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NOVEL ID CASES

Fulminant Hepatic Failure as the Initial Presentation of Hodgkin Lymphoma in 4 Patients With Human Immunodeficiency Virus

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In the era of antiretroviral therapy (ART), Hodgkin Lymphoma (HL) is a common non-AIDS-defining cancer with increasing incidence in people with human immunodeficiency virus (PWH). Through review of these cases, we identify clinical patterns such as declining CD4 count despite ART, hyperbilirubinemia and recurrent fever, which preceded diagnosis. Identifying these important signs and symptoms may lead to earlier diagnosis and initiation of therapy. Fulminant hepatic failure limits the ability to give standard of care chemotherapy, likely jeopardizing outcomes in this patient population. Alternative bridging therapies should be considered until hepatic function improves.

Keywords. HIV; fulminant liver failure; Hodgkin lymphoma; non-AIDS-defining cancers.

The incidence of non-AIDS-defining cancers in people with human immunodeficiency virus (PWH) has been increasing over the last decade of the antiretroviral therapy (ART) era [1, 2]. One such example, Hodgkin lymphoma (HL), is becoming increasingly common and can often go unrecognized early in its presentation.

While HL is associated with the immunosuppression due to human immunodeficiency virus (HIV) infection, the risk of developing HL is higher with increased CD4 counts, a phenomenon inverse to the usual association of opportunistic infections and AIDS-defining cancers (eg, non-Hodgkin lymphoma) [3, 4]. This unusual relationship has not been fully explained, but as PWH maintain higher CD4 counts in the later ART era, it may account for the rising incidence of HL. It is notable that HL in PWH presents with more aggressive histologic subtype and more advanced disease [5]. Concomitant extranodal involvement of the bone marrow, spleen, and liver is also more common in PWH [3, 6].

Despite these differences, primary presentation of HL in the liver still remains extremely uncommon. While several cases of fulminant hepatic failure in HL have been reported [7–13], only 1 was in a patient with HIV infection [14]. In this series we report 4 cases of HL in PWH from our institution who presented with fulminant hepatic failure to make clinicians aware of the potential for this aggressive, extranodal presentation and to highlight the phenomenon of the rapid decline in CD4 cells that may be seen prior to an HL diagnosis.

CASE REPORTS

Case 1

A 59-year-old woman presented with fever of unknown origin. She had a history of HIV infection diagnosed 20 years earlier. She was taking ART for the previous 8 months with a recent undetectable (<48 copies/mL) HIV RNA load.

On initial admission, she was treated with a 7-day course of moxifloxacin for a presumptive infectious syndrome. A month later, liver and bone marrow biopsies were performed that demonstrated noncaseating granulomas and no evidence of malignancy. She was discharged on empiric therapy for both *Mycobacterium tuberculosis* and *Mycobacterium avium* complex with cultures pending. On readmission, physical examination was notable for icteric sclerae and a distended and tender abdomen with hepatomegaly and ascites, but no splenomegaly. Small, anterior cervical lymph nodes were palpable. Upon admission, antimycobacterial therapy was immediately stopped to avoid drug-induced hepatoxicity.

Admission laboratory values included a white blood cell (WBC) count of 2200 cells/μL (74% neutrophils, 18% lymphocytes, 6% monocytes), hemoglobin of 9.8 g/dL, and platelet count of 87 000/μL. Liver function tests were markedly elevated, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase (Table 1). Lactate dehydrogenase (LDH) was 188 IU/L. Her absolute CD4 count had decreased from 391 to 29 cells/μL over the preceding 7 months (Table 1).

An abdominal ultrasound showed hepatomegaly (21.9 cm) with coarse echotexture. Transjugular liver biopsy (Figure 1*A* and 1*B*) showed intact hepatic architecture but with marked expansion of portal tracts by nodular proliferation of large mononuclear cells with very prominent nucleoli consistent with Reed-Sternberg (RS) cells. There was marked steatosis, predominantly in the

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Table 1. Clinical Characteristics of 4 Patients With Human Immunodeficiency Virus Presenting With Fulminant Liver Failure at Time of Hodgkin Lymphoma Diagnosis

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age, y	59	39	50	30
Sex	Female	Male	Male	Female
Duration of HIV, y	19	8	New diagnosis	3
Duration of ART	8 mo (continuous)	7 y (intermittent, stopped 2 mo prior)	None	8 mo (intermittent)
CD4 count during hepatic failure, cells/μL	29	47	5	25
HIV RNA load, copies/mL	<48	<48	23 763	<40
Antiretroviral therapy	Yes	No	No	Yes
AST/ALT, U/L	272/56	494/136	404/120	58/63
Alkaline phosphatase, U/L	1789	121	124	2102
Peak total bilirubin, mg/dL	33.1	24.0	25.0	11.6
LDH at presentation, IU/L	188	1452	1104	1160

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase.

periportal rather than centrilobular regions. Immunohistochemical stains showed neoplastic mononuclear cells positive for CD30, CD15, BCL-6, and Epstein-Barr virus (EBV) latent membrane protein 1. The neoplastic cells had a high proliferative index of >80% based on Ki-67 stain and were positive for EBV. The final diagnosis was classical HL, lymphocyte-depleted subtype.

