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CASE REPORT | LIVER

Primary Hepatic EBV-DLBCL Lymphoma in the Setting of COVID-19 Infection

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ABSTRACT

This case study describes an instance of primary hepatic diffuse large B cell lymphoma (DLBCL) in a patient who had prolonged coronavirus disease 2019 (COVID-19). DLBCL rarely presents as a primary hepatic mass. The 53-year-old man sought emergency care because of fatigue and weight loss. Diagnostic tests showed mildly elevated liver enzymes and imaging pointed to several low-density liver lesions. A liver biopsy paired with immunohistochemical testing verified the DLBCL diagnosis. Notably, the patient had COVID-19 4 months before the liver-related symptoms. The link between COVID-19 and the emergence of solid tumor cancers is unclear, but this case underscores its potential significance and the need for further research. This report stresses the importance of recognizing and documenting instances where COVID-19 might influence the onset of solid tumor cancers, including primary hepatic DLBCL.

KEYWORDS: COVID-19; primary hepatic lymphoma; oncogenic features of COVID 19; DLBCL

INTRODUCTION

Hepatic lymphomas often occur as a result of metastatic disease, but primary hepatic lymphoma is a rare occurrence.[1] While primary hepatic lymphomas have been associated with acute viral illness, no association has been established between primary hepatic lymphoma and COVID-19.

Malignant lymphomas are a group of diseases that arise from the abnormal growth of lymphocytes. Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are 2 types of lymphoma that account for 90% and 10% of cases of malignant lymphoma, respectively.[2–4] NHL primarily affects the lymphoid and hematopoietic systems, and symptoms may include abdominal pain, fever, weight loss, fatigue, and night sweats. Diffuse large B cell lymphoma (DLBCL) is the most common type of NHL worldwide, comprising 30%–40% of cases.[2,5,6] Liver involvement as a secondary complication is observed in a significant proportion of cases, affecting 16%–46% of patients during the disease's progression.[7]

Numerous studies have elucidated the link between chronic inflammatory states, such as those seen in acute infections (e.g., hepatitis C virus [HCV]) and autoimmune disorders, and the emergence of primary hepatic lymphoma (PHL) through hepatic B cells. In this case, we aim to explore the potential association between COVID-19 and the development of DLBCL in the liver.

Kikuma et al[8] have previously discussed how persistent liver inflammation may serve as a precursor for hepatic lymphoma. There is evidence suggesting that SARS-CoV-2, the virus responsible for COVID-19, disrupts the renin–angiotensin–aldosterone system through its interaction with the ACE2 receptor. Such disruption can result in a range of adverse effects, including inflammation, vasoconstriction, fibrosis, oxidative stress, and increased capillary permeability, potentially expediting cancer progression and development.[9]

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Furthermore, SARS-CoV-2 is hypothesized to have oncogenic properties. This is believed to stem from the virus's capacity to inhibit key tumor suppressors, such as pRB and p53, through its proteomic interactions and mechanisms. In addition, SARS-CoV-2 may facilitate cellular transformation by activating oncogenic pathways and concurrently inducing inflammation and tissue damage, as well as evading the immune response.[10]

We present a distinct case study: a previously healthy 53-year-old man diagnosed with primary hepatic Epstein–Barr virus (EBV) DLBCL after an extended COVID-19 infection. This case underscores a possible connection between SARS-CoV-2 and the onset of oncogenesis.

CASE REPORT

A 53-year-old man with a history of hypertension and a recent COVID-19 infection 3 months prior presented to the emergency department with fatigue. He reported significant weight loss of approximately 25 pounds after treatment with steroids and azithromycin for COVID-19. Laboratory investigations revealed several abnormal findings: leukocytosis with a normocytic anemia and increased liver function enzymes. Abdominal ultrasound displayed a normal-sized liver with 2 cysts, measuring 0.8 cm near the gallbladder and 1.1 cm in the right lobe. Serum protein electrophoresis (SPEP) indicated elevated Kappa and Lambda light chains with a normal ratio. EBV titers showed high IgG antibodies and elevated nuclear antigen, indicative of prior exposure without active infection. The patient was initially diagnosed with prolonged COVID-19 syndrome and discharged.

