Lymphoma Presenting as Cranial Nerve Neuropathies in HIV-Infected Patients

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Patients with HIV infection are at increased risk for several types of malignancy. After Kaposi sarcoma, non-Hodgkin lymphoma (NHL) is the second most common HIV-associated cancer.1 HIV-related lymphomas can be classified into 3 types: systemic NHL, the most common, followed by primary CNS lymphoma and primary effusion lymphoma.2

In the HIV-infected population, those with systemic NHL usually present with extranodal disease involving the bone marrow, meninges, or GI tract as well as with systemic symptoms. Patients with HIV infection and primary CNS lymphoma typically present with focal neurological symptoms and associated single or multiple contrast-enhancing lesions in the brain parenchyma. Isolated cranial nerve involvement is an uncommon presentation for lymphoma. We discuss here 2 patients who manifested isolated cranial neuropathy as their initial clinical presentation of lymphoma.

CASE SUMMARY

Patient M

M was a 38-year-old woman with a history of poorly controlled HIV infection diagnosed in 2000. She did not have a history of opportunistic infections despite a reported nadir CD4+ cell count of 36/µL. Multiple antiretroviral regimens had been prescribed for her, but her adherence was consistently poor.

M presented to the HIV clinic complaining of 2 weeks of worsening blurry vision and diplopia associated with difficulty raising her left eyelid. Her CD4+ cell count was 18/µL and HIV RNA level was 23,000 copies/mL. Results of visual testing and ophthalmoscopic examination were normal. She denied eye pain, headaches, neck stiffness, hearing loss, tinnitus, and confusion. She reported a recent hospitalization for fevers and cough, and at that time she was treated for presumed community-acquired pneumonia. She was admitted to the hospital for further evaluation.

M’s examination revealed a low-grade fever (temperature of 38.3°C [101°F]) with a normal physical examination other than an isolated left-sided third cranial nerve palsy. Ophthalmological examination demonstrated a left eye ptosis, a dilated and fixed 5-mm left pupil, and nystagmus in the right upward and downward gaze. An initial laboratory evaluation with complete blood cell count, chemistries, and liver function tests revealed no leukocytosis, a normocytic anemia with a hemoglobin level of 9.7 g/dL (normal, 11.7 to 16.0) and mean corpuscular volume of 81 fL (normal, 81 to 100), and a lactate dehydrogenase level of 464 U/L (normal, 96 to 200). All other test results were within normal limits. Cerebrospinal fluid (CSF) analysis revealed no white blood cells, normal protein and glucose levels, and significantly increased Epstein-Barr virus (EBV) DNA levels (more than 200,000 copies/mL using polymerase chain reaction [PCR] assay). Culture and PCR test results for JC virus, Cytomegalovirus, and varicella in the CSF were negative. CSF cytology was negative for malignant cells. An MRI demonstrated focal enhancement of the left third cranial nerve. This finding was felt to be consistent with an inflammatory process although neoplastic involvement could not be ruled out.

Her hospital course was significant for progression of the left-sided third cranial nerve palsy to involve the left-sided fourth, fifth, and sixth cranial nerves and the right-sided third cranial nerve. Positron emission tomography (PET)/CT scans obtained on hospital day 6 showed hypermetabolic nodes encasing the small bowel and mesenteric lymphadenopathy, with increased uptake in left paraspinal muscles, the sphenoidal sinus, and external iliac lymph nodes.

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Figure 1. Postcontrast T1-weighted MRI scan of the brain, axial image. The image shows enhancement and thickening of cranial nerve III bilaterally. (Courtesy of Dr Linda Heier, department of radiology, New York-Presbyterian Hospital/Weill Cornell Medical Center.)

