastrointestinal bleeding that could not be controlled by medical or endoscopic interventions. Eventually the patient underwent distal gastrectomy. A liver wedge biopsy was obtained during the procedure which demonstrated hepatitis and cirrhosis. During the early postoperative phase, the patient had developed ascites and became decompensated while the fever was continuing. After two months of in-patient investigation and treatment, the patient was discharged and referred to our clinic for further evaluation and liver transplantation.

At admission, the patient had fever, fatigue and abdominal distention. His fever had lasted for almost 4 months with sustained pattern, consistently elevated unless intervened with antipyretics. In physical examination, his general condition was very poor, looking cachectic with loose skin folds. Besides, dryness of the skin and mucosa, and massive ascites and splenomegaly were detected. Initial laboratory investigation revealed pancytopenia (Table 1). Since the patient had ascites and fever, we performed paracentesis and drained 2250 ml transudate ascites. In the cell count of fluid, WBC was 75/mm³ with 35% neutrophils. Therefore, spontaneous bacterial peritonitis was excluded. Along with the culture of ascites, the blood and urine cultures were also obtained, results of which were all negative. However, empirical antibiotic treatment was begun according to the febrile neutropenia protocol. All viral markers were negative

with the exception of anti-HCV antibody and HCV-RNA (5x10⁶ copy/ml). To detect a focus of infection, we performed abdominal ultrasonography and thoracoabdominal computed tomography (Figure 1). The appearance of liver was consistent with cirrhosis, and splenomegaly was detected (longitudinal axis was 192 mm) while there was no sign of infection. Upper gastrointestinal endoscopy was performed, and there were no esophageal varices.

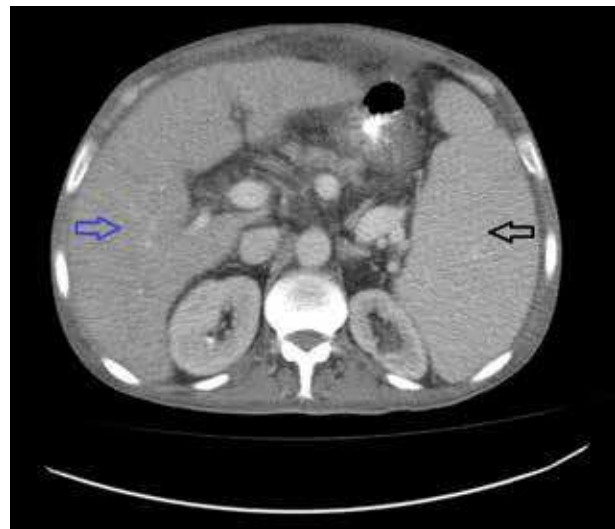


Fig 1: CT screening of the patient. Cirrhotic liver (blue arrow) and splenomegaly (black arrow).

For the investigation of anemia, ferritin levels were analyzed and these revealed very significant hyperferritinemia (12096 ng/ml, ranges 22 - 322 ng/ml). Serum ferritin was repeated for confirmation, which was much higher (15409 ng/ml). Autoantibodies and markers of vasculitis were negative. Given the fever that was not responding to antibiotics, marked hyperferritinemia and splenomegaly, adult onset Still disease and HLH were considered. Additionally, while the fever, massive splenomegaly and the geographic region where the patient came from (Adana, Turkiye, an endemic area for leishmaniasis) was taken into account, VL was also added to the list of differential diagnosis. At this stage, bone marrow aspiration and biopsy were performed to investigate hematologic malignancies, HLH and leishmaniasis. While the level of fasting triglycerides were normal and hemophagocytosis could not be demonstrated in bone marrow aspirate, given the clinical and laboratory findings of the patient including pancytopenia, fever, splenomegaly, hypofibrinogenemia (68 mg/dl; reference value: 200-500 mg/dl), hyperferritinemia and hepatitis, the diagnosis of HLH was made. As an underlying cause, the patient was examined for leishmaniasis. Serum leishmania Ig G test was positive. The aspirated bone marrow material was inoculated into NNN culture and examined in a Giemsa stained smear. Amastigotes were visualized on the smear (Figure 2), ELISA and IFA tests for rK-39 antigen found positive, therefore diagnosis of VL was also