The patient's condition continued to worsen. Total bilirubin increased to 33.1 mg/dL. High-dose steroids were initiated, but she was too ill to tolerate systemic chemotherapy. She died 2 months after her initial presentation. Autopsy revealed diffuse involvement by HL throughout the body, including the bone marrow, lung parenchyma, pancreas, ovary, spleen, and multiple lymph nodes.

Case 2

A 39-year-old man was transferred to our hospital for management of acute renal and hepatic failure. He had a history of HIV infection diagnosed 7 years previously. He had been taking ART intermittently but had self-discontinued his regimen 2 months prior to admission. At that time the CD4 count was 47 cells/μL and HIV RNA load was <48 copies/mL.

One week prior to transfer he presented with a chief complaint of progressive fatigue. He had a creatinine level of 6.4 mg/dL and elevated liver function tests (Table 1). The albumin was 1.3 g/dL, LDH 867 U/L, and international normalized ratio (INR) 1.7 (Table 1). He was treated with empiric broad-spectrum antibiotics while managing his renal and electrolyte dysfunction.

Upon transfer to our hospital, physical examination revealed a temperature of 36.1°C, icteric sclerae, and minimal cervical lymphadenopathy, but no other appreciable lymphadenopathy. The abdomen was distended but nontender. The liver and spleen were not palpable.

The patient developed worsening transaminitis and hyperbilirubinemia of 24 mg/dL. Ultrasonography measured an enlarged liver at 15.8 cm. Transjugular liver biopsy (Figure 1*C*–*E*) demonstrated focal portal areas of atypical lymphocytic infiltrates containing cells strongly positive for CD15, CD30, and CD45 consistent with HL with associated EBV positivity. Bone marrow biopsy confirmed involvement with HL.

Due to hepatic failure, he was unable to receive systemic chemotherapy. His clinical condition worsened, and the patient died approximately 40 days after his initial presentation.

Case 3

A 50-year-old man presented to an outside hospital with shortness of breath and malaise. On admission he had renal failure and hepatic dysfunction. He developed worsening respiratory distress over 1 week. An HIV test was positive. He was transferred to our hospital for further management. On arrival, he was admitted to the intensive care unit with fever to 38.1°C, hypotension, hypoxia, and icteric sclerae. He was started on hemodialysis and vasopressor support.

Laboratory values were notable for creatinine 5.6 mg/dL and elevated liver function tests (Table 1). LDH was elevated at 1104 U/L, and the INR was 1.5. The CD4 count was 5 cells/μL with HIV RNA of 23 763 copies/mL. Ultrasound of the liver showed mild hepatomegaly (15.8 cm) but was otherwise normal. The spleen was unremarkable. A bone marrow biopsy was hypocellular but negative for lymphoma.

Testing for HIV-related opportunistic infections, as well as blood, urine, and sputum cultures, was negative; EBV serum immunoglobulin G (IgG) and EBV DNA polymerase chain reaction from blood were both positive. Empiric treatment with broad-spectrum antibiotics, antifungals, and antivirals was started. His respiratory condition worsened and he was placed on mechanical ventilation. Anuria developed and liver function worsened. A transjugular liver biopsy revealed multifocal infiltration by RS cells and was positive for EBV. The patient's clinical condition continued to worsen, and the patient died after his family elected not to further escalate care.