After 17 days in the hospital, a repeat MRI scan of the head showed progressive left-sided cranial nerve III enhancement with new diffuse leptomeningeal disease consistent with lymphoma (Figure 1). On hospital day 19, the patient underwent a partial small-bowel resection with biopsy; the biopsy specimen showed mixed natural killer (NK)/T-cell lymphoma with high proliferative index. Bone marrow biopsy was consistent with peripheral T-cell lymphoma. She was started on an antiretroviral regimen while in the hospital and began a regimen of modified DeAngelis chemotherapy using methotrexate, vincristine, procarbazine, and intrathecal liposomal cytarabine. Within 13 weeks, resolution of right eye symptoms and decreased ptosis of the left eye were noted, but immobility of the left eye persisted. By the end of her treatment course, she had no cranial nerve symptoms. MRI and PET/CT scans of the brain obtained 17 weeks after treatment showed no evidence of lymphoma.

Patient R

R was a 44-year-old man in whom HIV infection was diagnosed in 2003. He had started antiretroviral therapy when his CD4+ cell count fell below 350/µL, approximately 10 months before his presentation to his primary care physician with nausea, vomiting, and weight loss. Upper endoscopy revealed an ulcer of the stomach. He was treated with proton pump inhibitors and antiemetics, but his nausea and vomiting persisted and he continued to lose weight.

Two weeks after his initial endoscopy, R presented to the emergency room with headache, left facial numbness and drooping, and an inability to close his left eye. He also complained of nausea, vomiting, and anorexia. He had no nuchal rigidity, rashes/vesicles, vision changes, eye pain, hearing loss, or confusion.

Figure 2. Postcontrast T1-weighted MRI scan of the brain, axial images. A: Abnormal enhancement and enlargement of cranial nerve III bilaterally. B: Diffuse enlargement of cranial nerve V bilaterally from its origin.
A review of systems revealed a 30-lb weight loss over the past month and paresthesias over both arms with no loss of sensation or strength. On examination, left-sided seventh cranial nerve palsy, with left-sided facial paralysis and inability to close the left eye, was noted. No visible vesicles or rashes were seen. An MRI scan of the brain revealed enlargement of cranial nerve V bilaterally with enhancement of cranial nerves III, V, VII, VIII, IX, X, and XI (Figure 2). CSF analysis revealed the following: red blood cell count of 3/µL (normal, 0 to 10); protein concentration of 355 mg/dL (normal, 40 to 70); glucose level of 22 mg/dL (normal, 40 to 70); and white blood cell count of 211/µL (normal, less than 5/µL), 84% of which were large, immature, blastlike cells. Morphological examination of the white blood cells showed abundant cytoplasm, nucleoli, and convoluted nuclei with some cells in mitosis (Figure 3).

The results of Gram staining, cultures, viral PCR assays (including assays for EBV DNA), and a VDRL test were negative. The CSF flow cytometry was consistent with diffuse large B-cell lymphoma. A PET/CT scan revealed diffuse hypermetabolic activity, consistent with leptomeningeal enhancement of multiple cranial nerves and the cervical, thoracic, and lumbar spine. A bone marrow biopsy was performed, but the specimen showed no evidence of lymphoma. The patient was started on a regimen of DeAngelis chemotherapy and intrathecal liposomal cytarabine. His nausea and vomiting resolved almost immediately, and he began to gain weight. The seventh nerve palsy persisted but was notably improved.

### EPIDEMIOLOGY OF HIV-RELATED NHL

According to the World Health Organization classification of tumors, the most common HIV-associated NHLs are Burkitt lymphoma, diffuse large B-cell lymphoma (often involving the CNS), primary effusion lymphoma, and plasmablastic lymphoma of the oral cavity. These are all aggressive B-cell tumors. The incidence of NHL is 60 to 200 times higher in HIV-infected persons than in the general population; it is the initial AIDS-defining diagnosis in approximately 4% of persons and is fatal in 12% to 16% of HIV-infected persons.

In the post-HAART era, it has been postulated that as persons with HIV infection live longer, there would be an increased incidence of lymphoma. Data for this increase have been lacking. In fact, one large collaborative study compared the incidence of cancer in 48,000 HIV-positive adults in the pre- and post-HAART eras. The study’s results showed that there was a 42% decline in the incidence of NHL (both primary CNS lymphoma and systemic lymphoma) when the period 1997 to 1999 was compared with the period 1992 to 1996. This difference was attributed to the introduction of highly active antiretroviral treatments during the interval between the 2 study periods. One explanation for antiretroviral therapy being the driver of this decrease in NHL is that effective treatment of HIV infection reduces the proportion of the HIV population with low CD4 counts—the group most likely to develop high-grade NHL.

