CASE REPORT

Isolated Abducens Palsy Heraldng Occult Human Immunodeficiency Virus–Related Lymphoma

Brandon J. Baartman^{a,b} and Chrysavgi Adamopoulou^b

^aCole Eye Institute, Cleveland Clinic, Cleveland, Ohio, USA; ^bDepartment of Ophthalmology, MetroHealth Medical Center, Cleveland, Ohio, USA

ABSTRACT

A 40-year-old African American man with recently diagnosed Human Immunodeficiency Virus (HIV) presented with isolated left abducens palsy. Initial neuro-imaging and laboratory evaluation, including cerebrospinal fluid (CSF) analysis, were unremarkable. Continued search for causative aetiology revealed systemic lymphoma diagnosed ultimately by bone marrow biopsy. Systemic lymphoma is commonly encountered in the HIV patient population, but presentation can be unusual and has been seen, albeit rarely, in the setting of isolated cranial neuropathy. This case demonstrates the often diligent investigation required in the setting of isolated cranial neuropathies in patients with HIV.

ARTICLE HISTORY

Received 7 April 2016
Revised 18 April 2017
Accepted 18 April 2017

KEYWORDS

Abducens palsy; HIV-related lymphoma; occult malignancy

Introduction

Human Immunodeficiency Virus (HIV) may cause a large number of ocular and neurologic symptoms that, when present, can evoke a broad differential diagnosis, and ophthalmologists are often involved in the detection and documentation of these manifestations.¹ Importantly, infectious aetiologies are often the early focus of evaluation, depending on severity of immunosuppression. Isolated cranial neuropathy can present a stressful and challenging evaluation, which may be magnified by the presence of HIV. In the report presented herein, we review the literature and present a case of an isolated left abducens palsy heralding an occult systemic non-Hodgkin lymphoma in the setting of HIV.

Case report

A 40-year-old African American man with a past medical history of HIV compliant on highly active anti-retroviral therapy (HAART) presented to the emergency department with complaints of non-focal headache, body aches, and double vision for the past 2 weeks. The patient had been wearing an eye patch over his left eye to relieve his symptoms

of double vision. Ocular review of systems was positive for photophobia and occasional aching of the left eye. Systemically, he endorsed night sweats, fatigue, and nausea. He denied symptoms of ocular redness, flashing lights, floaters, blurred vision, or pain with extraocular movements.

Visual acuity without correction was measured to be 20/20 in both eyes. Intraocular pressure was normal. There was no afferent pupillary defect, and visual fields were full to confrontation. Anterior examination was significant for conjunctival pallor; the remainder of the ocular examination was unremarkable. Ocular motility evaluation is represented in Figure 1. The patient demonstrated a 20 prism dioptre (PD) left esotropia in primary gaze, increasing to 50 PD in left gaze without evidence of vertical deviation, suggestive of a left sixth nerve palsy. The fundus examination was unremarkable in both eyes.

The patient was admitted for further medical work-up. Laboratory evaluation revealed mild pancytopenia with blood smear revealing a neutrophilic leukocytosis. CD4 count was 416 cells/mm³ (reference range: 599–1662 cells/mm³) and viral load 959 copies/mL (reference range: <1 copies/mL). Blood cultures drawn at time of admission were negative,

CONTACT Chrysavgi Adamopoulou, MD chadamopoulou@gmail.com Department of Ophthalmology, MetroHealth Medical Center, 2500 MetroHealth Dr., Cleveland, OH 44109, USA.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ioph.

© 2017 Taylor & Francis

Figure 1. Ocular motility examination in the patient demonstrated limitations in abduction of the left eye, suggestive of left sixth nerve palsy.

urinalysis was normal, and an Epstein-Barr Virus (EBV) screen was unremarkable. Serum Venereal Disease Research Laboratory (VDRL), tuberculosis QuantiFERON, and urine *Histoplasma* antigen were negative. Leukaemia and lymphoma panels demonstrated a mixed population of T, B, and natural killer (NK) cells without evidence of clonality, with presence of some activated T cells; the myeloid fraction demonstrated an elevated level of myeloid precursor cells.

