CASE REPORT

Unusual cause of cholestatic jaundice in a patient with AIDS

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SUMMARY

A 61-year-old man with AIDS on chronic highly active antiretroviral treatment (HAART) presented with lethargy and jaundice and was found to have abnormal liver function tests (LFTs). Investigations including viral/autoimmune markers and imaging were unrevealing, except for positive Epstein-Barr virus. HAART was held, however, transaminases and total bilirubin continued to rise. The liver biopsy revealed classical Hodgkin's lymphoma (HL). HL presenting only with liver findings without lymphadenopathy is rare. Extreme cases can lead to fulminant liver failure. The bone marrow biopsy and dramatic elevation in serum ferritin were consistent with haemophagocytic lymphohistiocytosis. Finding a chemotherapy regimen was challenging given abnormal LFTs and HAART interactions. Initial chemotherapy regimen has successfully decreased LFTs; however, it was limited by pancytopenia. The patient's regimen was changed, however second regimen was complicated by neuropathy. LFTs improved and the patient was able to receive the standard care chemotherapy for HL with significant clinical, laboratory and radiological improvement.

BACKGROUND

Every year, 0.6% of newly diagnosed cancer in developed countries is Hodgkin's lymphoma (HL)^{1–3} and this accounts for less than 5% of malignant lymphomas.² Individuals with Epstein-Barr virus (EBV) infection and AIDS are thought to have higher incidence compared with the general population.⁴ HL classically presents with peripheral painless lymphadenopathy. Abnormal liver function tests and/or jaundice are unusual presentations of HL that consist of 1–4% of the cases.²

We report a case with HL solely presenting with cholestasis and elevated transaminases. Because of this unusual presentation, the diagnosis on our patient was delayed. Such a delay in diagnosis of critical disease may end up with a devastating outcome including death. In our case, the patient's bone marrow biopsy was also suggestive of haemophagocytic lymphohistiocytosis (HLH). HLH is a clinical entity characterised by hyperinflammation often confused for sepsis, and may be due to genetic causes or various secondary conditions including infections, autoimmune disorders, malignancies, immunosuppression and organ transplantation. Untreated HLH can be rapidly fatal and hence the presence of all diagnostic criteria is not essential for initiation of therapy.⁵ It was thus crucial to recognise this atypical presentation of HL

and HLH to initiate early therapy which was potentially lifesaving.

CASE PRESENTATION

A 61-year-old man from Jamaica with well-controlled HIV (CD4 count 343/ μ L, viral load 220 copies/mL) on treatment with highly active antiretroviral treatment (HAART) with tenofovir, emtricitabine, darunavir and ritonavir presented with fatigue, anorexia, weight loss and jaundice for 1 month. Examination was unremarkable except for jaundice. Investigations showed deranged liver function with alkaline phosphatase 2639 U/L, total bilirubin 6.3 mg/dL, direct bilirubin 5.1 mg/dL, aspartate aminotransferase 219 U/L, alanine aminotransferase 352 U/L and lactate dehydrogenase 319 U/L. Workup including autoimmune disease markers, hereditary hepatopathies and toxicology screen did not reveal any abnormality. Viral serology was positive for EBV early antigen and IgG, with negative IgM.

An initial CT imaging was unyielding, except for lymphadenopathy which was attributed to AIDS. HAART was discontinued due to possible liver toxicity. Liver function did not improve and patient's total bilirubin rose to 25.3 mg/dL (direct of 19.7 mg/dL). Given that liver function tests did not improve after cessation of HAART, HAART was restarted 2 months later. Repeated CT scan was unyielding. Five months after the initial presentation, MRI of the abdomen was performed which revealed para-iliac and para-aortic lymph nodes and several small liver cysts without any evidence of obstruction, findings which were attributed to AIDS. The patient was now experiencing daily fevers which did not improve with empirical antibiotics and severe progressive weakness with worsening performance status. Given persistent and now worsening symptoms and inconclusive imaging and investigations, a liver biopsy was performed which revealed large atypical neoplastic cells especially in the periportal areas, with Reed Sternberg cells, focal inflammatory infiltrates and granulomas. Staining for acid-fast bacilli was negative. Pathology interpretation of the liver biopsy was classical Hodgkins lymphoma with CD30, MUM-1, Ki-67, PAX-5 positive and CD10, CD23, BCL-2, CMV, AE1/AE3, EBER negative. T cells were positive for CD3, CD5 and CD43. Rare cells were positive for CD20. The diagnosis of stage IV classical HL was based on these findings and was discussed in the intradepartmental meeting at the department of pathology. A bone marrow biopsy