Patients with HIV-related lymphoma typically have advanced HIV disease, but there are differences among the various lymphomas. HIV-infected patients with NHL usually have CD4+ cell counts below 100/µL. Those with primary CNS lymphoma are even more immunosuppressed, with CD4+ cell counts of less than 50/µL at the time of diagnosis. In one study, the incidence of a prior AIDS diagnosis was higher (73% vs 37%), the median number of CD4+ lymphocytes was lower (30/µL vs 189/µL), and the median survival time was shorter (2.5 months vs 6.0 months) for HIV-infected
patients with primary CNS lymphoma versus those with systemic lymphomas.9

**ETIOLOGY OF HIV-ASSOCIATED LYMPHOMAS**

The etiology of HIV-associated lymphoid neoplasms is multifactorial and is thought to be associated with a deficient immune surveillance of oncogenic viruses (eg, EBV and human herpesvirus 8/Kaposi sarcoma-associated herpesvirus), defective immune regulation, and chronic antigenic stimulation. EBV is thought to be a cofactor in the etiology of some types of NHL. The EBV genome has been detected in varying numbers of persons with AIDS-related lymphomas, and molecular analysis suggests that the cells were infected before clonal proliferation began.10 The rates of EBV infection in NHLs differ according to the histological features of the neoplasm, ranging from 30% in AIDS-related Burkitt lymphoma to 80% in systemic diffuse large B-cell lymphoma. In nearly all cases of primary CNS lymphoma, tests of the CSF are positive for EBV.11

**PRIMARY CNS LYMPHOMA**

Primary CNS lymphoma is an uncommon clinical entity and is defined as a lymphoma limited to the cranial-spinal axis without systemic disease. The incidence of primary CNS lymphoma in HIV-infected persons is 2% to 6% but has been reported to be as high as 10% in autopsy series.12,13 While primary CNS lymphoma more commonly presents as a single contrast-enhancing lesion on an MRI scan, it can also present as multiple lesions. Other anatomical distributions include leptomeningeal disease, oculary lymphoma and, rarely, spinal cord disease.

Leptomeningeal lymphoma, which is defined as primary CNS lymphoma limited to the meninges without cerebral parenchymal disease or systemic lymphoma, is rare and accounts for approximately 7% of all cases of primary CNS lymphoma in immunocompetent persons. Such cases have been described in persons with HIV infection as well, but their incidence is unknown.14

Epidemiologically, the typical age of HIV-infected persons at presentation with primary CNS lymphoma is 31 to 35 years, with a male predominance (male to female ratio of 7.38:1).15 In persons with AIDS, advanced disease is the most important predisposing factor, demonstrated by a median CD4+ cell count of 30/µL.16

The pathogenesis of primary CNS lymphoma has been strongly linked to EBV infection. One study found PCR detection of EBV DNA in the CSF to be 80% sensitive for AIDS-associated primary CNS lymphoma and 100% specific.17 Thus, CSF PCR testing for EBV DNA appears to be a sensitive and specific test for AIDS-associated primary CNS lymphoma and may obviate the need for biopsy.

**NK/T-CELL LYMPHOMA**

M’s case was atypical, not only because of her presentation with cranial neuropathy but also because of the histological classification of her lymphoma. The overwhelming majority of lymphomas in persons with HIV infection are B-cell in origin. From a study of 6788 cases of AIDS-related lymphomas in the United States, only 1.4% were found to be T-cell lymphomas.18 There is scant literature on NK/T-cell lymphomas associated with HIV. Our search revealed a single case report from India of a 42-year-old HIV-infected man receiving antiretroviral treatment, with a CD4+ cell count of 40/µL, who presented with third and fifth cranial nerve palsy.19 This case was remarkably similar to M’s presentation. Of note, in Asia and in some areas of South and Central America, there are higher rates of extranodal NK/T-cell lymphoma (specifically the nasal type), which is rarely seen in the United States or Europe.20-22