A magnetic resonance imaging test with angiography (MRI/MRA) of the brain and orbits failed to reveal evidence of acute ischaemia or inflammatory process; however, there were multiple patchy areas of abnormal signal intensity in the bones of the calvarium and skull base with abnormal soft tissue enhancement in the bilateral cavernous sinuses, left greater than right

(Figure 2). A lumbar puncture was performed, and cerebrospinal fluid (CSF) Gram stain and culture were unremarkable; spinal fluid was also negative for *Cryptococcus*, syphilis, and acid-fast bacilli. CSF cytology panel was negative for malignancy.

During hospitalisation, the patient developed a mild abdominal discomfort that together with persistent suspicion for lymphomatous process prompted a computed tomography of the chest, abdomen, and pelvis. Abnormal findings included bilateral hydronephrosis, bibasilar atelectasis, bilateral pleural effusions, prominence of precarinal lymph nodes, and bilateral axillary lymphadenopathy, which heightened suspicion for systemic lymphoma despite the prior negative laboratory results. The patient underwent bone marrow biopsy, which revealed the presence of large

Figure 2. (A) T2-weighted coronal image demonstrating multiple patchy areas of irregular enhancement in the calvarium (arrow). (B) T1-weighted axial image demonstrating abnormal soft tissue of the bilateral cavernous sinuses (arrow).

B-cell lymphoma. Unfortunately, after the diagnosis was made, this patient left the hospital against medical advice and was lost to further follow-up.

Discussion

In the immunocompromised patient, the presence of a cranial neuropathy must incite a wide differential diagnosis as previously described.^{2,3} Diagnoses of critical consideration include infectious causes such as syphilis, tuberculosis, *Cryptococcus*, herpes simplex, and herpes zoster, as well as other inflammatory causes such as sarcoidosis. Initial testing in this patient included neuro-imaging, which failed to demonstrate any focal lesions of the brain or meninges; however, the abnormal soft tissue of the cavernous sinus and patchy enhancement of the bones of the calvarium were suggestive of lymphomatous infiltration when considered in retrospect.

Lymphoma is a known cause of morbidity and mortality in the HIV patient population and is known to occur at rates as high as 60 times that of the general population.⁴ It has been suggested that a lack of immune surveillance for oncogenic viruses, such as EBV and human herpesvirus 8/Kaposi sarcoma-associated herpes virus, may play a role in the development of HIV-related malignancies.² Of the various categories of lymphoma, HIV-related lymphoma most commonly presents as a systemic non-Hodgkin lymphoma (NHL),² with Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL) being the most commonly encountered subtypes.^{1,2} The majority of patients with HIV-related NHL present with constitutional symptoms and advanced extranodal disease involving the bone marrow, meninges, and/or the gastrointestinal tract.³

Neurologic manifestations of HIV-related lymphoma are variable in presentation but can be found in up to one third of HIV-related lymphoma presentations.³ Primary central nervous system (CNS) lymphoma, a distinct category of HIV-related malignancy that must be considered in cases of advanced disease, is isolated to the cranial-spinal axis and may present as single or multiple lesions isolated in the cerebral parenchyma, intraocular lymphoma, or leptomeningeal disease,² and it often arises in patients with CD4 counts less than 50/uL.⁵ In this setting, neurologic symptoms are common

and can include single or multiple cranial neuropathies, which can be present in up to 31% of cases.² The disease is often diagnosed with single or multiple lesions on MRI of the brain and can be confirmed with CSF cytology.²

Less commonly, neurologic disease in the HIV patient may also be caused by the development of systemic NHL with secondary CNS involvement, as in the case presented here. This type of lymphoma often arises in patients with less advanced HIV disease and higher CD4 counts.²

The isolated cranial nerve involvement as seen in our case is infrequently reported in the setting of HIV-related systemic lymphoma. Across all patients with systemic lymphoma, cranial neuropathy has been cited to occur in only 1.2% of cases.⁶ Reports of isolated cranial neuropathy in the setting of HIV-related lymphoma is exceedingly rare, with reported cases involving cranial nerves III, VI, and VII.^{2,3,7} It has been speculated that the cranial neuropathy in these cases may be secondary to leptomeningitis in association with lymphomatous bone marrow involvement.³ It is also possible that in our patient's case of isolated abducens palsy, lymphomatous involvement of the bones of the skull base along the pathway of the abducens nerve (e.g., Dorello's canal or the walls of the cavernous sinus) may have resulted in compression of the nerve and eluded diagnosis by either imaging or CSF sample.

