Unusual presentation of more common disease/injury

Right upper quadrant pain and mass in a 41-year-old previously healthy man: a presenting feature of HIV-associated extranodal diffuse large B cell lymphoma with cardiac involvement

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Summary

With an increasing pandemic of HIV/AIDS, the incidence of HIV-associated lymphoma is expected to rise. Here, the authors report a case of a 41-year-old man who presented with right upper quadrant pain and mass, and was subsequently diagnosed with HIV-associated diffuse large B cell lymphoma (DLBCL) with cardiac involvement. This case illustrates some of the uncommon and interesting aspects of DLBCL: primary extramedullary extranodal stage IV disease as the presenting feature; cardiac involvement at presentation; DLBCL as the only clue to the diagnosis of HIV; and management of HIV-associated DLBCL. This case is also a reminder of the importance of the routine HIV screening for all patients between the ages of 13–64 years, as advocated by centres of disease control and prevention.

BACKGROUND

Diffuse large B cell lymphoma (DLBCL), one of the most common subtypes of Non-Hodgkin's lymphoma with an incidence of approximately seven cases per 100 000 person years in the USA,¹ is an AIDS-defining malignancy. With an increasing pandemic of HIV/AIDS and an increase in the life expectancy of people living with HIV/AIDS, the incidence of HIV-associated lymphoma is expected to increase.² HIV-associated lymphoma has unique characteristics and can present complex diagnostic and therapeutic challenges.² Here, we report an interesting case of a HIV-associated primary extranodal DLBCL with cardiac involvement in a previously healthy man.

CASE PRESENTATION

A 41-year-old man presented to the emergency department with complaints of 3-month history of right upper quadrant abdominal pain and mass, 15-lb weight loss, fever, chills and night sweats. He denied nausea, vomiting, belly pain or change in bowel habit. He did not have any yellowish discolouration of his skin or any change in the colour of his urine or stool. He denied any other complaints. History was significant for Fournier's gangrene and scrotal surgery. He denied smoking, drinking, any prescribed or illicit drug use, drug allergy or any significant family history.

On evaluation, the patient had blood pressure of 115/73 mm Hg, pulse of 76/min, respiratory rate of 16/min and normal temperature. Abdominal examination revealed a 15×10 cm non-pulsating right upper quadrant mass; rest of the physical examination was otherwise unremarkable.

INVESTIGATIONS

Laboratory tests revealed: white blood count of 3400/ μ l, haemoglobin of 11.2 g/dl, platelet count of 160000/ μ l and normal uric acid, glucose, electrolytes and liver and renal function tests. Tests for tumour markers carcinoembryonic antigen, CA 19-9 and α feta protein level as well as hepatitis profile were normal. CT scan of the abdomen with oral and intravenous contrast showed a 14.9×13.1×10.3 cm heterogeneous, lobulated mass arising from the liver with areas of central hypodensity causing central intrahepatic duct dilatation and compression of the intrahepatic inferior vena cava and right renal artery and vein without any invasion. A 2.7×1.3 cm filling defect was noted in the right atrium (figure 1). MRI of the abdomen confirmed these findings (figure 2). Transthoracic echocardiogram

Figure 1 CT scan of the abdomen (axial view) showing huge liver mass compressing the adjacent structures.

confirmed the presence of a right atrial mass (figure 3). Histopathological examination and immunohistochemistry of CT-guided fine needle aspiration biopsy of the liver mass revealed CD20+, PAX-5+, CD 10+, BCL-6+, CD 43+ diffuse large B cell lymphoma (figure 4). Ki-67 antigen was expressed in 70–80% of the total cells. A bone marrow aspiration and biopsy showed normocellular bone marrow with trilineage haematopoiesis without any evidence of increased blast population or monoclonal B cell. Further testing revealed lactate dehydrogenase of 931 U/l, β_2 microglobulin of 4947 μ g/ml, positive HIV test, CD 4 count of 67 cells/ μ l and no genotypic evidence of resistance to any of the three major classes of antiretroviral medications. Given the positive HIV test, lumbar puncture was considered but not performed since a recent MRI of the lumbar spine showed prominent and dilated epidural veins likely as a result of the compression of the inferior vena cava. Whole body positron emission tomography (PET) scan showed increased focal uptake in the liver (SUV of 25.4), right atrium (SUV of 24.1) and right adrenal gland (SUV of 15.4) (figure 5). The patient subsequently underwent placement of a port-a-cath as well as an ommaya reservoir for prophylactic intrathecal chemotherapy. Cerebrospinal fluid (CSF) analysis sent from the ommaya reservoir revealed cytology and flow cytometry negative for lymphoma cells.

TREATMENT

The patient was started on highly active antiretroviral therapy (HAART) with efavirenz and tenofovir/emtricitabine combination as well as prophylactic co-trimoxazole. Given low CD4 count, it was decided to start chemotherapy with CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) and to hold rituximab until the CD4 count increased to 100 cells/ μ l. He received intravenous chemotherapy, along with appropriate premedications, at the following doses: cyclophosphamide 750 mg/m², adriamycin 50 mg/m², and vincristine 2 mg on day 1 and oral prednisone 100 mg once a day for 5 days. The patient also received filgrastim starting on the day 2 of the chemotherapy. As a part of the chemotherapy regimen, the patient also received intrathecal methotrexate 12 mg. His CD4 count increased to 232 cells/ μ l before second cycle of chemotherapy; hence rituximab 375 mg/m² was added to CHOP therapy from the second cycle.