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was performed as well and showed signs suspicious for HLH, without involvement by lymphoma. Dysplastic features were seen on the bone marrow as well suspicious for concomitant myelodysplastic syndrome. Patient's ferritin level was checked and was found to be elevated at 45 367 µg/L.

INVESTIGATIONS

An autoimmune (antinuclear antibody/extractable nuclear antigen) panel, hepatitis panel (hepatitis A, B, C) were negative. An abdominal CT showed hepatic cysts that were too small to characterise and enlarged retroperitoneal lymph nodes, with borderline enlarged lymph nodes along the celiac axis, peripancreatic region, as well as mesenteric lymph nodes. MRI/MR cholangiopancreatography (MRCP) showed no evidence of intrahepatic or extrahepatic biliary dilation. Few liver and renal cysts are noted as well as marked thickening of the gallbladder wall with enhancement of the gallbladder mucosa. Findings were most consistent with HIV/AIDS with lymphadenopathy and hepatocellular disease with no evidence of biliary obstruction. Following MRI/MRCP, a liver biopsy was performed, which showed cholestatic liver with lobular and periportal infiltrates, Reed Sternberg cells (figure 1) and granulomas with atypical cells. A bone marrow biopsy revealed slightly hypocellular marrow with marked erythroid hyperplasia, increased iron storage with ringed sideroblasts consistent with sideroblastic anaemia. Dyspoietic megakaryocytes and small lymphohistiocytic aggregate also noted. An immunohistochemical study was positive for CD30 (figure 2), CD15 (figure 3), PAX 5 and MUM1 consistent with classical HL. Increased histiocytes were noted on biopsy, some containing red blood cells. EBV early antigen and IgG was positive on serology and negative on bone marrow biopsy.

DIFFERENTIAL DIAGNOSIS

In a patient with HIV/AIDS, viral hepatitis is a potential aetiology of elevated LFTs (table 1).

However, the clinical scenario is usually a parenchymal liver disease or mixed picture that is different than our patient's scenario which showed cholestasis. In addition, the patient's hepatitis serology was negative. Patient's HAART medications themselves can be associated with transaminitis. HAART hepatotoxicity prevalence is around 10% in some retrospective studies; it can cause hepatotoxicity due to hypersensitivity reactions, direct drug toxicity, immune reconstitution inflammatory

syndrome and mitochondrial toxicity. HAART hepatotoxicity usually presents with increased aspartate aminotransferase/alanine transaminase but can also present with hyperbilirrubinaemia or even be mild and asymptomatic.⁶ However, our patient's hepatotoxicity was persistent and clinical course worsened, therefore we sought other aetiologies for the patient's worsening condition.

Last, the patient's HIV/AIDS itself can cause rising LFT's; however, this was an unlikely aetiology in this patient with a well-controlled disease.

EBV infection can be associated with elevated LFTs as well; however, patient did not have IgM antibodies.

TREATMENT

Optimal chemotherapy regimen was a challenge given abnormal liver function and interaction with HAART. In addition, given the poor performance status at the time of diagnosis, there was a significant concern in starting systemic chemotherapy in this patient. The patient was thus initiated on prednisone 1 mg/kg daily with hope to temporarily control the lymphoma and decrease LFTs to allow for initiation of systemic chemotherapy.

