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CLINICAL VIGNETTE

Mystery Lymphadenopathy

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Case

A 56-year-old African American male presents with a 2-month history of low-grade fevers, night sweats, and unintentional weight loss of 10 pounds. He also reports decreased appetite and fatigue but denies any history of travel, recent illness, or significant exposure to known infectious agents. He immigrated to the United States from Nigeria about five years prior and has not returned. His past medical history includes hypertension, hyperlipidemia, and chronic hepatitis B, for which he has been on a stable regimen of tenofovir for the past 5 years. He reports no recent medication changes or any known drug allergies.

Upon examination, vital signs are notable for a temperature of 100.4°F, a heart rate of 90 beats per minute, and a blood pressure of 130/85 mmHg. His physical examination reveals mild tenderness in the right upper quadrant, but no obvious hepatomegaly or splenomegaly. He also has lower extremity edema that has worsened. There is no palpable lymphadenopathy and no jaundice.

Evaluation

Given the patient's history of chronic hepatitis B, elevated liver enzymes (AST 120 U/L, ALT 85 U/L), and systemic constitutional symptoms, the differential diagnosis initially focused on exacerbation or reactivation of hepatitis. The patient's laboratory testing and imaging included:

- Mild leukocytosis (WBC $12.5 \times 10^3/\mu\text{L}$), Anemia (Hgb 8.3), with a normal platelet count
- Elevated AST (120 U/L), ALT (85 U/L), and mild elevation of alkaline phosphatase (150 U/L).
- Positive for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and elevated HBV DNA viral load (200,000 IU/mL).
- Chest X-Ray: No acute findings.
- CT Scan of the Abdomen and Pelvis: Reveals enlarged lymph nodes in the mesentery and retroperitoneum, with some involvement of the liver.

The initial thought was possible reactivation of hepatitis B. This is a known complication in patients with chronic hepatitis B with immune suppression or altered immune surveillance. With possible Hep B reactivation, as well as lymphadenopathy on CT abdomen and pelvis and symptoms of fever, night sweats, and weight loss, further evaluation was warranted to rule out an underlying malignancy or other systemic infectious process.

Blood cultures and multiple fungal serologies were negative. The patient was started on empirical antibiotics without resolution of fevers. FNA of accessible lymph nodes was attempted without significant yield and an excisional inguinal lymph node biopsy was performed. This established the diagnosis of diffuse large B-cell lymphoma (DLBCL), a type of non-Hodgkin lymphoma.

The patient's elevated liver enzymes, fever, and constitutional symptoms are ultimately attributed to hepatitis B reactivation triggered by the newly diagnosed diffuse large B-cell lymphoma (DLBCL). Lymphoma, particularly DLBCL, has been shown to impair immune function, which can allow for the reactivation of latent infections such as hepatitis B, an established risk factor for liver disease and hepatocellular carcinoma. Given the immune suppression associated with lymphoma and the need for cytotoxic chemotherapy will require careful management of the patient's hepatitis B.

In addition to initiating treatment for DLBCL with chemotherapy (rituximab-CHOP), the patient also started antiviral therapy to suppress HBV replication and prevent further hepatic complications.

Discussion

Hepatitis B reactivation is a well-recognized complication in patients with compromised immune systems, including those undergoing chemotherapy or those with hematologic malignancies. The immunosuppressive effects of lymphoma, whether due to the malignancy itself or the treatments, can trigger reactivation of hepatitis B virus (HBV), leading to elevated liver enzymes, jaundice, and hepatic dysfunction. This patient's symptoms and initial laboratory findings led to consideration of hepatitis reactivation. However, the unexpected persistence of systemic symptoms raised concern for an underlying malignancy, which proved to be diffuse large B-cell lymphoma.¹

Lymphoma may present with non-specific symptoms, especially in early stages. Common symptoms, such as low-grade fever, weight loss, and night sweats (referred to as "B symptoms"), overlap with a wide range of infectious, inflammatory, and autoimmune conditions. These symptoms can easily be mistaken for a viral infection or an exacerbation of a chronic condition, especially in patients with known comorbidities like chronic hepatitis B. Clinicians should maintain a broad differ-

ential diagnosis when evaluating patients with unexplained fever and systemic symptoms.

In patients with chronic viral infections like hepatitis B, it is crucial to recognize that the immune system may be compromised. Immunosuppression can occur due to the viral infection itself, the use of immunosuppressive medications, or the presence of hematologic malignancies such as lymphoma. Reactivation of HBV during lymphoma chemotherapy is associated with an increased risk of hepatic decompensation, cirrhosis, and liver failure if not properly managed. Studies report use of antiviral therapy to suppress HBV replication in these patients significantly reduces the risk of severe liver injury.²

Conclusion

This case underscores the importance of considering malignancy, particularly lymphoma, in the differential diagnosis of patients with chronic infections who present with new systemic symptoms such as fever, weight loss, and night sweats. Maintaining a broad differential and determining the etiology of immunosuppression in Hep B reactivation could be crucial. Hepatitis reactivation, especially in the setting of immunosuppression or hematologic malignancy, must be carefully managed to avoid significant complications. Prompt recognition and appropriate antiviral treatment can help reduce risks of liver damage and allow for safer treatment of the underlying malignancy.³

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