However, the patient returned a month later with exacerbated symptoms, including high-grade fevers and a total weight loss of 40 pounds. A complete blood count revealed a myelophthisic pattern and bandemia (47%). The comprehensive metabolic panel showed further elevation in liver function tests with alanine aminotransferase and aspartate aminotransferase levels at 200 U/L and 132 U/L, respectively, while alkaline phosphatase remained normal at 115 U/L. Lactate dehydrogenase was significantly elevated at 443 IU/L (Table 1).

Contrast-enhanced computed tomography of the chest, abdomen, and pelvis revealed a right-sided pleural effusion, periaortic and mesenteric adenopathy, and multiple hypodense lesions in the liver, the largest being 3.1 × 3.8 cm. Flow cytometry ruled out B-cell or T-cell NHL and acute leukemia. Follow-up magnetic resonance imaging identified multiple ill-defined hepatic masses, with the largest measuring 13.5 × 6.1 cm, displaying signs of necrosis. No other solid organ lesions were noted (Figure 1).

A liver biopsy with cytometry confirmed the diagnosis of surface kappa light chain-restricted large B cell lymphoma, with dual expression of B cell lymphoma-2 (BCL-2) and c-Myc. A subsequent bone marrow biopsy was negative for myelodysplasia, leukemia, or lymphoma, leading to the final diagnosis of DLBCL of hepatic origin.

Table 1. **Serum laboratory evaluation**

	Laboratory value	Reference range
White blood cell	11.7	4.0–10.5 × 10^9/L
Hemoglobin	8.8	13.8–17.2 g/dL
Neutrophils	88.0	40%–60%
Band %	47	0%–10%
Aspartate aminotransferase	132	8–33 U/L
Alanine aminotransferase	200	7–55 U/L
Alkaline phosphatase	115	44–147 U/L
Lactate dehydrogenase	443	105–333 IU/L
Total bilirubin	2.3	0.1–1.2 mg/dL
Direct bilirubin	1.4	<0.3 mg/dL
D-dimer	851	≤500 ng/mL

DISCUSSION

While EBV-positive DLBCL can occur in immunocompetent patients, it is primarily seen in elderly patients (aged 65 years or older).[10] In immunocompromised patients, EBV-positive DLBCL is associated with HIV and preferentially targets the central nervous system. Interestingly, our patient was not immunocompromised; he tested negative for HIV and other

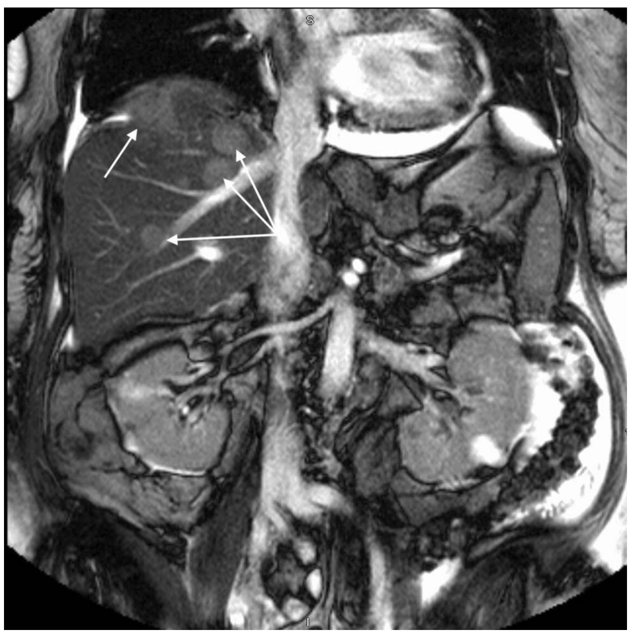

Figure 1. Magnetic resonance imaging abdomen with and without contrast. Multiple ill-defined masses are seen throughout the liver. The largest mass, which measures 13.5 × 6.1 cm, is located at the junction of the medial segment of the left and the anterior segment of the right lobe of the liver.

chronic viral infections. While it is difficult to determine with certainty whether this DLBCL developed as a result of persistent inflammation secondary to prolonged COVID syndrome or a history of an EBV infection, we can conclude that the recent history of a prolonged acute COVID-19 infection served as a precipitating immunocompromising factor that allowed for his disease process.