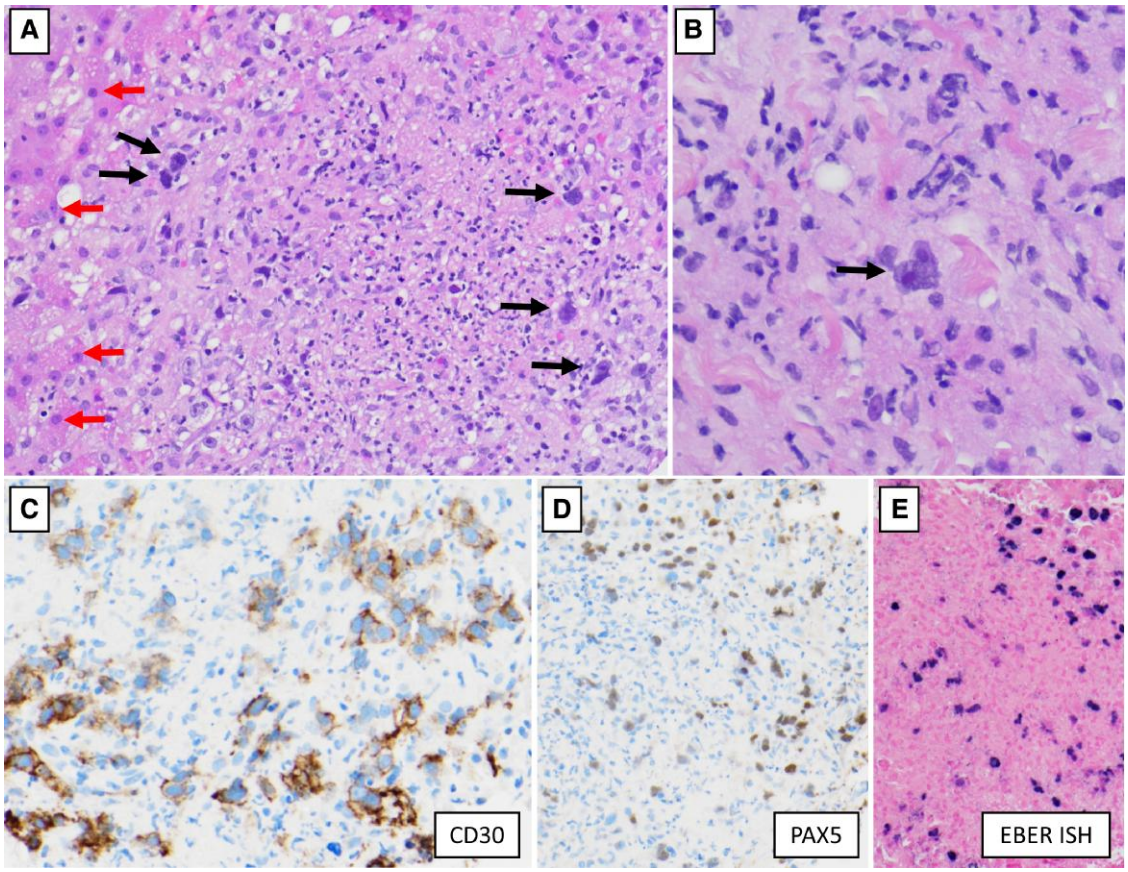

Figure 1. Photomicrographs of liver biopsies from study patients. *A* and *B*, Hematoxylin and eosin–stained sections from patient in Case 1 demonstrate a nodular atypical lymphoid infiltrate with numerous background neutrophils and small lymphocytes, as well as scattered Reed-Sternberg cells (black/right-pointing arrows). Seen at the left of panel *A* are background hepatocytes (red arrows/left pointing arrows; *A*: ×100 magnification, *B*: ×400 magnification). *C*–*E*, In Case 2, the Reed-Sternberg cells demonstrate immunohistochemical expression of CD30 (*C*: ×200 magnification) and dim-to-moderate expression of PAX5 (*D*: ×100 magnification), as well as positivity for Epstein–Barr virus–encoded small RNA (EBER) by in situ hybridization (ISH) (*E*: ×100 magnification). The histologic and immunophenotypic findings confirm the diagnosis of classic Hodgkin lymphoma.

Case 4

A 30-year-old woman with a history of HIV infection was admitted with fever and painless jaundice. She was diagnosed with HIV 3 years earlier and was started on ART but stopped after a few weeks due to side effects.

Laboratory values were significant for elevated liver function tests (Table 1). Her CD4 count was 110 cells/μL and HIV viral load was 8711 copies/mL. She restarted ART. She was persistently febrile but without a clear infectious etiology. Imaging was without notable findings. Liver biopsy was suggestive of autoimmune hepatitis, and she was started on daily prednisone.

Five months later she was lethargic at a clinic visit and noted fevers, headaches, and intermittent blurry vision for several weeks. She was admitted to the hospital.

Laboratory testing showed a new pancytopenia. She had a WBC count 2400 cells/μL (85% polymorphonuclear leukocytes, 7.4% lymphocytes, 3.3% monocytes), hemoglobin 9.2 g/dL, and platelet count of 106 000/μL. The CD4 count was 22 cells/μL with HIV RNA of <40 copies/mL. AST and ALT improved, but alkaline phosphatase was 2102 U/L and total bilirubin had increased to 9.2 mg/dL. LDH was 1160 U/L.

Positron emission tomography/computed tomography demonstrated diffuse lymphadenopathy with increased metabolic activity with splenic and bone marrow involvement. Liver biopsy demonstrated periportal areas of fibrosis, lymphoplasmahistiocytic aggregates, and scattered atypical cells with immunohistochemical staining confirming classical HL.

Given hyperbilirubinemia, brentuximab was initiated as bridging therapy. One week following her second dose of brentuximab, the patient was readmitted for multiple tonic-clonic seizures. She was found to have a subdural hematoma and was treated via subdural drain.