**CLINICAL PRESENTATIONS OF LYMPHOMA**

The vast majority of patients with HIV-related systemic lymphoma present with advanced stage extranodal disease involving the bone marrow (30%), meninges (10% to 20%), or GI tract (10% to 25%).23,24 These persons also typically present with systemic B symptoms, including unexplained fever, drenching night sweats, and/or weight loss in excess of 10% of normal body weight.24 CNS presentation occurs in approximately 33% of AIDS-related lymphomas, and the most common presentation is lymphomatous leptomeningitis.25 Clinical features of symptomatic lymphomatous leptomeningitis include headache, altered mental status, seizures, cranial neuropathies, and radiculopathies. The major differences between systemic NHL and primary CNS lymphoma are summarized in Table 1.
Lymphoma presenting as isolated cranial neuropathies is uncommon. Williams and colleagues reported an incidence of 1.2% for isolated cranial nerve involvement in their review of 5778 cases of lymphoma and leukemia. NHLs may involve the cranial and peripheral nerves directly through neoplastic infiltration or compression from adjacent lymph nodes or other masses of lymphoid tissue, or indirectly through paraneoplastic or infectious effects.

Lymphomatous infiltration of cranial or peripheral nerves is an infrequent occurrence and has been termed “neurolymphomatosis.” In a review of neurolymphomatosis cases associated with NHL, researchers found that 21% of cases presented with involvement of a single cranial nerve. The incidence of cranial nerve palsies among persons with primary CNS lymphoma has been reported to range from 5% to 31%.

Both systemic NHL and primary CNS lymphoma can result in cranial nerve dysfunction caused by leptomeningeal disease, and cranial nerve VII is the most commonly affected, as was the case with our second patient, R. Interestingly, M’s isolated cranial nerve III involvement as the initial manifestation of NK/T-cell lymphoma involving the CNS is rare, and one review found only 10 cases reported in the literature.

Differential Diagnosis

In HIV-infected patients with advanced disease, the differential diagnosis of cranial neuropathy contains a wide variety of possibilities, including infectious and neoplastic meningitides and mass lesions (Table 2). One review of cranial neuropathies occurring in 31 adults with AIDS characterized 18 as multiple and 13 as single, with the sixth and seventh cranial nerves most commonly affected. Lymphoma was the etiology in 26% of these adults.
TREATMENT AND PROGNOSIS

Treatment of systemic NHL in HIV-infected persons can be difficult because of baseline immunodeficiency, leukopenia, and the tendency for the lymphomas to involve the bone marrow and nervous system. Chemotherapy regimens often cause profound neutropenia and result in complications related to opportunistic infections. Currently, treatment with low-dose or standard-dose m-BACOD chemotherapy (ie, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) is recommended. The low-dose regimen is associated with fewer cytological toxic effects and has similar efficacy when compared with the standard-dose regimen in HIV-infected patients with lymphoma. Alternative chemotherapy regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Not surprisingly, the median duration of survival with chemotherapy has improved in the post-HAART era to 15 to 34 months, from 2 to 13 months in the pre-HAART era.

Historically, the standard treatment for primary CNS lymphoma had been whole brain radiation therapy, which results in complete radiographic response in more than 80% of patients. However, recurrence is common, and median survival can be expected to be less than 18 months from time of diagnosis with a 5-year survival rate less than 5%. Various chemotherapy treatments have been studied, and the consensus is that methotrexate-based therapies are the most active. Currently, chemotherapy with the DeAngelis regimen (intravenous and intrathecal methotrexate, procarbazine, vincristine, followed by whole brain radiation therapy and cytarabine) is widely used. Both of the case patients presented here received modified versions of the DeAngelis regimen for treatment.

CONCLUSION

Although isolated cranial nerve palsy is an uncommon presentation for lymphoma, the diagnosis should be considered in HIV-positive persons regardless of their level of immunosuppression. Both of the patients presented here—one with advanced disease and one with good HIV control—have thus far responded well to therapy for their lymphoma.


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