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Splenic marginal zone B-cell lymphoma in a HIV-positive patient: a case report

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Dear Editor,

A 47-year-old man was hospitalized in November 2006 for hyperthermia into the Division of Tropical Infectious Diseases. The patient had been diagnosed with HIV infection 14 years before and was in antiretroviral therapy since 9 years; his CD4-positive cells ranged between 300 and 650 cells per microliter and viral load remained less than <50 copies per microliter with didanosine, lamivudine, and atazanavir. Since the diagnosis, he did not show any relevant HIV-related clinical event.

At admission, the physical exam revealed organic decay, weight loss, multiple small superficial adenopathies and marked splenomegaly (spleen palpable in left iliac region). The patient was initially treated with antipyretics, hydration, and continued antiretroviral therapy.

The blood cell count showed white blood cells 3,840 per microliter (lymphocytes 66%, absolute count 2,534 per microliter), platelets 1,233,000 per microliter, and hemoglo-

bin 10.3 g/dl. The biochemistry showed lactate dehydrogenase 818 mU/ml, β_2 -microglobulin 4,100 μ g/l, alkaline phosphatase 1,093 U/l, erythrocyte sedimentation rate 17, C-reactive protein 0.6 mg/dl, total protein 6.1 g/dl, α -fraction 8%, gamma globulin 10%; microbiological analyses of blood and urine were negative as well as hepatitis C virus (HCV) serology; hepatitis B virus (HBV) serology showed HbsAg, HBsAb, and HbcAb positive. Computed tomography (CT) scan documented splenomegaly (diameter 30×22 cm) without any focal lesion and an accessory spleen (diameters 10×4 cm), multiple adenopathies at splenic hilus and along the spleen vessels, ectasia of the spleen–portal system, and little ascites in the pelvic cavity. Bone marrow biopsy revealed a nodular lymphoid infiltration suspicious for lymphoma involvement.

In December 2006, the patient underwent splenectomy. At laparotomy, spleen appeared occupying the whole left hemiabdomen and displacing the stomach and bowel with an accessory spleen (diameter 10 cm) at inferior pole of spleen (Fig. 1a); at the splenic hilus, multiple confluent lymph nodes surrounded splenic artery and vein and the tail of the pancreas. Spleen, accessory spleen, and hilus lymph nodes were removed; distal pancreatectomy and a wedge-shaped biopsy of third hepatic segment were also performed.

The resected spleen (38×22×8 cm) weighted 4,400 g and showed, on the cut section, a multimicronodular pattern. Histologically, the micronodular lymphoma infiltrate involved both the white pulp and the red one (partially). Nodules consisted of a prevalent small- to medium-sized lymphoid population with round nuclei and moderate clear cytoplasm; a minority (<10%) of large blastic cells were present.

The lymphoma cells were positive for CD20+, CD79a+, bcl2+, DBA44+/-; immunostainings for CD5, CD10, cyclin D1, bcl6, CD23, CD25, TRAP, IgM, and IgD were negative. The growth fraction (evaluated by means of MiB1/Ki67) was 10%. Immunohistochemistry and in situ hybridization search for Epstein-Barr virus (EBV) was negative. A diagnosis of