Unfortunately, prednisone has shown no effect on patient's LFTs and after extensive review of literature, dexamethasone, cisplatin and high-dose cytarabine (DHAP) regimen was chosen over a standard doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). McCarthy⁷ reported a case of a patient with liver HL who had a total bilirubin level of 13.2 mg/dL; DHAP was used for about five cycles that improved bilirubin to 1.2 mg/dL followed by AVBD for two cycles that led to complete response. Finally the patient underwent peripheral blood stem cell transplant successfully. Based on these findings we started our patient on DHAP with 50% dose reduction since our patient had higher bilirubins than the above mentioned patient and his poor overall clinical condition. Liver function tests started to normalise soon after initiation of DHAP. However, the patient developed grade 4 pancytopenia with DHAP, thus treatment was switched to cisplatin, gemcitabine and dexamethasone (GDP) based on another case report from the Chilean literature.⁸ After receiving three cycles of GDP, the patient experienced recurrent

Figure 1 Reed Sternberg cells.

Figure 2 CD30.

Figure 3 CD15.

syncopal episodes which after extensive work-up has revealed that it is likely secondary to cisplatin-induced autonomic neuropathy. Liver function has improved significantly, however, secondary to adverse side effects; patient's regimen was changed to ABVD with major improvement and near normalisation of his liver function tests.

OUTCOME AND FOLLOW-UP

His liver functions nearly normalised after two cycles of DHAP and three cycles of GDP. However, the patient developed repeated syncopal episodes, which was attributed to cisplatin-induced neuropathy and his regimen was switched to ABVD. CT imaging is consistent with 87% resolution of lymphadenopathy, and in retrospect was due to HL, rather than AIDS. His recent positron emission tomography imaging shows no further disease activity. Ferritin level has trended down from

45 367 to 3367 $\mu\text{g/L}$ which indicates his HLH was from HL rather than AIDS itself. The patient continues to follow-up in oncology clinic and has now completed his two cycles of ABVD chemotherapy. He lives an independent life without assistance.

DISCUSSION

HL presenting with cholestasis is unusual. In patients without AIDS, primary gastrointestinal (GI) HL accounts for less than 5% of lymphomas.² A higher incidence of HL in the AIDS population can be demonstrated given the higher incidence of EBV infection in the same population. Ironically, patients with better controlled AIDS have a higher chance of developing HL than patients who are not on HAART and may have unusual presentations.⁴ In patients who were HIV positive, the incidence of HL was nearly 14 times higher than that of the general population, with variation based on the era of diagnosis; standardised incidence was 4.5 times higher than the general population in the pre-HAART era (1983–1985) compared with 32 times higher in the HAART era (2002–2007).⁹ This subset of patients also has better response to chemotherapy.⁴ Lymphomatous involvement of liver may present with cholestasis and vanishing bile duct syndrome on pathology.¹⁰ Since most of the patients with cholestatic findings also have fever, sepsis is usually suspected in the beginning, which results in delayed diagnosis.¹

Cervantes *et al*¹ reviewed 421 HL cases and only six patients (1.4%) had presentations purely with hepatic abnormalities. Four of the six patients had jaundice on presentation. HL presenting with liver involvement is generally thought to have a poor outcome. Cervantes reported that the three elderly patients died within 1.5 months in this study due to sepsis or GI bleeding but only one patient was able to receive a cycle of chemotherapy. On the other hand, the three younger patients responded dramatically to chemotherapy with MOPP/ABVD or C-MOPP. Two patients relapsed but responded to ABVD and MOPP/ABV regimens. According to these findings, patients who were exposed to ABVD did achieve some degree of response even in the relapsed setting.¹ ABVD was introduced in 1976 by the Milan cancer institute group, with subsequent trials

