Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type in an Elderly Man with Human Immunodeficiency Virus Encephalopathy

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Sir,

A new World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification of cutaneous lymphomas was proposed recently (1), and has been widely accepted as an important consensual advance for the characterization and management of cutaneous lymphomas (2, 3). In this classification, primary cutaneous B-cell lymphomas (PCBCLs) were divided into the following three main groups: primary cutaneous follicular centre lymphoma, primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT) and primary cutaneous marginal zone B-cell lymphoma (4). PCLBCL-LT shows positive staining for the Bcl-2 protein. The expression of Bcl-2 characterizes not only PCLBCL-LT, as previously demonstrated, but also PCLBCL-LT defined on the basis of morphology (5–8). We report here a case of an elderly man who presented with human immunodeficiency virus (HIV) encephalopathy in association with PCLBCL-LT.

CASE REPORT

A 68-year-old man presented with a 2-week history of a cutaneous tumour on his left Achilles tendon. The patient continued to have fevers, night sweats, and worsening of his general status and decreased appetite with progressive mental status changes; symptoms which had developed within the previous 2 months. His motor strength was documented as 4/5 in all four extremities. Laboratory evaluation showed a white blood cell count of 1.9×10^3/μl (normal range $4–9 \times 10^3$/μl), haematocrit 26.4% (normal 43–51%), platelet count 147×10^3/μl (normal $180–370 \times 10^3$/μl), and C-reaction protein 6.7 mg/dl (normal > 0.3 mg/dl). His serum enzyme-linked immunosorbent assay revealed the presence of HIV antibodies; confirmatory tests detected HIV1 gp160, gp110, gp41, p68, p52, p40, p34 and p25. His HIV1-RNA viral load was 1.6×10^3 copies/ml and the CD4 cell count was 8 cells/μl (2.5%). Examination revealed a well-defined, solitary, red-to-violaceous, firm ulcerated tumour measuring 17 mm in diameter, surrounded by a region of erythematous induration with a thick hemorrhagic crust on his left Achilles tendon (Fig. 1). Histopathology showed a dense infiltration of the entire dermis by cohesive aggregates of large lymphoid cells and partial destruction of the epidermis. The atypical cell infiltration extended to the subcutaneous fat (Fig. 2a). The tumour cells were round or polygonal, with abundant cytoplasm and large, vesicular nuclei with irregularly shaped, large nucleoli. Immunohistochemical analysis revealed that the tumour cells were positive for CD20 (Fig. 2b), CD79a, and Bcl-2 (Fig. 2c). However, the cells were negative for CD3, CD10, CD30, CD31, and CD34. Brain magnetic resonance imaging (MRI) revealed bilaterally high signal-intensity lesions on fluid-attenuated inversion recovery in the periventricular white matter and centrum semiovale. This patient's clinical picture was consistent with HIV encephalopathy, and the diagnosis was based on exclusion of other possible causes of mental status change. There was no evidence of lymphadenopathy on computed tomography scans of the chest and abdomen. In addition, the results of ultrasound examination of the lymph nodes, bone marrow aspiration and biopsy were all normal. As the cutaneous lesion developed without any detectable lymph node involvement, the histological and immunohistochemical findings of his leg tumour corresponded with PCLBCL-LT.

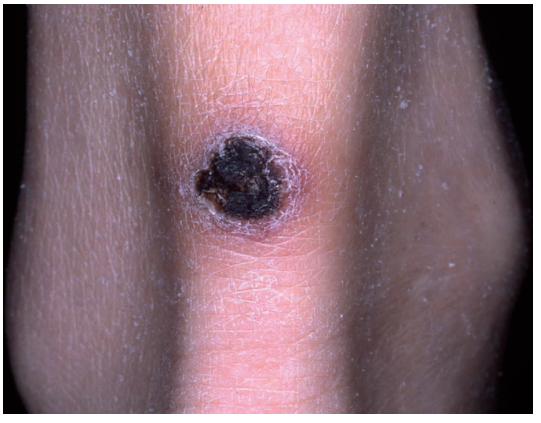

Fig. 1. A violaceous and slightly infiltrated cutaneous tumour with a thick hemorrhagic crust present on the patients left Achilles tendon.

