Rare AIDS-Associated Plasmablastic Lymphoma as the Initial Presentation of AIDS

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Introduction

Non-Hodgkin lymphoma (NHL) is the sixth leading cause of cancer death in the United States and accounts for 2–3% of primary neoplasms.[1] Plasmablastic lymphoma (PBL) is a rare AIDS-associated NHL of diffuse large B-cell lymphoma (DLBCL) type. It typically presents in HIV infection in the oral cavity.[2] Here we discuss a case of a young woman who presented with PBL in the rectum as the initial manifestation of AIDS.

Case Report

A 40-year-old woman with no medical history presented to the emergency room with a Bartholin cyst; the cyst was excised and drained. Two months later, the patient presented with complaints of brown vaginal discharge that had persisted for approximately 2 weeks. She also complained of intermittent episodes of rectal bleeding. In the emergency room evaluation, a gynecologist identified a mass that extended onto the vaginal introitus. Another mass was noted during a rectal examination.

A computed tomography (CT) scan of the abdomen and pelvis was obtained to evaluate for a possible enterovaginal fistula. It showed a large mass (10 cm x 9.8 cm) in the pelvis that extended from the vaginal introitus to the sacral promontory (Figure 1). Additionally, 3 soft tissue masses were attached to the large mass. They consisted of a central 4.8 cm x 4.7 cm mass, a mass measuring 2.8 cm x 4.7 cm located anterior to the external iliac artery, and a mass measuring 3.0 cm x 2.1 cm located lateral to the bladder. Ultrasound of the abdomen re-identified a large, ovoid, mixed echogenic mass measuring 8.9 cm x 9.9 cm x 8.6 cm. Sigmoidoscopy showed a large, exophytic mass extending from the dentate line by 5 cm (Figure 2). There was no clear evidence of a fistulous tract. Endoscopic ultrasound was performed and demonstrated involvement of the muscularis propria (Figure 3).

Biopsies of the mass revealed a plasmablastic lymphoma (Figure 4). The cells were strongly positive for multiple myeloma oncogene-1 (MUM-1), CD138 (Figure 5), Epstein-Barr encoded RNA, and aberrant CD3 expression by in situ hybridization. Because this finding is commonly associated with HIV, blood was sent for testing for HIV antibodies. The results were positive. The HIV RNA load was 427,976, and the CD4 count was 60.

The patient underwent staging work-up with CT of the chest and neck, which was negative. A bone marrow biopsy demonstrated hypercellular bone marrow with reactive plasmacytosis and increased hematopoiesis in all cell lines. No tumor or granuloma was seen. The patient began treatment with rituximab (Rituxan, Genentech), etoposide, prednisone, vincristine, cyclophosphamide,

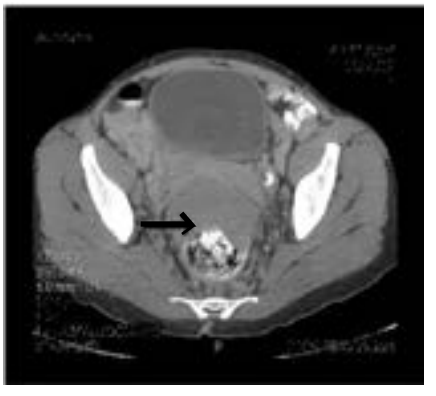

Figure 1. Computed tomography scan of the abdomen shows a large pelvic mass.

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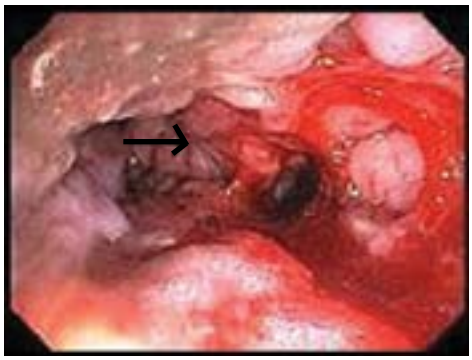

Figure 2. Sigmoidoscopy shows a large, bleeding exophytic mass.

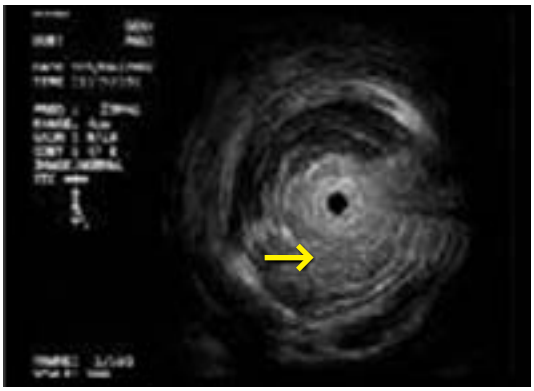

Figure 3. Endoscopic ultrasound shows a mass extending to the muscularis propria.

