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SHORT COMMUNICATION

Burkitt's lymphoma presenting as oculomotor palsy in an HIV-positive patient

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PURPOSE. *To report a case of Burkitt's lymphoma (BL) in an HIV-positive patient presenting as complete third nerve palsy.*
METHODS. *Interventional case report. A 34-year-old man presented with headache, left eye pain, diplopia, and complete ptosis of several hours' duration. Left eye examination disclosed complete third nerve palsy with pupillary involvement. Significant hepatomegalia was noted at physical examination and computed tomography (CT) scan of the abdomen showed multiple solid lesions.*
RESULTS. *Liver biopsy was consistent with Burkitt's lymphoma. Bone marrow biopsy was normal. Brain imaging was normal. Work-up also revealed positivity for human immunodeficiency virus. Chemotherapy treatment was started. Two months later, ocular motility examination was normal.*
CONCLUSIONS. *Although BL affects the central nervous system very rarely, BL should be considered in any immunosuppressed patient presenting with diplopia or ophthalmoparesis.*
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KEY WORDS. *Burkitt's lymphoma, Human immunodeficiency virus, Ophthalmoparesis, Third nerve palsy*

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INTRODUCTION

Burkitt's lymphoma (BL) is an uncommon high-grade non-Hodgkin's lymphoma. Initial manifestation of BL with central nervous system (CNS) involvement is rare. BL presenting with ophthalmoparesis is even rarer, with only a few reports in the literature.

Case report

A 34-year-old man presented to the emergency room with a history of headache, left eye pain, and complete ptosis of several hours' duration. One month earlier he was admitted to the Neurology Department because of headaches and vomiting. Visual examination was then normal. Physical examination showed meningeal signs. Work-up studies disclosed positivity for human immunodeficiency virus (HIV). Computed tomography (CT) and magnetic resonance imaging (MRI) brain scans were normal. Highly active antiretroviral therapy (HAART) was started but the patient discontinued the treatment. Four weeks later, the patient complained of severe headaches, left eye pain, and diplopia. Visual acuity was 6/6 bilaterally. Left eye presented with complete ptosis, exotropia, and mild hypotropia (Fig. 1). Complete absence of supraduction, infraduction, and adduction was observed. Abduction was normal, and a minor incyclotorsion was noted. The left pupil was middilated and was minimally reactive to light. The rest of the ophthalmic examination was normal. CT scan of brain and orbit showed enlargement of the left inferior rectus muscle (Fig. 2). At physical examination significant hepatomegalia was noted. CT scan of the abdomen showed multiple solid liver lesions. Biopsy of one of these lesions was consistent with BL. Bone marrow biopsy was normal. Patient's CD4 count was 99 with a viral load of 62,000. Cerebrospinal fluid analysis (CSF) revealed protein of 65 mg/dL (normal less than 50 mg/dL), glucose of 69 mg/dL, and white blood

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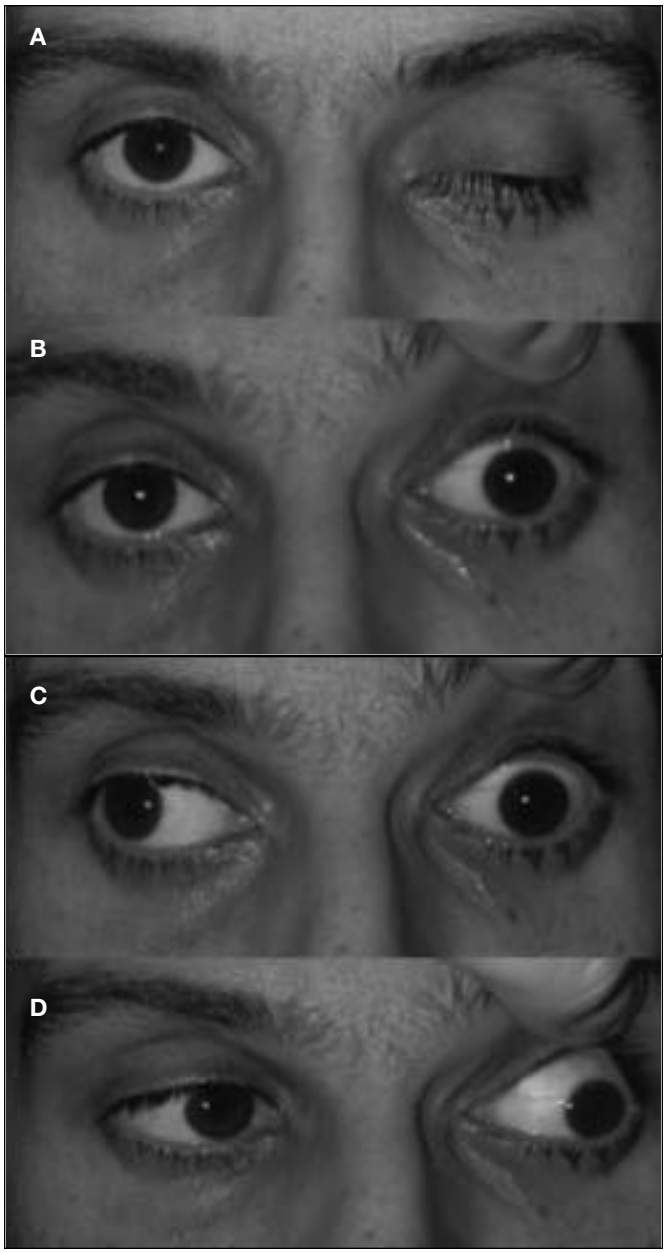