He was started on a highly active antiretroviral therapy (HAART) regimen containing sanilvudine, lamivudine and nelfinavir, and the leg tumour was completely removed by local surgical excision. At a follow-up examination performed 7 years after hospital discharge, cranial MRI showed almost complete resolution. The patient was found to have complete neurological recovery and there was no evidence of any cutaneous lymphomas. The HIV1-RNA viral load was undetectable and the CD4 cell count was 1386 cells/μl at the last visit to our hospital.

DISCUSSION

Malignant lymphoproliferations are complications of the immunosuppression induced by HIV. It is documented that patients with HIV infection have a higher incidence of non-Hodgkin's lymphoma compared with the general population (9). Approximately 3–10% (10) of patients with acquired immunodeficiency syndrome develop non-Hodgkin's lymphoma at some stage of the disease and most are B-cell lymphomas. Among those patients that develop non-Hodgkin's lymphoma, there is rarely cutaneous presentation of symptoms (11). PCBCLs are defined as non-Hodgkin's B-cell lymphomas that are manifested on the skin without evidence of extracutaneous disease (1). The present patient is a rare case of the subtype of PCBCLs seen in an HIV-infected individual. In the 2008 WHO lymphoma classification, HIV-associated lymphomas were discussed in a sepa-

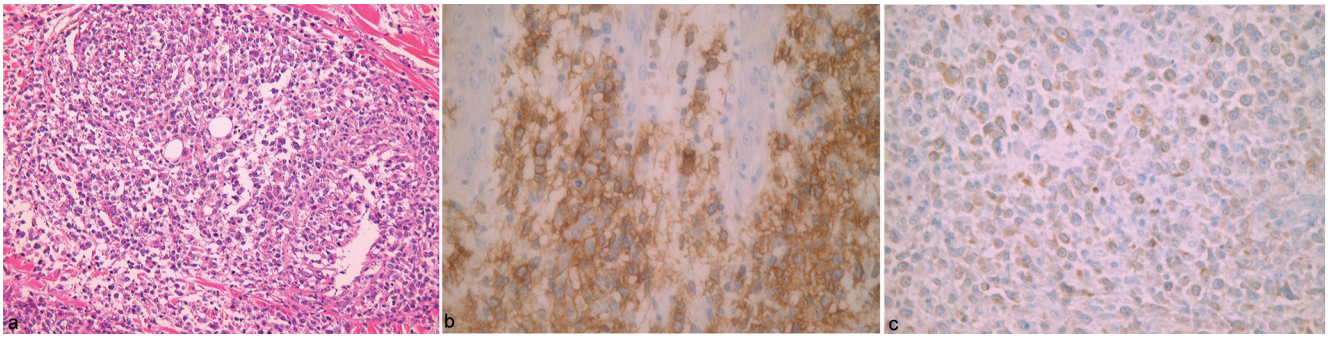

Fig. 2. (a) Histopathology showed a dense infiltration by cohesive aggregates of large lymphoid cells in the dermis (haematoxylin and eosin stain; original magnification ×200). (b) Immunohistochemical staining showed most of the infiltrating cells were positive for CD20 (original magnification ×400). (c) Bcl-2 was highly expressed by atypical cells (original magnification ×400).

rate chapter (12). We also suggest that the patient may be primarily a HIV-associated B-cell lymphoma with clinicopathological features of a PCLBCL-LT rather than a genuine PCLBCL-LT.