OUTCOME AND FOLLOW-UP

A repeat PET scan after the first cycle showed significant decrease in the size (6.3×5.0×5.0 cm) and 80% decrease in the activity of the previous PET positive central hepatic mass as well as complete resolution of the previous foci in the right adrenal gland and the right atrium. The patient has received five cycles of chemotherapy so far and continues to do well at 3-month follow-up.

DISCUSSION

Up to 40% of all cases of DLBCL have extranodal disease on presentation³; the common sites include gastro-intestinal tract, head and neck (including nose/sinuses and thyroid), skin and soft tissues, bone and lung and pleura.^{3–6} Bone marrow can be involved in up to 8% of extranodal cases.³ Although cardiac lymphoma as a part of systemic

Figure 2 MRI of the abdomen (axial view) confirming the CT scan findings.

Figure 3 Transthoracic echocardiogram showing a right atrial mass.

Figure 4 Histopathological examination of liver biopsy specimen showing diffuse lymphoid infiltrate composed of medium to large cells with irregular nuclei and scant to moderate cytoplasm.

disease has been shown to be present in up to 10% of patients with lymphoma as an autopsy finding,⁷ primary cardiac lymphoma is a rare entity shown to be present in only 0.05% of autopsies in a large study (n=12 485).⁸ Several cases of cardiac lymphoma in HIV positive patients have been reported, however, they are present in patients known to have advanced HIV/AIDS.⁹ Cardiac involvement at presentation in healthy patients with subsequent diagnosis of concomitant HIV/AIDS, as in our patient, is very rare,¹⁰ however, it is important to be aware of such a possibility due to the expected rise in the incidence of HIV-associated DLBCL.

In a large study, significant differences were found between extranodal versus nodal disease; extranodal disease was associated with older age, poorer performance status and more frequent stage I and stage IV disease, however, there was less bone marrow involvement and low tumour burden as indicated by lower lactate dehydrogenase levels and B symptoms. Although there was no difference in overall survival (OS) between nodal and extranodal diseases, stage I extranodal disease had significantly shorter OS whereas stage IV extranodal disease had longer OS compared with nodal disease.³ Even though it is generally accepted that there are clinic-pathological differences between nodal and extranodal disease, the addition of rituximab to CHOP therapy has equalised the OS between nodal and extranodal disease.^{5 6}

DLBCL behaves more aggressively in HIV patients, as in our patient, with frequent involvement of extra nodal sites such as bone marrow, gastrointestinal tract, central nervous system and liver. Clinical features can masquerade manifestations of HIV or its complications such as opportunistic infections, thus challenging timely diagnosis. Furthermore, before the advent of HAART, HIV-associated lymphoma was associated with poor outcome and CD4 cell count at the time of diagnosis was among the most important prognostic factor for OS.²

Proper management of DLBCL in patient with HIV/AIDS requires consideration of several important factors. Because of the associated risk of reactivation with R-CHOP therapy, it is recommended to screen for the presence of concomitant hepatitis B virus infection. Central nervous system involvement can be present on disease presentation or during the course of the treatment. Therefore, lumbar puncture with CSF cytology and flow cytometry is indicated in all patients with lymphoma and HIV. Furthermore, baseline viral load and CD4 cell count should be measured. Although the optimal treatment has not been fully established, it is recommended to treat these patients with combination chemotherapy such as EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and adriamycin), CHOP, CDE (cyclophosphamide, doxorubicin, etoposide) or CDOP (cyclophosphamide, doxorubicin, vincristine and prednisone). Rituximab is added if lymphoma is CD20+, however, patients on HAART therapy with persistently low CD4 count of less than 100/ μ l is associated with higher risk of infectious complications. Hence, it is suggested to avoid rituximab if CD4 cell count is less than 100/ μ l. Our patient had a CD4 cell count of 67/ μ l, hence, rituximab was initially omitted. With the use of HAART, CD4 cell count, however, increased to above 100/ μ l before the second cycle, hence we subsequently added rituximab to our patient's chemotherapy. In all

Figure 5 Positron emission tomography scan (coronal view) showing increased focal uptake in the liver and right atrium.

patients, it is recommended to use growth factors such as granulocyte colony stimulating factor with full dose of chemotherapy. Use of prophylactic intrathecal methotrexate in HIV-associated DLBCL is somewhat controversial; it is used in all patients at some centres whereas it is used in selected high-risk patients such as those with involvement of ≥ 2 extra nodal sites (National Comprehensive Cancer Network guidelines; available at http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf). Our patient had HIV-associated lymphoma as well as involvement of ≥ 2

extranodal sites; hence we decided to administer intrathecal methotrexate.

Early and concomitant use of HAART with chemotherapy is feasible,^{11 12} may reduce the number of opportunistic infections that develop during or shortly after completing chemotherapy and improves overall survival.¹² Therefore, we started concomitant chemotherapy and HAART in our patient. In the HAART era, HIV-associated DLBCL has similar response rates to chemotherapy, disease-free survival and OS compared with HIV negative DLBCL.¹³

Learning points

- ▶ Cardiac involvement in DLBCL, although rare, can occur at the time of presentation.
- ▶ DLBCL can be the only clue to the diagnosis of HIV, hence the need for HIV testing as a part of initial investigation. This case also highlights the importance of the routine HIV screening for all patients between the ages of 13 and 64 years, as advocated by centres for disease control and prevention.
- ▶ Management of HIV-associated DLBCL requires consideration of several aspects such as exclusion of concomitant hepatitis B infection, need of lumbar puncture, administration of intrathecal methotrexate in all or at least high-risk patients and avoidance of rituximab until CD4 cell count is above 100/ μ L.
- ▶ With the early and concomitant use of HAART with chemotherapy, HIV-associated DLBCL has similar outcomes compared with HIV negative DLBCL.

Competing interests None.

Patient consent Obtained.

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