Fig. 1 - (A) *External appearance of the patient at presentation showing left ptosis.* **(B)** *After manual elevation of the left upper lid, left exotropia and hypotropia, and mid-dilated pupil can be observed.* **(C)** *Deficit in adduction of the left eye is shown.* **(D)** *Normal abduction of left eye is present.*

cells of 226 (normal less than 5), 95% of which were monocytes. CSF analysis for venereal disease research laboratory test, cryptococcal antigen, and HSV testing were negative. After hemato-oncologist specialist consultation, treatment with intravenous methotrexate, intrathecal cytarabine prophylaxis (CODOX-M), and intravenous

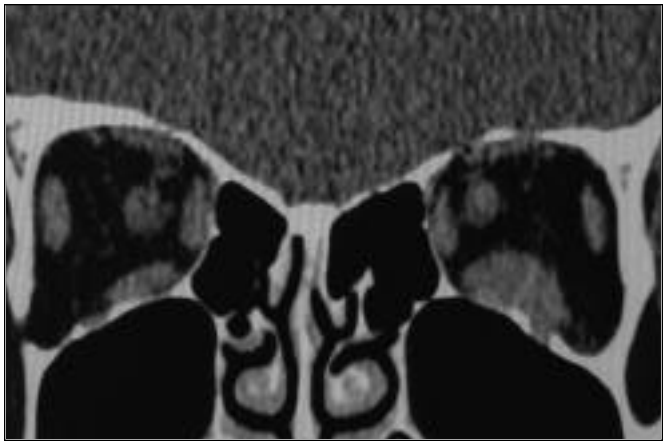

Fig. 2 - *Coronal orbital computed tomography scan at presentation demonstrated an enlarged left medial rectus muscle.*

cytarabine (IVAC) was started. Two months after the first cycle of chemotherapy, the diplopia and left ptosis disappeared. Ocular motility examination was normal. Repeated CT and MRI scans of brain and orbit were normal. Fewer and smaller liver lesions were observed on CT scan of the abdomen. At the last follow-up visit, 5 months after the presentation, the patient continues with HAART therapy and chemotherapy.

DISCUSSION

BL is an uncommon high-grade non-Hodgkin's lymphoma (NHL). It was first described in 1958 by Dennis Burkitt, who reported a form of lymphoma involving the jaws of African children (1). It can grow extremely rapidly with a doubling time as short as 24 hours. BL is one of the most aggressive malignancies of lymphoid origin and accounts for 3 to 5% of all lymphomas (2). Usually found in the pediatric population, BL represents 40% of childhood NHL.