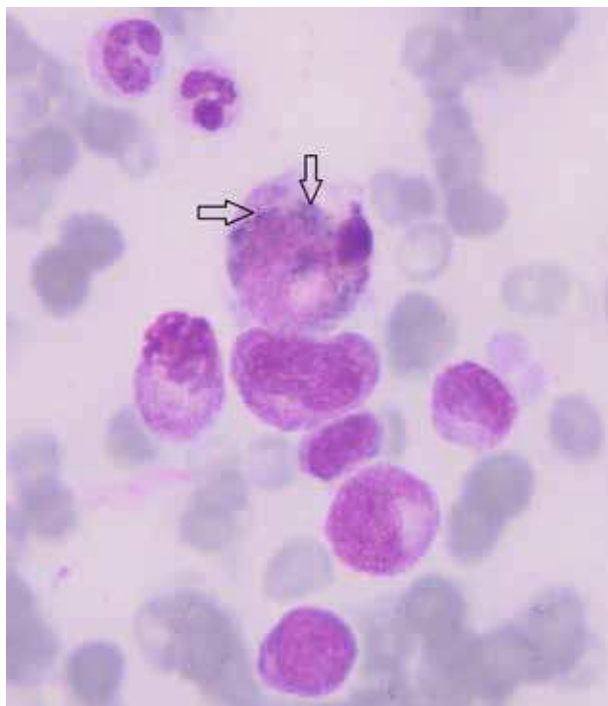


Fig 2: Bone marrow aspiration material stained by Giemsa. Amastigotes are demonstrated by the arrows.

made. The diagnosis of HLH was considered as associated with VL. Treatment protocol was targeted to the causative disease, and liposomal amphotericin B was commenced for the Leishmaniasis. Due to the high HCV viral load, steroid or immunosuppressant treatments were postponed to see the response to amphotericin, and intravenous immunoglobulin was also added to the treatment protocol.

On the third day of treatment, the patient's complete blood count improved dramatically. On the second day, WBC: 1200/mm³; neutrophils 640/mm³; hemoglobin: 7.31 gr/dl and platelets: 40000/mm³; whereas on the third day WBC: 2900/mm³; neutrophils: 1770/mm³; hemoglobin: 8.9 gr/dl and platelets: 56000/mm³. However, liver function tests worsened and at the third day of the initiation of treatment for VL, the patient developed confusion and dyspnea. He was transferred to the intensive care unit. An infiltration was detected on chest x-ray. Subsequently, anuria and hypotension developed, his mental status worsened. Despite intensive care and mechanical ventilation support, the patient could not be recovered.

DISCUSSION

VL presents a sub-acute or chronic course and if not treated with a specific therapy, the disease almost invariably leads to death. Our case was interesting because a number of considerations can be made. First of all, the presence of anti-HCV positivity, together with liver dysfunction and hepatosplenomegaly, may lead to the diagnosis of HCV-related liver cirrhosis. This was the case in our patient whose HCV-RNA was also positive. Although he has a biopsy-proven cirrhosis, the possibility of leishmaniasis as the cause of decompensation of the liver disease, is more likely. A similar case describing a patient with leishmaniasis and misdiagnosed as chronic liver disease has been reported^[3]. In that report, presence of the anti-HCV positivity contributed to the delay in the true diagnosis. The authors stated that the diagnosis of VL was made by chance. The liver and spleen were much larger than the volume expected in HCV-associated liver cirrhosis, and initial suspicion was a possible lymphoproliferative disorder.

Prakash *et al* have presented a patient with clinical and biochemical features of liver cirrhosis in whom a correct diagnosis of VL was made after liver biopsy, in which parasite in the Kupffer cells were demonstrated. Unfortunately, the patient died after commencing therapy with sodium antimony stibogluconate^[4]. In addition to the chronic liver disease, manifestation of VL can also mimic acute hepatitis, as reported by Hervas *et al*^[5]. In our case, since HCV-RNA was also positive in addition to anti-HCV antibody, the diagnosis HCV infection seems to be correct. The

patient was investigated for the presence of an infection without any positive results. The fever and markedly elevated ferritin levels directed us to HLH. After determining the patient was fulfilling the diagnostic criteria suggested for HLH, we looked for a triggering etiology. Because of the patient's hometown, which was endemic for leishmaniasis, and consistent clinical findings, VL had a high probability. Consequently, the diagnosis was confirmed with serological tests. It can be speculated that our patient had no HLH since hemophagocytosis could not be demonstrated in bone marrow aspiration. However, it should be kept in mind that in approximately 20% of patients with HLH, detecting hemophagocytosis on the first bone marrow specimen is quite difficult, perhaps even impossible^[6]. Moreover, it had been recommended that not demonstrating hemophagocytosis on the first attempt, as long as the patient fulfilled the suggested criteria, should not delay timely initiation of treatment^[7].

The other criteria of HLH, low or absent natural cell activity and soluble CD-25 value, could not be tested because of the technical insufficiency of our laboratory. Actually, we could not exactly determine whether the hepatitis was associated with HCV or HLH. Presumably, it could not be differentiated in such a complicated case but co-existence of both may have been the case in our patient.

CONCLUSION

This is the first case of HLH secondary to VL in a patient with HCV cirrhosis to the best of our knowledge. Since most of the clinical findings are similar, making a correct diagnosis remains a challenge. However, we expect that this case will help to raise awareness of this rare entity and keep clinicians suspicious for exploring all clinical and laboratory abnormalities which are inconsistent with the diagnosis made.

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