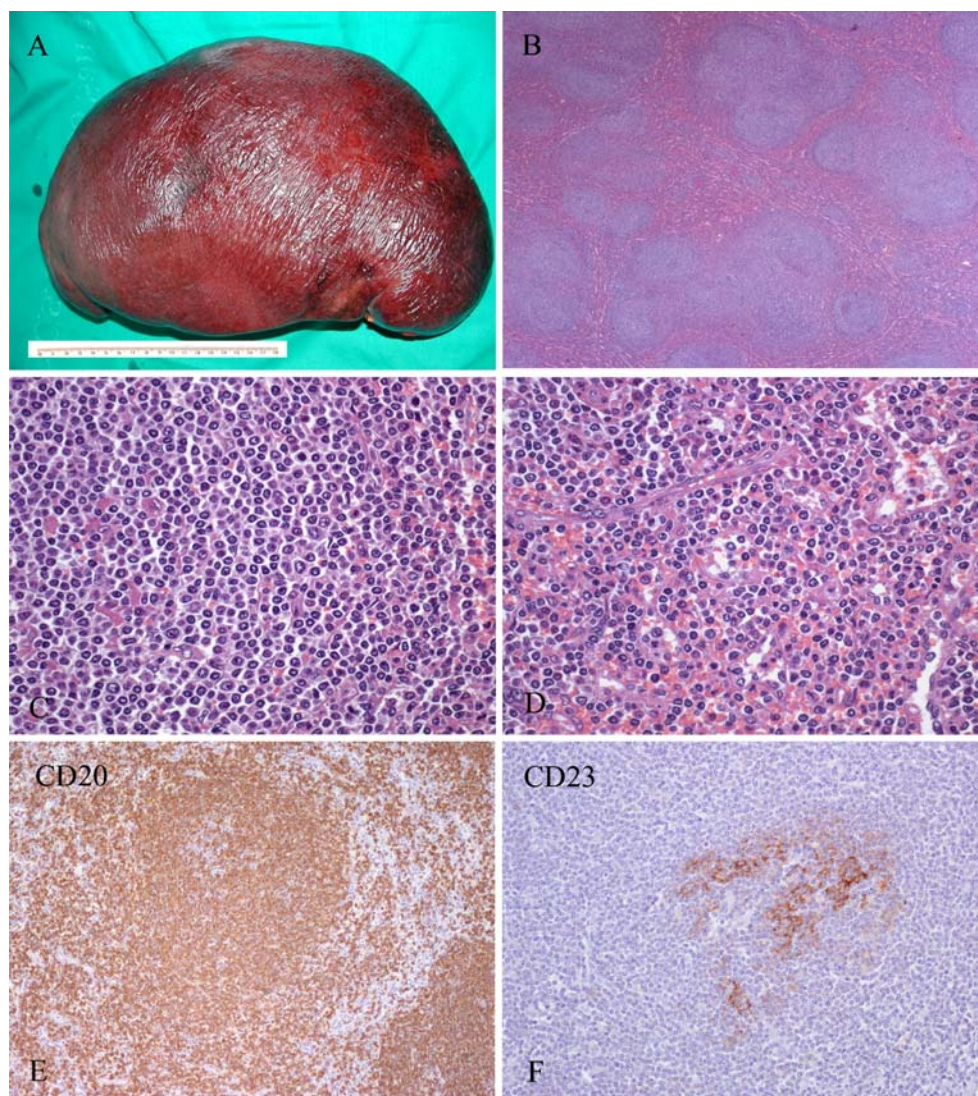
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Fig. 1 a The splenic parenchyma was infiltrated by a lymphoma growing in a micronodular pattern (H & E, $\times 20$). **b** Lymphoma infiltrate comprised a predominant population of small- to medium-sized cells with ovoid nuclei and often abundant pale cytoplasm. Rare large cells with immunoblastic or centroblastic features were observed (H & E, $\times 400$). **c** Lymphoma cells infiltrated red pulp and sinuses (H & E, $\times 400$). **d** Strong expression of CD20 by lymphoma population (SABC method, $\times 100$). *Inset:* in a residual CD23+, dendritic meshwork, consistent with colonization of follicular centers, was present in some nodules (SABC method, $\times 200$)



splenic marginal zone B cell lymphoma was made according to WHO classification (2001). Fig. 1: (a) macroscopic appearance of removed spleen and spleen histology; (b) the splenic parenchyma was infiltrated by a lymphoma growing in a micronodular pattern (HE, $\times 20$); (c) lymphoma infiltrate comprised a predominant population of small- to medium-sized cells with ovoid nuclei and often abundant pale cytoplasm. Rare large cells with immunoblastic or centroblastic features were observed (HE, $\times 400$); (d) lymphoma cells infiltrated red pulp and sinuses (HE, $\times 400$); (e) strong expression of CD20 by lymphoma population (streptavidin–biotin–peroxidase complex (SABC) method, $\times 100$); (f) in a residual CD23+, dendritic meshwork, consistent with colonization of follicular centers, was present in some nodules (SABC method, $\times 200$). Localization of lymphoma was detected in accessory spleen, hilus lymph nodes, and peripancreatic adipose tissue and in liver biopsy. After splenectomy, the patient presented a partial thrombosis of

the splenic vein which resolved with low-molecular-weight heparin.

