CASE REPORT

Primary pulmonary lymphoma in a patient with advanced AIDS

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SUMMARY

Non-Hodgkin's lymphoma (NHL) is an AIDS defining lesion and risk of NHL most likely correlates with the degree of immunosuppression from HIV. Risk of NHL is highest among patients with CD4 count <50 cells/mL. Primary pulmonary lymphoma (PPL) is an infrequent cause of AIDS-related lymphoma. The authors report a patient with advanced AIDS presenting with recurrent fever and pulmonary nodule seen on the CT scan. The patient remained febrile despite being on broad spectrum antibiotics with no clear source of infection. The patient underwent a bronchoscopy with biopsy of the pulmonary lesion which was most consistent with diffuse large B-cell lymphoma. The patient was started on dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone (EPOCH) and was noted to be afebrile and a repeat CT scan few weeks later showed resolution of her pulmonary nodule. This case highlights the importance of considering NHL in patients with advanced AIDS presenting with pulmonary nodule and fever.

BACKGROUND

Non-Hodgkin's lymphoma (NHL) is an AIDS defining lesion and risk of NHL most likely correlates with the degree of immunosuppression from HIV. Risk of NHL has been noted to be highest among patients with CD4 count <50 cells/mL.^{1–2} After the widespread availability and use of antiretroviral therapy (ART), the risk of NHL decreased initially and later stabilised, and has been hypothesised to be secondary to improved CD4 counts.^{2–3} Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of NHL and accounts for approximately 75% of NHL cases in the HIV population.⁴ Primary pulmonary lymphoma (PPL) is an infrequent cause of AIDS-related lymphoma, and is usually of the diffuse large-cell type.⁵ AIDS-related PPL was defined by Ray *et al*⁵ as: (1) histologically proven lymphomatous pulmonary involvement; (2) absence of mediastinal and/or hilar adenopathy; (3) absence of extrathoracic lymphoma extension diagnosed before, during or 3 months after the diagnosis of pulmonary lymphoma. The authors report a patient with advanced AIDS presenting with recurrent fever and pulmonary nodule, later been diagnosed pathologically with PPL and had favourable response to therapy.

CASE PRESENTATION

The authors report a 41-year-old African woman presenting to her physician with fever and

weakness. Patient mentioned her symptoms started 2 weeks prior to her presentation and she was having daily fevers. She also reported of associated shortness of breath which was present at rest and worsened with activity. She denied cough or any cardiac symptoms which could contribute to her dyspnoea. The patient medical history was positive for HIV infection diagnosed 5 years ago, however uncontrolled secondary to poor medication adherence. She was currently on treatment for disseminated *Mycobacterium avium* complex (MAC) infection which was diagnosed 2 months ago on workup of hilar and mediastinal lymphadenopathy. Blood cultures and cultures obtained from the lymph node were positive for *M. avium* and the patient was started on clarithromycin, ethambutol and rifabutin for the same. Her other medication included zidovudine, lamivudine, lopinavir and ritonavir in liquid formulations for her HIV infection and sulfamethoxazole-trimethoprim for *Pneumocystis jirovecii* pneumonia prophylaxis. She admitted to not taking her medication in the past month secondary to gastrointestinal side effects. Patient was originally from Nigeria and mentioned acquiring her HIV secondary to unprotected heterosexual intercourse. She denied any recent sexual contact and denied any sick contacts.

On examination the patient was febrile (T=38.6°C) and tachypnoeic (respiratory rate=28/min). She was in mild respiratory distress and rales were auscultated over her left upper lobe. Remainder of her physical examination was within normal limits.

INVESTIGATIONS

Laboratory investigation revealed the patient to have mild anaemia (haemoglobin =10.1 g/dL) and mild leukopenia (WCC count=3500 cells/mm³) with associated lymphopenia (245 cells/mm³). Her renal and liver function tests were within normal limits. Her CD4 count was 35 cells/mL and HIV—1 viral load of 695 000 copies/mL. Patient had mildly elevated lactate dehydrogenase level (503 IU/L) and normal β -2 glycoprotein levels.