Currently, three clinical variations are recognized: an endemic (African) form, a nonendemic form, occurring throughout the world, and an acquired immunodeficiency syndrome (AIDS)–associated form, similar to the nonendemic form but clinically more aggressive. The typical African (endemic) BL is a tumor of the jaw and face in children between the ages of 3 and 8 years. It accounts for 50% of childhood malignancies in the "lymphoma belt" of equatorial Africa (3). Exophthalmos results when the tumour extends out from the maxillary bone in advanced disease. Significant intraocular involvement has

only rarely been reported. It responds well to single or multiple chemotherapeutic agents applied in low dosage. In contrast, the nonendemic BL appears in older children and young adults, although it has been seen in adults up to 70 years of age. In adults, the increasing frequency of AIDS, immunosuppression therapy, and organ transplantation has led to an increased incidence of this nonendemic form of BL (4). The abdomen is most commonly involved first and there is bone marrow involvement (5). The nonendemic BL does not respond to chemotherapy as well as its endemic counterpart. This therapeutic difference has been attributed, at least in part, to a more occult manifestation of abdominal tumor, which is less strongly apparent in its early phases as compared with the visible jaw involvement in the endemic African variant.

Although accounting for less than 1% of adult NHL, BL has reportedly been found in as many as 35% of HIV-associated NHL cases. Like sporadic BL, the HIV-associated variant often involves the gastrointestinal tract and reportedly afflicts the bone marrow in 30% of cases. Unlike immunoblastic lymphomas, BL arising in HIV-positive patients occurs at a time when such patients are not yet seriously immunocompromised (6).

Initial manifestation with CNS involvement is rare (7). As mentioned before, lymphoproliferative lesions occur with greater frequency in immunosuppressed patients, especially in AIDS or after organ transplantation (8). Lymphomas may involve the cranial and peripheral nerves in several ways, some direct and others remote. Infectious complications and paraneoplastic syndromes are causes of remote neural involvement. In a more direct fashion, lymphomas can cause peripheral and/or cranial neuropathies by direct compression from adjacent lymph nodes or other masses of lymphoid tissues. Alternatively, malignant lymphocytes can invade the meninges and result in multiple cranial neuropathies, radiculopathies, and peripheral neuropathies, without CNS parenchymal involvement (8). Rarely, lymphomatous infiltration will be angiotropic and result in ischemic damage to peripheral nerves (8).

Ophthalmoparesis due to BL can be the result of direct orbital, cavernous sinus, brainstem, or meningeal involvement (9, 10). Newman described a patient with BL and meningeal involvement causing multiple cranial neuropathies after liver transplantation (8). Snider et al and Bomfim da Paz and Kölmel reported six patients with AIDS with ophthalmoparesis and CSF containing lymphomatous cells of the Burkitt's type (11, 12). Painful incomplete or complete ophthalmoplegia is the most common presentation of cavernous sinus syndrome. Because the cavernous sinuses contain four cranial nerves (i.e., III, IV, first two divisions of V, and VI), retroorbital pain and sixth nerve palsy followed by second and fourth nerve palsies are the dominant signs suggesting cavernous sinus syndrome (13). Grassi and Lee reported an HIV-positive patient who presented with severe headache and diplopia (14). Examination disclosed partial third, fifth, sixth, and seventh cranial nerve palsies. Our patient presented with complete third nerve palsy involving the pupil with complete recovery 2 months after starting chemotherapy. Although less frequent, diplopia has been also reported as a presenting symptom of BL in immunocompetent patients (6). CSF analysis may be normal, although microscopic meningeal involvement is usually present on autopsy. Brain CT and MRI may be normal, as in our patient (8). Flow cytometry has been demonstrated to increase the detection rate whenever a malignancy is suspected.

Diagnosis of bone marrow involvement, initial CNS manifestation, and older age all carry a poor prognosis (15). Despite irradiation and chemotherapy, no one who has presented with CNS involvement has survived as long as 40 weeks (16).

The primary therapeutic modality for BL is chemotherapy. As BL is one of the fastest growing tumors, with a high mitotic index, neoplastic cells are highly sensitive to cytotoxic agents. Current chemotherapy regimens in patients with disease limited to the head and neck yield 90% long-term survival. Patients with extensive disease (i.e., involvement of the bone marrow and/or CNS) and those with HIV-associated BL fare less well. Most chemotherapy regimens are cyclophosphamide-based (17). Newer intensive treatment regimens with multiagent intensive chemotherapy and aggressive early intrathecal treatment offer better clinical outcomes.

In conclusion, systemic lymphoma with neural infiltration should be suspected in the immunosuppressed patient who presents with cranial or peripheral neuropathies.

The authors have no proprietary interest in any of the materials or techniques used in this study.

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