Given concern for disease progression, the patient was started on ABVD (doxorubicin, bleomycin, vincristine, and dacarbazine). Vincristine and doxorubicin were dose reduced given elevated bilirubin. The patient received 6 cycles of ABVD and remains in remission 3 years later.

DISCUSSION

Although HL is not an AIDS-defining cancer, PWH have an increased risk of HL, with studies estimating a relative risk of 5 to 15 times that of the general population and mortality from HL in PWH twice that of the non-HIV population [3, 15]. With the increased use of ART, the incidence of many AIDS-related cancers has markedly declined, but the incidence of HL in PWH is paradoxically rising [3, 4, 16–19]. This inverse relationship is not fully understood, but it appears that moderate immunosuppression in PWH creates an ideal environment for HL cells to proliferate.

Immunosuppression correlates with increased risk for many non-AIDS-defining cancers, particularly those caused by oncogenic viruses [2]. HIV infection leads to loss of EBV immune control. Continued antigen stimulation by EBV leads to polyclonal B-cell expansion, which increases the risk for malignant monoclonal B cells such as RS cells to arise. RS cells release cytokines and chemokines to recruit $CD4^+$ cells along with macrophages and other immune cells. With severe immunosuppression there are too few CD4 cells present to recruit and facilitate these required feedback signals. Once CD4 cell counts recover with ART, there are adequate $CD4^+$ cells available for recruitment by the malignant RS cells to lead to proliferation of disease [3, 20, 21]. This mechanism was seen in our case series, with 2 patients receiving ART for at least several months prior to diagnosis.

An acute, precipitous decline in CD4 count can also be observed immediately prior to HIV-associated HL diagnosis, which was seen in 2 cases discussed above. These patients were on ART with undetectable viral loads, and unexpected acute drops in their CD4 counts occurred. This decrease may be due to HL-related immunosuppressive cytokines or the redistribution of CD4 cells from peripheral blood into HL tissue [22, 23]. A decline in CD4 cell count may be a harbinger of HL diagnosis, and early recognition by clinicians could lead to faster diagnosis.

Fulminant hepatic failure is typically a rare presenting feature of HL and can often confound the diagnostic workup. HL can cause hepatic dysfunction through a number of pathways. Infiltration of the hepatic parenchyma by HL cells leads to necrosis and infiltration of the hepatic bile ducts, which causes obstruction and cholestasis [12, 13]. Paraneoplastic processes such as idiopathic cholestasis can also occur [8]. Last, the HL phenomenon known as vanishing bile duct syndrome develops from cytokine release, producing bile duct destruction and portal fibrosis [24]. This is characterized by ductopenia and loss of interlobular bile ducts in more than 50% of portal tracts. Notably in our case series, 1 biopsy demonstrated ductopenia. Evidence of these findings on liver biopsy should place HL high on the differential.

Once HL diagnosis is confirmed, choice of therapy can be difficult in the setting of significant liver dysfunction and hyperbilirubinemia. While initial therapy for HL consists of an ABVD backbone, hepatic dysfunction limits administration [25]. Alternative bridging therapy may be required until liver function recovers. Brentuximab vendoitin (BV), an antibody–drug conjugate which directs an antitubulin agent monomethyl auristatin E to CD30-positive cells, can be used in this setting [26, 27]. In the BREVITY (A Study of Brentuximab Vedotin in Patients With Hodgkin Lymphoma Unsuitable for Chemotherapy Due to Age, Frailty or Co-morbidity) trial, patients with HL unable to receive ABVD received BV. An objective response rate of 83.9% was seen, but progression free survival and overall survival were decreased [26]. In a case series BV was used as bridging therapy for 5 patients with untreated HL with liver dysfunction. Despite varied tumor response, all patients demonstrated improvement in liver function with BV [27]. Using BV to temporize HL disease and improve hepatic function can be a lifesaving therapeutic intervention until a patient can receive definitive chemotherapy.

CONCLUSIONS

Given the increasing rates of HL in PWH over the last decade, clinicians should be aware of fulminant hepatic failure as an initial presentation of disease. Including HL on the differential diagnosis of a PWH who develops hepatic dysfunction is imperative to ensure adequate pathologic review and prompt therapeutic intervention. Clinicians caring for PWH should recognize that a sudden drop in the CD4 count, despite ART compliance, may be a possible harbinger of HL.

Notes

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Patient consent. This case series was reviewed by the University of Maryland, Baltimore Institutional Review Board, which determined that this work does not necessitate patient consent. The information, which includes information about biospecimens, is recorded by our team in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator did not contact the subjects, and the investigator did not reidentify subjects.

Potential conflicts of interest. All authors: No reported conflicts.

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