Unusual presentation of more common disease/injury

Extranodal lymphoma masquerading as carcinoma of the breast in an HIV-positive male patient

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Summary

This report describes a male patient infected with the HIV, with antiretroviral therapy (ART)-induced gynaecomastia. He presented with a right-sided breast mass which clinically resembled a carcinoma. A core biopsy suggested non-Hodgkin's lymphoma of diffuse large B cell histology. Also presented are his 18-fluoro-deoxy-glucose - positron emission tomography (FDG PET)-CT scan findings which showed a highly avid mass (standardised uptake value (SUV) 34.5) in his right breast. In spite of a very good clinical response after the first cycle of chemotherapy, his disease relapsed at multiple sites and progressed early. This case illustrates the aggressive course of HIV-associated extranodal lymphomas, and also highlights the issues concerning the use of ART and chemotherapy.

BACKGROUND

Male breast cancers are rare, and lymphomatous involvement of the male breast is even the rarer. This is a very rare scenario of a lymphoma presenting as a lump in a patient with gynaecomastia which was in-turn consequential of antiretroviral therapy (ART). While extranodal lymphomas are more common in patients infected with HIV, there exist dilemmas which a team could face in the decision-making process with regard to the management of lymphomas with a coexisting issue of decreased CD4 count. The optimum sequencing of ART and chemotherapy is controversial even though both are necessary.

CASE PRESENTATION

We report the case of a 48-year-old male patient who presented with a painful lump in his right breast (figure 1). He stated that the lump progressed rapidly within a month from a small, painless mass to an extremely painful mass that caused redness of the overlying skin. The patient reported that he was serum positive for HIV for the past 4 years. Our patient reported that he was started on an ART regimen (containing zidovudine, lamivudine and efavirenz) 4 years ago after he was diagnosed to be HIV positive. However, he had voluntarily (without consultation) stopped ART after 1 year of use, his reason being that 'he was doing well even without ART'. He further reported that he had developed bilateral gynaecomastia after ART use, which did not subside even 3 years after cessation.

A fine needle aspiration cytology (FNAC) performed at a local hospital suggested 'lymphoma'. A subsequent core-biopsy revealed a diffuse large B cell lymphoma (DLBCL) which was CD20 positive. The patient was hence referred to our centre. At presentation, his CD4 T-cell count was 144 cells/ μ l and his HIV viral load was 4650 copies/ml.

Given that we already had histological proof at hand, we decided to omit CT-scan and we directly proceeded to FDG-PET/CT scan with an intention to stage the

non-Hodgkin's lymphoma (NHL). The FDG-PET/CT scan showed an intense mass with SUV_{max} of 34.5 in the right breast (figure 2). It measured 4.7×4.8 cm and seemed to involve the overlying skin as well as the chest wall. The mass was contiguous with another intense mass in the ipsilateral internal mammary area (presumably an involved internal mammary lymph node).

TREATMENT

He was started on the cyclophosphamide-hydroxydaunorubicin-ondcovin-prednisone (CHOP) regimen. The doses used were cyclophosphamide (100 mg intravenous), hydroxydaunorubicin (75 mg intravenous), vincristine (2 mg intravenous) on day 1, and prednisone (100 mg orally) given on days 1–5. Oral prophylaxis with fluconazole and trimethoprim-sulfamethoxazole were also initiated.

Figure 1 Right breast lump, with redness and induration of the overlying skin was the presenting complaint.

Figure 2 PET-CT image showing a highly FDG-avid lump in the right breast. What seems to be a direct extension to the ipsilateral internal mammary lymph node can also be seen.

OUTCOME AND FOLLOW-UP

As early as on the seventh day, the patient had a clinically complete response (figure 3). However, on the 15th day, the patient developed septicaemia. His CD4 count had dropped to 23/ μ l (from a prechemotherapy value of 144/ μ l). His HIV viral load remained almost static at 4900 copies/ml (prechemotherapy value of 4650 copies/ml). There were multiple palpable nodal as well as extranodal masses, which on FNAC were positive for DLBCL. He was treated supportively with antibiotics and antifungals. However, the patient succumbed to multiorgan failure on the 19th day of initiation of chemotherapy.