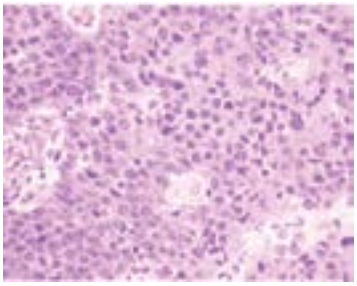

Figure 4. Hematoxylin and eosin stain of the sigmoid colonic mucosa shows a monomorphic population of lymphoid tumor cells (original magnification: X 200).

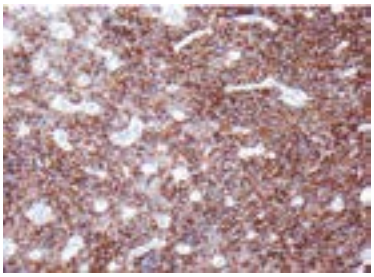

Figure 5. Immunohistochemical stains of the sigmoid colon mucosa show positivity for CD138.

and doxorubicin (R-EPOCH) therapy for plasmablastic lymphoma and highly active antiretroviral therapy (HAART) for HIV. Her vaginal discharge improved and she was discharged in stable condition.

Discussion

PBL most frequently presents in the oral cavity,[3] with local invasion and rapid dissemination to extra-oral sites. It has also been reported in other sites such as the stomach,[4] cervical lymph nodes,[5] lungs,[6] orbit,[7] and paranasal sinuses.[8] Only a few cases of anorectal PBL have been reported.[9-11] Although PBL has been reported mostly in patients with HIV infection, it can also be seen in immunocompromised patients who are HIV-negative.[12] Extra-oral PBL is rare, but it has a similar invasive and rapidly disseminative capability as PBL of the oral cavity, and frequently presents as disseminated disease in HIV/AIDS individuals.[11]

Plasmablastic lymphoma can arise independently or against the background of human herpesvirus 8–driven multicentric Castleman's disease. The characteristic immunophenotype includes the lack of expression of the pan B-cell antigen CD20, but includes expression of both MUM-1 and CD138, markers of plasma cell differentiation. Rearrangement of the immunoglobulin heavy chain is variable. The designation of PBL is based on plasmablastic morphology of the neoplastic cells, as well as an expression of plasma cell differentiation antigens.

Patients with HIV/AIDS are at a significantly increased risk of developing NHL, which is classified as an AIDS-defining illness. The most common types of AIDS-associated NHL are Burkitt lymphoma and DLBCL, which includes immunoblastic lymphoma. Rare types include primary effusion lymphoma (PEL), primary central nervous system lymphoma (PCNSL), and PBL. Viral activation is thought to play a significant role in the development of NHL in HIV patients. Evidence of

Epstein-Barr virus infection is found in approximately 30% of Burkitt lymphoma patients, 40–90% of DLBCL, approximately 90% of PEL patients, almost all patients with PCNSL, and most patients with PBL.[13] According to a recent series of patients with AIDS-associated NHL, PBL accounts for approximately 2–4% of all AIDS-related lymphomas.[13-15]

Historically, the prognosis for patients with AIDS-associated PBL has been poor, with very few long-term survivors; however, the introduction of modern HAART appears to be associated with better prognoses in large series of patients with AIDS-related lymphomas.[15,16] As in other types of NHLs, combination chemotherapy forms the backbone of therapy for PBL, and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)–like regimens are considered first-line therapy. Rituximab, an anti-CD20 monoclonal antibody that has been incorporated into the standard therapy for many B-cell NHLs, does not play a role in PBL therapy because CD20 is not usually expressed by PBL cells.

In addition, there is a case report of a patient with PBL who achieved remission with antiretroviral therapy alone, which suggests that there may be a role for immune reconstitution in the control of this aggressive lymphoma.[17] Thus, initiating or continuing HAART as part of supportive therapy is recommended when treatment for HIV-positive patients with PBL is commenced.

The occurrence of PBL in sites other than the oral cavity expands our knowledge of AIDS-related lymphoproliferative disorders and increases our insights into this rare entity. Pathologists should be aware that this tumor does appear in sites other than the oral cavity. Because of its cohesive histologic appearance, this tumor can be misinterpreted as a nonlymphoid tumor, particularly with the leukocyte common antigen negativity that is typical of this neoplasm.

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Review

Plasmablastic Lymphoma of the Oral Cavity Type as the Presenting Manifestation of HIV Infection

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The case study by Khan and colleagues[1] describes an interesting case of HIV-associated plasmablastic lymphoma (PBL) of the pelvis, which occurred as the initial presentation of AIDS. A 40-year-old woman, with no medical history, presented with a large mass in the pelvis that extended from the vaginal introitus to the sacral promontory in absence of a computed tomography scan, and sigmoidoscopic evidence of enterovaginal fistula.