In order to investigate her respiratory symptoms better patient underwent a chest X-ray which showed some infiltrates in the right upper lobe. This was followed by a CT chest which demonstrated a new 2×2 cm pulmonary nodule in the right upper lobe and associated bulky bilateral hilar lymphadenopathy (figure 1). The hilar lymph nodes conglomerate measured approximately 4.5 cm×3 cm by 2.5 cm bilaterally, which was smaller when compared to a CT scan performed 2 months ago during the diagnosis of MAC infection.

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Figure 1 CT chest demonstrating pulmonary nodule in the right upper lobe and associated bulky hilar lymphadenopathy.

DIFFERENTIAL DIAGNOSIS

Considering the patient's fevers and these new respiratory findings, infectious disease consult was ordered. Differential diagnoses considered by the infectious disease team were relapse of her MAC infection due to medication non-adherence. Fungal aetiologies such as histoplasmosis, coccidioidomycosis, blastomycosis, cryptococcosis, invasive aspergillosis or an atypical form of *P. jirovecii* pneumonia were considered in this immunocompromised host. Bacterial infection leading to a lung abscess, a pneumonic form of *Mycobacterium tuberculosis* and pneumonia due to *Rhodococcus equi* were possibilities. Finally, malignant entities common in patients infected with HIV, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, Castleman's disease and pulmonary lymphomatoid granulomatosis were considered. A primary lung cancer or metastatic lesions to the lung were also considered in the differential diagnosis.

TREATMENT

To further proceed with the diagnosis the patient underwent a bronchoscopy with biopsy of the pulmonary lesion. Bacterial, acid-fast bacilli (AFB) and fungal cultures of the bronchoalveolar fluid were negative. Serum aspergillus galactomannan was also negative.

The biopsy revealed large, lymphoid cells with high nuclear to cytoplasmic ratios, vesicular chromatin and occasional nuclei. Immunohistochemical stains were positive for CD20, PAX-5, CD45, BCL-2 (subset), BCL-6 (subset) and MUM-1 (subset). Stains were negative for CD10, CD3, CD5, CD23, Cyclin D1, Epstein-Barr virus-encoded small RNA (EBER) and Epstein-Barr virus latent membrane protein (EBV LMP). The proliferation index (Ki-67) appeared to be approximately 80–90% in the neoplastic cells. This was most consistent with diffuse large B-cell lymphoma with high proliferation index. Expression of B-cell leukaemia/lymphoma 2 (BCL-2) protein (25–80%), B-cell lymphoma 6 (BCL-6) protein (70%); and other markers such as MUM1/IRF4 (35–65%) in DLBCL has been reported in the literature.^{6–8}

A CT-guided biopsy of the hilar lymph node at this time demonstrated multiple necrotising and non-necrotising granulomas with positive AFB smear result, however negative AFB cultures. The hilar lymph nodes were associated to the recent MAC infection and not secondary to the lymphoma. The concomitant CT scan of the abdomen and pelvis did not show liver or spleen enlargement or any adenopathy, excluding the possibility of systemic involvement. The patient remained febrile despite being on broad spectrum antibiotics with no clear source of infection. At this time the patient's fever were presumed to be secondary to her lymphoma.

The oncology team was consulted at this time and they planned to start the patient on dose-adjusted EPOCH⁹ (dose-adjusted infusional etoposide, vincristine and doxorubicin and dose-adjusted bolus cyclophosphamide in addition to oral prednisone). A prospective single arm trial evaluated the dose-adjusted EPOCH regimen in 39 patients with newly diagnosed AIDS-related lymphoma (80% DLBCL).⁹ Results showed complete response in 74% of patients and estimated rates of progression-free and overall survival at 5 years were 73% and 60%, respectively.