Table 1 Liver function test

Date	Alkaline phosphatase	Total bilirubin	Direct bilirubin	AST	ALT	LDH	Total protein	Albumin
10/24/11	100	0.4	0.1	24	59	173	7.2	4
2/22/12	2639	4.5		219	352	284	7.5	3.9
3/7/12	1557	11.1	10.1	57	95	206	7.9	4.1
3/19/12	722	19.5	14.4	112	73		7.2	3.6
4/30/12	2446	11.4	9.4	108	152	261	7.4	3.5
6/6/12	3551	17.6		175	118	306	6.8	2.8
6/15/12	6586	253		424	317		7.2	2.9
6/22/12	2994	21.2		92	83		5.6	2.2
6/30/12	1218	20.4		185	49		5.7	2.4
7/4/12	694	16.6		154	56		4.9	2
8/15/12	1855	10.5	8.9	93	76	240	4.8	2.5
9/14/12	2148	8.3	6.8	132	110		5.7	3.1
10/9/12	2357	7.1		224	123		5.4	2.9
11/20/12	2409	3.2		48	29		6.2	3.2
12/25/12	1243	1.6		88	58		4.9	2.9
2/5/13	1535	1.1		67	70		6.9	4
3/11/13	1972	0.3		87	80	203	6.8	4
5/12/13	1021	0.3		153	181		5.7	3.5
6/18/13	1014	0.5	0.2	100	156	248	6.9	4.2

ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

compared with MOPP which was the standard of care for HL around that time. ABVD has shown to be one of the most effective treatments for HL in the early and late stages. At this point literature is not clear about the prognosis for liver HL after ABVD age since literature is scarce about this clinical scenario. McCarthy⁷ used DHAP in a patient with liver HL and bilirubin of 13.2 mg/dL, however our patient had even higher bilirubin levels that did respond to our aforementioned management. McCarthy⁷ and Orellana used DHAP and GDP as initial treatment, respectively; however, both patients were followed by ABVD with successful treatment.⁷ In our case, we used DHAP with good clinical response, however side effects such as cytopenias were a limiting factor. GDP was also effective but patient developed autonomic neuropathy. Despite toxicities, this approach decreased liver tests dramatically and patient finally was able to receive standard of care ABVD with significant clinical/laboratory response.

Our patient presented a significant diagnostic challenge, since HL presenting only with abnormal liver function tests with minimal lymphadenopathy can be easily confused with AIDS. In addition, HLH without any cytopenias is difficult to diagnose in a patient with AIDS, not only because it is rare but because it also can easily be confused with AIDS-related sepsis. Secondary HLH can manifest with fevers, hepatosplenomegaly, elevated ferritin levels, neurological and skin manifestations and lymph node enlargement.⁵ Untreated HLH can be rapidly fatal and hence presence of all the criteria is not essential for initiation of therapy.⁵ Our literature review showed five case reports of patients with AIDS who had malignancy which was associated with HLH. Therapies for patients with HL and AIDS in the setting of cholestasis and liver function abnormalities require extracautious given that chemotherapy agents and interactions with HAART can worsen liver function. However, when the appropriate regimen is selected, there is a good chance for a positive outcome.⁷ In our patient, HLH improved with chemotherapy for HL, and serum ferritin was used as a marker for resolution of HLH.

Learning points

- ▶ Hodgkin's lymphoma (HL) presenting only with liver function abnormalities is extremely rare, and often can be confused with an infectious process since fever is one of the presenting symptoms.
- ▶ Overall, the prognosis of a patient who presents with hepatic abnormalities in HL is poor, and early recognition and initiation of therapy may be lifesaving.
- ▶ Choosing a chemotherapy regimen in patients with AIDS who have HL with liver involvement needs further caution given interactions between highly active antiretroviral treatment and chemotherapy.
- ▶ HLH may be easily missed due to non-specific symptoms. However, it should be considered in the differential diagnosis of patients with AIDS in particular, due to high mortality rate if missed.
- ▶ Bone marrow biopsy and immunohistochemical should be considered in patients with AIDS and unexplained non-specific symptoms since lymphadenopathy may be mistakenly attributed to AIDS itself.

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Competing interests None.

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