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Table 1. Lymphomas Specifically Occurring in HIV-Positive Patients and Showing a Phenotype Related to Plasma Cells

Lymphoma Type	Infection By	
	EBV	HHV-8
Burkitt lymphoma, plasmacytoid	+	-
Systemic immunoblastic lymphoma, plasmacytoid	+	-
Primary central nervous system lymphoma (immunoblastic lymphoma, plasmacytoid)	+	-
Primary effusion lymphoma and its solid variant	+	+
Plasmablastic lymphoma of the oral cavity type	+	-
Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman's disease	-	+

EBV=Epstein-Barr virus; HHV-8=human herpesvirus 8; -=negative; +=positive.

Additionally, 3 smaller masses were found attached to the large mass. Biopsies of the mass revealed an Epstein-Barr virus (EBV)–associated PBL. After the diagnosis of PBL, blood was sent for testing for HIV antibodies, with positive results; the CD4 count was 60. The patient was started on rituximab (Rituxan, Genentech), etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) therapy for PBL and highly active antiretroviral therapy (HAART) for HIV infection. She was discharged in stable condition.

PBL is one of the unusual lymphoproliferative entities occurring in the setting of HIV infection.[2,3] Initially, PBL has been described as a rapidly progressive and almost invariably fatal CD20-, VS38c+ diffuse large-cell lymphoma with plasmablastic features, exclusively involving the jaw and oral mucosa in HIV-positive patients.[4] Several studies have also reported that this neoplasm has occurred in patients without HIV infection and in sites other than the head and neck.[5-8]

This lymphoma has a heterogeneous morphologic presentation but a distinct phenotype. Morphologically, most PBL cases are composed of a monomorphic, sheet-like proliferation of immunoblasts. Tumor cells express a plasma cell–related phenotypic profile (CD38+, MUM1+, EMA+/-, CD30+/-, CD45+/- [weak], and conventional B-cell and T-cell markers). The lymphoma cells are positive for CD138 and weakly positive or negative for CD79a. The neoplastic cells are positive for EBV and negative for Kaposi sarcoma–associated herpesvirus (KSHV)/human herpesvirus 8 (HHV-8; Table 1). EBV viral association is found in 80% of PBL patients.

Among HIV–non-Hodgkin lymphoma patients, the other tumors with plasmablastic differentiation tend to have a predominance of immunoblasts but show some cells with plasmacytoid differentiation. The body cavity and extracavitary primary effusion lymphomas had significant nuclear pleomorphism, with plasmacytoid morphology in some cells. PBL with plasmacytoid differentiation and diffuse large B-cell lymphoma with secretory differentiation (immunoblasts and plasmacytoid cells) could be distinguished by the presence of centroblasts in the latter. CD138 and MUM1, markers of post–germinal center/terminal B-cell/plasmacytoid differentiation, are useful in identifying the lymphoid and B-cell origin of these tumors, which show variable or negative expression of CD20 and CD45. Because of the common absence of these markers and its histologic features, PBL, in particular, can be misinterpreted as a nonlymphoid tumor (Table 2).

Uncommonly, primary effusion lymphoma (PEL) may present as a solid form that predominantly involves the distal digestive tract and poses major diagnostic problems, especially when it is unassociated with body cavity effusions. The solid forms of both PEL and PBL display plasmablastic features. Demonstration of KSHV/HHV-8 presence excludes a PBL and establishes the diagnosis of a solid form of PEL. The need to investigate KSHV/HHV-8 in any plasmablastic-looking lymphoma, especially in HIV-infected patients, is relevant.[9-11]

As noted earlier, the prognosis of PBL had initially been very poor. However, increased survival times have

Table 2. Differential Diagnosis

- Plasmablastic lymphoma
- Primary or metastatic, undifferentiated carcinoma
- Metastatic melanoma
- Diffuse large B-cell lymphoma
- Burkitt lymphoma

been observed in HIV-infected patients with the combination of HAART and chemotherapy. Lymphoma-specific chemotherapy has included cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); CHOP with intrathecal methotrexate, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP); and EPOCH.[8] The role for rituximab, an anti-CD20 monoclonal antibody, in PBL has not been defined. PBL is a subtype of diffuse large B-cell lymphoma, and rituximab may provide some benefit, although it may not play a role in PBL therapy because CD20 is not usually expressed by PBL tumor cells. On the contrary, it is imperative to include prophylaxis against opportunistic infections for HIV patients receiving chemotherapy. A characteristic feature of PBL is its rapidly progressive clinical course. However, recent reports have noted improved survival when treatment with both HAART and appropriate chemotherapy is used, similar to outcomes of HIV-infected patients with other non-Hodgkin lymphomas.

In conclusion, the consistent association of PBL with HIV (80–90%) and immunosuppression (90%), and the apparent improved prognosis when HAART is combined with chemotherapy indicate that patients diagnosed with PBL should be tested for HIV. In fact, the diagnosis of PBL may be the presenting manifestation of HIV infection,[8,12] such as in the case reported by Khan and colleagues.[1]

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