It is remarkable that HIV encephalopathy in our patient has shown an optimal clinical and immunological evolution after the initiation of HAART, with undetectable viral loads and normal CD4 cell counts at 7 years post-treatment. Numerous studies have documented that HAART successfully prevents HIV encephalopathy (13). In addition, our patient showed no evidence of further manifestations or relapse of PCLBCL-LT after surgical excision of the tumour. PCLBCL-LT is characterized by rapidly growing tumour masses on the lower leg, with a poor prognosis due to frequent spread of the disease to lymph nodes and internal organs (14, 15). PCLBCL-LT with Bcl-2 positive is characterized by a poor prognosis and requires effective therapies (4). The cutaneous lesion in our case completely healed after therapy, with no evidence of recurrence during the following 7 years. This is the first report that PCLBCL-LT is healed after excision. The exact pathogenesis of HIV-related lymphomas is not known, but the continued HIV viral burden on B cells is believed to play a role (16). The apparent improvement of HIV encephalopathy following treatment of PCLBCL-LT with HAART suggests that this is not simply an isolated coincidental development of HIV and PCLBCL-LT. We believe that the effect of HIV on B cells could induce the development of HIV encephalopathy in direct association, and not coincidentally, with PCLBCL-LT.

The authors declare no conflict of interest.

REFERENCES

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105: 3768–3785.
2. Burg G, Kempf W, Cozzio A, Feit J, Willemze R, Jaffe ES, et al. WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. J Cutan Pathol 2005; 32: 647–674.
3. Slater DN. The new World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas: a practical marriage of two giants. Br J Dermatol 2005; 153: 874–880.
4. Xie X, Sundram U, Natkunam Y, Kohler S, Hoppe RT, Kim YH, et al. Expression of HGAL in primary cutaneous large B-cell lymphomas: evidence for germinal center derivation of primary cutaneous follicular lymphoma. Mod Pathol 2008; 21: 653–659.
5. Geelen FA, Vermeer MH, Meijer CJ, Van der Putte SC, Kerkhof E, Kluin PM, et al. Bcl-2 protein expression in primary cutaneous large B-cell lymphoma is site-related. J Clin Oncol 1998; 16: 2080–2085.
6. Paulli M, Viglio A, Vivenza D, Capello D, Rossi D, Riboni R, et al. Primary cutaneous large B-cell lymphomas of the leg: histogenetic analysis of a controversial clinicopathologic entity. Hum Pathol 2002; 33: 937–943.
7. Hoefnagel JJ, Dijkman R, Basso K, Jansen PM, Hallermann C, Willemze R, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005; 105: 3671–3678.
8. Grange F, Beylot-Barry M, Courville P, Maubec E, Bagot M, Vergier B, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007; 143: 1144–1150.
9. Cote TR, Bigger R, Rosenberg PS, Devesa SS, Percy C, Yellin FJ, et al. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. Int J Cancer 1997; 73: 645–650.
10. Schulz TF, Boshoff CH, Weiss RA. HIV infection and neoplasia. Lancet 1996; 348: 587–591.
11. Fardet L, Blanche S, Brousse N, Bodemer C, Fraitag S. Cutaneous EBV-related lymphoproliferative disorder in a 15-year-old boy with AIDS: an unusual clinical presentation. J Pediatr Hematol Oncol 2002; 24: 666–669.
12. Delsol G. The 2008 WHO lymphoma classification. Ann Pathol 2008; 28:S20–S24.
13. Shah P, Paul R, Gold R, Tashima K, Flanigan T. Treating HIV encephalopathy with antiretroviral therapy: a clinical case demonstrating the success of HAART. Clin Infect Dis 2004; 39: 1545–1547.
14. Querfeld C, Guitart J, Kunzel TM, Rosen ST. Primary cutaneous lymphomas: a review with current treatment options. Blood Rev 2003; 17: 131–142.
15. Sü A, Simon JC, Sticherling M. Primary cutaneous diffuse large B-cell lymphoma, leg type, with the clinical picture of chronic venous ulceration. Acta Derm Venereol 2007; 87: 169–170.
16. Gates A, Kaplan L. Biology and management of AIDS-associated non-Hodgkin's lymphoma. Hematol Oncol Clin North Am 2003; 17: 821–841.