DISCUSSION

NHL is a disease known for its heterogeneous possibilities with regard to presentations. Although extranodal NHL is not uncommon, the breast is a rare site of NHL, with breast lymphomas making up for just 0.4–0.7% of all

Figure 3 Resolution of the lesion, as early as on the seventh day after chemotherapy.

NHL, and only 1.7–2.2% of extranodal NHL.^{1 2} Primary breast lymphoma (PBL) is reported to be as common as secondary lymphomatous involvement of the breast, though both forms are rare in absolute terms.^{3 4} DLBCL is the most common variety in both primary and secondary lymphomas of the breast.² Lymphomatous involvement of the male breast is extremely rare.²

There have been a limited number of studies that have attempted to characterise the nature of breast lumps among patients who are HIV-positive. Possibilities in male patients include gynaecomastia, Kaposi sarcoma, tuberculomas and abscess.^{5 6} Various classes of drugs used in ART regimens have been documented to induce gynaecomastia. Although the exact mechanism of ART-induced gynaecomastia is not elucidated, possible mechanisms include disturbances in oestrogen metabolism, decreased testosterone synthesis, altered lipid metabolism and even direct effect of the drugs upon the breast tissue.^{7 8}

A thorough literature search yielded no previously reported cases of primary lymphomas developing in a male patient with ART induced gynaecomastia. This report is possibly the first ever such case. Going by the Wiseman and Liao⁹ Criteria for PBL (four criteria formulated in 1972), we have classified our patient as a case of PBL.

FDG-PET-CT scan is currently a valuable tool for staging NHL, and the use of FDG-PET-CT indeed helped us rule out other sites of lymphomatous involvement at presentation.¹⁰

After establishing the stage, and given the poor performance status of the patient, we initiated him on the standard CHOP regimen. Rituximab was omitted as there is no proven benefit of adding rituximab to CHOP in primary extranodal lymphoma, whose behaviour is different from nodal DLBCL. Moreover, there is no proof of safety or efficacy of anti-CD20 blockade in the already-immunocompromised HIV-positive patients.^{11 12}

We did not initiate HAART (highly active ART) concurrently with chemotherapy due to lack of consensus regarding the integration of chemotherapy and HAART in HIV-positive NHL patients. The optimum timing and sequencing of ART in relation to chemotherapy in HIV-positive patients with lymphoma is unknown and various clinical trials performed to answer the issue have yielded no clear answers. Chemotherapy without concomitant ART has been studied due to concerns of drug interactions of ART and chemotherapy, added toxicity and poor patient adherence due to nausea. The NCI-EPOCH study observed that CD4 T-cell counts decrease during chemotherapy, but improve following reintroduction of ART after completion of chemotherapy. It has been suggested that temporary discontinuation of ART for 4–6 months to allow chemotherapy did not lead to persistent and deleterious immunological consequences.^{13 14}

However, it is arguable that HAART, if initiated prior to the initiation of chemotherapy could possibly have helped the recovery of CD4 counts. Given that HIV is lymphotoxic to CD4 T-cells, it must be recognised that systemic chemotherapy too has a strong lymphopenic effect. It has even been argued that the lymphotoxic effect of chemotherapy is a more potent T-cell destroyer than is HIV, 'by several orders of magnitude'.^{15 16}

HAART can reduce the incidence of dangerous opportunistic infections, and hence improve tolerability of

chemotherapy. Afterall, the recent improvements in survival in HIV-associated NHL patients have not been due to the recent advances in chemotherapy, but due to the advances in HAART.^{17 18}

Learning points

- ▶ Extranodal non-Hodgkin's lymphoma (NHL) is commonly manifested in HIV-positive patients and patients who present with extranodal NHL should be offered HIV testing.
- ▶ CD4 T-cell counts should be tested in all patients of extranodal lymphoma, even if the patient refuses HIV testing.
- ▶ Chemotherapy can deplete CD4 T-cell counts rapidly and to a higher magnitude in comparison with the HIV-mediated process of CD4 T-cell depletion.
- ▶ The optimal management in HIV-associated NHL is yet to be defined. Highly active antiretroviral therapy and chemotherapy are both necessary, but their optimal sequencing is yet to be known.

Competing interests None.

Patient consent Obtained.

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