Systemic lymphoma underlying new-onset neurologic symptoms can be exceedingly difficult to detect. In evaluation of CSF for neoplastic cells, false-negative rate has been reported as high as 50%.⁸ Berger and colleagues reported three patients with isolated cranial neuropathy eventually diagnosed with acquired immunodeficiency syndrome (AIDS)-related systemic lymphoma, all of which had initially unremarkable CSF cytology, one even undergoing six total lumbar punctures, all repeatedly negative for lymphomatous cells.³ Each of the cases described in this report were eventually diagnosed by bone marrow biopsy, similar to the case presented here, likely owing to the frequent association between bone marrow and CNS infiltration by systemic lymphoma.^{4,9} The ability of MRI to detect lymphomatous involvement of the CNS has been discussed previously, with variable

sensitivity in demonstrating leptomeningeal disease ranging from 23% to 71%.⁷ Cases of cranial neuropathy secondary to AIDS-related lymphoma have been reported to improve or resolve with institution of directed chemotherapy,² and AIDS-related lymphomas have been recently reported to resolve with only institution of HAART.¹⁰

In summary, this case illustrates the importance of considering lymphoma in any new-onset cranial neuropathy among patients with HIV. This should be included in the differential diagnosis even in the absence of advanced-stage disease and should remain in the absence of negative CSF cytology. Because of the low sensitivity of CSF studies in detecting malignant cells, we echo previous sentiments and advocate a diligent search for lymphoma in this particular clinical setting.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

[1] Moraes HV. Ocular manifestations of HIV/AIDS. *Curr Opin Ophthalmol* 2002;13:397–403.

[2] Lee WW. Lymphoma presenting as cranial nerve neuropathies in HIV-infected patients. *AIDS Reader* 2008;18:606–610, 621.

[3] Berger JR, Flaster M, Schatz N, Droller D, Benedetto P, Poblete R, Donovan Post MJ. Cranial neuropathy heralding otherwise occult AIDS-related large cell lymphoma. *J Clin Neuro-ophthalmol* 1993;13:113–118.

[4] Little RF, Gutierrez M, Jaffe ES, Pau A, Horne M, Wilson W. HIV-associated non-Hodgkin lymphoma: incidence, presentation, and prognosis. *JAMA* 2001;285:1880–1885.

[5] Demario MD, Liebowitz DN. Lymphomas in the immunocompromised patient. *Semin Oncol* 1998;25:492–502.

[6] Williams HM, Diamond HD, Craver LF, Parson H. *Neurological Complications of Lymphomas and Leukemias*. Springfield, IL: Charles C. Thomas; 1959:4–5, 73–85.

[7] Bhatti MT, Schmalfuss IM, Eskin TA. Isolated cranial nerve III palsy as the presenting manifestation of HIV-related large B-cell lymphoma: clinical, radiological and postmortem observations: report of a case and review of the literature. *Surv Ophthalmol* 2005;50:598–606.

[8] Aparicio A, Chamberlain MC. Neoplastic meningitis. *Curr Neurol Neurosci* 2002;2:225–235.

[9] Levitt LJ, Dawson DM, Rosenthal DS, Moloney WC. CNS involvement in the non-Hodgkin's lymphomas. *Cancer* 1980;45:545–552.

[10] Hallit RR, Afridi M, Sison R, Szabela ME, Bajaj N, Alchaa R, Hallit S, Awkar N, Boghossian J, Slim J. AIDS-related lymphoma: resolution with antiretroviral therapy alone. *J Int Assoc Provid AIDS Care* 2014;13:313–315.