JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Haemophagocytic lymphohistiocytosis following a COVID-19 infection: case report

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Abstract

The case of a 57-year-old male patient with jaundice, high-grade fever, and upper abdominal pain who was recovering from a mild coronavirus disease-19 (COVID-19) infection is reported. Laboratory analysis showed liver injury with high levels of AST and ALT, as well as an elevated serum ferritin level. The patient underwent a bone marrow biopsy which showed features of hemophagocytic lymphohistiocytosis (HLH), a systemic syndrome caused by immune activation. The patient was successfully treated with etoposide and dexamethasone and kept on maintenance therapy with cyclosporine, with resolution of the HLH.

The discussion highlights that COVID-19 infection may cause liver injury, and in severe cases, patients may develop HLH as a cause for liver injury. The incidence of HLH in adults with severe COVID-19 infection is estimated to be lower than 5%. The association between HLH and COVID-19 infection has been studied due to immunological hyperactivation. Signs such as persistent high fever, hepatosplenomegaly, and progressive pancytopenia should raise suspicion for the diagnosis of overlapping HLH. A specific approach using steroids and etoposide, followed by maintenance therapy with cyclosporine, is proposed in the HLH-94 protocol as the mainstay of treatment. It is suggested that HLH should be suspected in patients with laboratory signs of liver injury following COVID-19 infection, especially in patients with high-grade fever and a history of rheumatic conditions.

Key words: COVID-19; hemophagocytic lymphohistiocytosis; liver injury; post-COVID-19 cholangiopathy; SARS-CoV-2.

J Infect Dev Ctries 2023; 17(3):302-303. doi:10.3855/jidc.16983

(Received 16 June 2022 – Accepted 13 January 2023)

Dear Editors,

COVID-19 infection might cause liver injury, which is generally mild and transient. However, in more severe cases, the patients might develop a novel clinical entity entitled “post-COVID-19 cholangiopathy” [1-5]. Nevertheless, these patients may also present haemophagocytic lymphohistiocytosis (HLH) as a cause for liver injury [6-8]. It is estimated that the incidence of HLH is lower than 5% in adults with severe COVID-19 infection [8].

A 57-year-old male patient sought care due to jaundice, high grade fever (above 40 °C) and upper abdominal pain. He was recovering from a mild coronavirus disease-19 (COVID-19) infection, diagnosed one month earlier with an oropharyngeal swab polymerase chain reaction, and no signs of any other current infection. He had a previous diagnosis of polymyalgia rheumatica and was in treatment for 10 years with use of leflunomide, and with a controlled disease status. He was admitted in the hospital. Magnetic resonance imaging (MRI) showed enlarged abdominal lymph nodes, liver and spleen. Laboratory analysis showed hemoglobin 12.5 g/dL, leukocytes 5,280/mm³, platelets 209,000/mm³, erythrocyte sedimentation rate 60 mm, aspartate aminotransferase (AST) 473 U/L, alanine aminotransferase (ALT) 128 U/L, total bilirubin 1.5 mg/dL, serum triglycerides 194 mg/dL, lactate dehydrogenase 331 U/L and a serum ferritin level above 2,000 ng/mL, which is the upper limit of detection in the laboratory used. He underwent a bone marrow biopsy, which showed hyperplasia and dysplasia of the megakaryocytes and histiocytosis with hemophagocytosis, suggestive of HLH. In this setting, the use of the classic HLH diagnostic criteria is limited, considering the challenge in measuring natural killer (NK) cell function and sCD25 levels. Thus, most studies use the HScore as a diagnostic tool. A HScore > 169 has a sensitivity of 93% and a specificity of 86% for HLH diagnosis [9]. In the case reported, the patient had a HScore of 238 points, which translates into a 98% to 99% probability of HLH. He was treated with etoposide and dexamethasone and kept on maintenance therapy with cyclosporine, with resolution of the HLH. Afterwards, his rheumatic condition worsened, and he

was started on golimumab. He is currently asymptomatic.

Clinically, HLH is a systemic syndrome resulting in multi-organic dysfunction caused by an immune activation [10]. The association between HLH and COVID-19 infection has been studied as a result of immunological hyperactivation. Since the clinical presentation of COVID-19 infection can be very heterogeneous, signs such as persistent high fever, hepatosplenomegaly, and progressive pancytopenia should raise suspicion for the diagnosis of overlapping HLH [8]. Once confirmed, a specific approach using steroids and etoposide, followed by a maintenance therapy with cyclosporine, is proposed in the HLH-94 protocol as the mainstay of treatment [11]. Therefore, combined with the rarity of this condition, the reported case is relevant as it illustrates well the association between these diseases, which might cause adverse outcomes if not promptly diagnosed and managed.

In conclusion, in patients with laboratory signs of liver injury following a COVID-19 infection, one should suspect HLH, in spite of the rise in cases of post-COVID-19 cholangiopathy, especially in patients with high grade fever and a history of rheumatic conditions.

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Conflict of interests: No conflict of interests is declared.