On initial presentation at the emergency department, the patient exhibited symptoms such as fatigue, weight loss, coughing, and shortness of breath. These symptoms were ambiguous, potentially indicative of either persistent COVID-19 infection or an underlying cancer. CT angiogram of the chest, which was performed at this time, showed no lesions in the liver, and blood tests indicated a slight increase in white blood cells. Notably, the patient did not experience fever or night sweats, which are typically early symptoms of DLBCL, complicating the diagnosis of DLBCL at that time. Despite a negative PCR test for COVID, the patient's clinical presentation and CTA findings—multiple patchy airspace opacities in the right lower lobe—raised the possibility of a persistent COVID-19 infection. This hypothesis was further supported by studies suggesting that COVID-19 might be present even when viral loads in the nasopharynx are too low for detection, implying a low viral load in the upper respiratory tract rather than a false negative PCR result.[11]

The patient had been experiencing COVID-like symptoms for over 3 months, pointing to a diagnosis of prolonged COVID-19 infection. In addition, the patient's serum angiotensin-converting enzyme (ACE) level was elevated at 170 U/L, significantly higher than the normal range of (9–67 U/L), aligning with previous literature linking elevated ACE levels with patients with COVID-19.[11] On a follow-up hospital visit, a repeat CTA of the chest revealed multiple hypodense lesions in the liver, which were further confirmed by CT and MRI of the abdomen and pelvis. A liver lesion biopsy was conducted, ultimately confirming a diagnosis of DLBCL.[11,12]

The emergence of primary hepatic DLBCL after COVID-19 infection is rare and intriguing. This case provides insight into the potential association between COVID-19 and the development of solid organ malignancies, specifically primary hepatic DLBCL.

Hepatic involvement is usually seen in about 10% of patients with NHL, suggesting progression of disease, while PHL is rarely discussed in the literature.[13,14] Most reported cases of patients with PHL were middle-aged men who presented with symptoms such as abdominal pain, nausea, and fever in addition to abnormal liver function tests, such as elevated lactate dehydrogenase and alkaline phosphatase. It is uncertain what causes PHL, but it may be related to viral hepatitis, particularly HCV.[13,15,16]

The relationship between viral infections and the development of lymphomas has been well investigated. EBV, HBV, and HCV have been implicated in the pathogenesis of PHL.[15,16] However, the specific mechanisms through which viral infections contribute to oncogenesis are complex and poorly understood.

Liver biopsy is necessary for the diagnosis of PHL because there are no specific clinical or imaging signs to confirm the disease.[2,13] PHL is similar in presentation to hepatoma and metastases from gastrointestinal cancers, so tumor markers such as alpha-fetoprotein and carcinogenic embryonic antigen can help differentiate PHL from other malignancies.[13] Treatment for PHL may include surgery, radiotherapy, and chemotherapy.[2,13] The use of rituximab has improved survival rates, but complications from chemotherapy remain a concern.[13]

In recent years, emerging evidence has suggested that SARS-CoV-2, the virus responsible for COVID-19, may have oncogenic potential. The virus has been found to induce dysregulation of immune responses resulting in chronic inflammation and genetic alterations, all of which can contribute to the development of malignancies.[17,18] In addition, COVID-19 has been associated with various hematological abnormalities and immune dysregulation, which may predispose individuals to developing lymphomas.[17,18]

In this case, the patient exhibited primary hepatic DLBCL, an infrequent manifestation of DLBCL.[1] The previous COVID-19 infection and the subsequent development of hepatic lymphoma raise questions about a potential causal relationship. It is still unclear whether his previous COVID-19 infection directly triggered the development of DLBCL in the liver or acted as a predisposing factor, exacerbating pre-existing conditions that led to immune dysregulation.[17]

Given the low number of reported cases of primary hepatic DLBCL after COVID-19 infection, increasing awareness and actively writing about similar issues is pivotal. By doing so, we can better understand the potential association between COVID-19 and solid organ malignancies. In addition, further research, including epidemiological studies and molecular investigations, is warranted to illuminate the underlying mechanisms and identify possible risk factors.

In addition, it is essential to consider the impact of COVID-19 on diagnosing and managing patients with lymphomas. The overlapping symptoms of COVID-19 and hepatic lymphomas, such as fatigue and hepatomegaly, pose diagnostic challenges. Delays in diagnosis and treatment can have significant consequences for patient outcomes. Therefore, health care providers should maintain a high index of suspicion for malignancies, particularly in individuals with a history of COVID-19 infection, and promptly initiate appropriate diagnostic investigations.

DISCLOSURES

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