Using rituximab was discussed for the patient as the lymphoma was CD 20 positive on immunochemical staining, however the oncology team deferred the use of rituximab because of the patient's low CD4 count (<50 cells/mL). Rituximab use is supported by a pooled analysis of 1546 patients that reported an association between rituximab use and superior complete remission rates, progression-free survival and overall survival; however, the number of patients with a CD4 count <50 cells/mL was 14%.¹⁰ An AIDS-Malignancies Consortium Trial, highlighted the addition of rituximab to standard chemotherapy in patients with HIV-NHL was associated with improved tumour response. However, treatment-related infectious deaths occurred in 14% of patients receiving rituximab compared with 2% in the chemotherapy-alone group ($p=0.035$). Of these deaths, 60% occurred in patients with CD4 counts less than 50 cells/mL. This trial highlighted that the benefits of addition of rituximab to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy may be surpassed by the increased risk of infectious deaths, particularly in those individuals with CD4 counts less than 50 cells/mL.¹¹ Similarly, addition of rituximab concurrently to dose-adjusted EPOCH, was associated with numerically higher death rate in patients with a baseline CD4 count of less than 50 cells/mL.¹² Secondary to the profound cellular and humoral immunodeficiency caused by rituximab and lack of data supporting its use in patients with CD4 count <50 cells/mL, the decision to omit the use of rituximab was made.

The patient after her course of chemotherapy was noted to be afebrile and a repeat CT chest few weeks later showed resolution of the pulmonary nodule. Along with chemotherapy the importance of controlling HIV infection was discussed with the patient. Patient's antiretroviral medications were changed to a combination pill of emtricitabine/tenofovir along with raltegravir. This combination was chosen for the patient based on better tolerability, decreased pill burden, and also decreased drug–drug interaction with the chemotherapeutic regimen and ongoing MAC treatment. With the help of an adherence counsellor and regular follow-up, the patient was able to achieve virologic suppression.

The patient is followed up in the oncology clinic has completed six cycles of the dose-adjusted EPOCH. She did not experience any infectious complications or treatment toxicity with this regimen and a follow CT scan of the chest at the end of therapy showed resolution of the pulmonary nodule.

DISCUSSION

As mentioned earlier, PPL is an infrequent cause of AIDS-related lymphoma, and is usually of the diffuse large-cell type.⁵ In a retrospective review of patients with AIDS undergoing autopsy, 5.8% of patients with NHL experienced isolated pulmonary localisation and the lung was the most common organ involved in those with an extranodal site of disease (70%). Patients with HIV infection with pulmonary NHL often present with pneumonic or pleural disease.¹³ Previous case reports have also reported patients presenting in severe distress

secondary to bronchial involvement accompanied with complete unilateral bronchial obstruction leading to death even prior to administration of chemotherapy.¹⁴

Use of ART has resulted in a marked improvement in the ability of patients to tolerate standard chemotherapy regimens and clinical outcomes are comparable to the general population. Studies have demonstrated similar response to full-dose chemotherapy for aggressive B-cell lymphomas comparing HIV-positive and HIV-negative patients treated with similar regimens.^{15 16} Survival in patients with AIDS-related lymphoma is influenced by factors related to both, the HIV infection and the lymphoma. Nearly half of the patients with AIDS-related NHL will have favourable long-term survival with conventional dose chemotherapy.^{9–12} The other half of the patients, die from progression or recurrence of the lymphoma or other AIDS-related complications, including opportunistic infections.^{9–12 16 17} ART and control of the HIV infection still remains a key element in both prevention and treatment of NHL in patients with HIV. The current literature suggests that HIV-associated aggressive lymphomas can be treated successfully with standard chemotherapy regimens without unusually severe toxicities in patients on ART and with well-controlled HIV and adequate immune function.^{15–17} This case highlights the importance of considering NHL in patients with advanced AIDS presenting with pulmonary nodule and fever.

Learning points

- ▶ Always consider non-Hodkin's lymphoma (NHL) in patients with AIDS presenting with pulmonary lesions and fever.
- ▶ Risk of NHL has been noted to be highest among patients with CD4 count <50 cells/mL.
- ▶ NHL rates have declined during the highly active antiretroviral therapy era.
- ▶ Infusional etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone chemotherapy is associated with better overall survival in patients with AIDS-related diffuse large B-cell lymphoma.

Competing interests None.

Patient consent Obtained.

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