Virologic reassessment after splenectomy was as follows: HIV-RNA <50 copies per milliliter, HBV-DNA <100 copies per milliliter, EBV-DNA 210 copies per 100,000 cells. Flow cytometry analysis on peripheral blood showed total lymphocyte of 3,643 per microliter, a normal CD4-to-CD8 ratio, CD4-positive T cells of 655 per microliter. A further bone marrow biopsy documented a persistent lymphoid infiltrate (30%) consisting of CD20+ small cells, arranged in paratrabecular and centrolacunar nodules.

Considering the ample surgical debulking without signs of lymphoma progression, no other treatment at that moment was administered.

In June 2008, at the last follow-up, the patient was asymptomatic and the physical examination was negative. Total body CT scan was negative for lymphoma and did not show any signs of thrombosis.

Lymphoma is one of the most frequent HIV-related neoplasia; in HIV patients, various types of lymphoma can occur, frequently including aggressive B cell lymphoma (i.e., diffuse large B cell lymphoma, Burkitt's lymphoma, plasmablastic lymphoma, and Hodgkin's disease) often with primary extranodal clinical presentation (primary effusion lymphoma and primary central nervous system lymphoma) [1, 2]. In contrast, indolent lymphomas are much rarer and only a few cases of mucosa-associated lymphoid tissue lymphoma have been described in both pediatric and adult patients with HIV infection [3–5]. Levine et al. [3] reported from the AIDS Lymphoma Registry at the University of Southern California ten cases of indolent non-Hodgkin lymphoma with only one case of marginal zone lymphoma (MZL).

In the general population, splenic marginal zone B cell lymphoma is a rare indolent lymphoma subtype which accounts for less than 1% of all non-Hodgkin's lymphomas [6]. High HCV seroprevalence is frequently reported in this type of lymphoma: in a recent study, HCV seroprevalence in splenic MZL was 19% [7]. A new clinical entity characterized by concurrent splenic MZL with villous lymphocytes, type II cryoglobulinemia, and HCV infection has been proposed [8]. The reported antilymphoma activity of interferon- α in patients with HCV-positive splenic marginal zone B cell lymphoma [9] as well as in other marginal zone lymphomas [10] supports a role of HCV infection in the lymphomagenesis of marginal zone lymphomas.

The association of HIV infection and splenic marginal zone B cell lymphoma is very rare. So far, only one case has been reported from Memorial Sloan Kettering Cancer Center: the patient presented with malaise, increasing abdominal girth, and pancytopenia and surgically treated with splenectomy [11]. Lymphoid expansion of splenic marginal zone is not reported during HIV infection; on the contrary, in an extensive autopsy survey of HIV-positive subjects, splenic marginal zone atrophy was significant and it has been suggested that reduced marginal zone function could explain the predisposition of HIV-positive patients to infection by encapsulated bacteria [12].

Our case of splenic marginal zone B cell lymphoma confirms the typical features reported for indolent lymphomas in HIV-positive patients in comparison to HIV-positive aggressive lymphomas (bone marrow involvement and higher CD4 cell counts) and to HIV-negative indolent lymphomas (male prevalence, younger age at onset, B symptoms) [3]. In the largest series of splenic marginal zone lymphoma reported so far [5], median age at onset was 64 years with a slight prevalence of females; B symptoms were present in only 20% of patients. In our case, the efficacious anti-HIV therapy

induced immunological reconstitution [13], delaying the diagnosis of lymphoma. As suggested by Levine et al. [3], different pathophysiologic mechanisms may be involved in the development of indolent and aggressive lymphomas among HIV-positive patients and it is arguable that indolent lymphomas may arise in HIV-positive patients regardless of HIV infection.

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