Orbital Burkitt Lymphoma in Immunocompetent Patients: A Report of 3 Cases and a Review of the Literature

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Purpose: To describe a series of 3 immunocompetent patients with the sporadic form of orbital Burkitt lymphoma and review the outcomes of such patients reported in the scientific literature.

Methods: Retrospective review of medical records and the literature. Cases of orbital Burkitt lymphoma in immunocompromised and African patients were excluded from the review. Measured parameters included gender, age, ocular signs, imaging results, the range of systemic involvement, and treatment.

Results: Current cases and review of the scientific literature resulted in 16 immunocompetent patients with sporadic orbital Burkitt lymphoma. The median age at presentation was 12 years. Most common ocular signs at presentation were proptosis (13/16), external ophthalmoplegia (9/16), and eyelid edema (7/16). Optic neuropathy was noted in 5 of 16 patients. Concomitant paranasal sinus involvement was present in 8 of 16 patients. Fourteen (88%) of the patients had systemic involvement, of which the most common locations were central nervous system (6/16), lymphatics (6/16), bone marrow (6/16), and liver (4/16). Survival data were available for 13 patients. Seven patients (54%) died within 12 months of presentation.

Conclusions: Sporadic orbital Burkitt lymphoma occurs in immunocompetent individuals with a wide age range. Fifty percent presented with adjacent paranasal sinus involvement. Concurrent or eventual systemic involvement is common. The large number of patients with central nervous system involvement in our review of the literature supports the role of lumbar puncture and neuroimaging in the workup of all patients with orbital Burkitt lymphoma. Prognosis remains guarded, with significant mortality within 1 year of presentation.

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Burkitt lymphoma (BL) is a small, noncleaved B-cell non-Hodgkin lymphoma that was first described in 1958 as a mandibular malignancy in African children.[1] BL is classified as a mature B-cell neoplasm under the World Health Organization classifications. It is now recognized to occur in 3 major variants: the endemic (African) form; the sporadic form; and the immunodeficiency-associated form. BL is endemic in certain regions of equatorial Africa, where it commonly involves facial bones, such as the mandible, maxilla, and orbit, and can invade adjacent orbital soft tissue structures, such as the eye.[2,3] It has also been reported to occur in association with Epstein-Barr virus (EBV) infection and as a manifestation of HIV infection and AIDS.[4–8] The sporadic form of the disease occurs in nonendemic areas around the world, including the United States, where it typically manifests as an abdominal tumor with bone marrow involvement, but rarely occurs with ocular or orbital involvement.

We report 3 cases of sporadic BL that presented with disease in the orbit and summarize the literature on this topic.

METHODS

An electronic search using Pubmed was performed for relevant articles dating back to 1958 using the search terms Burkitt lymphoma, orbital, and ocular. Patients with endemic and immunocompromised orbital BL were excluded, as were cases that exhibited ocular signs with no orbital involvement. The following data were collected for each case of orbital BL: Snellen visual acuity, gender, age, ocular signs, MRI and CT imaging results, range of systemic involvement, treatment modalities, and mortality.

Case 1. A 72-year-old black man presented with progressive right eye proptosis, chemosis, and decreased vision for 1 week, which had significantly worsened over the past few days. He was unable to open his right eye for 3 days. He had visited his dentist 1 week earlier for right-sided tooth pain and midfacial swelling, for which the dentist found no explanation and empirically started an oral antibiotic. The patient reported no recent illness, fever, sore throat, weight loss, or trauma. His medical history included hypertension and hypercholesterolemia, which was treated with valsartan and pravastatin. The patient had no family history of cancer and he denied smoking but had a history of alcohol use.

On ocular examination, visual acuity was counting fingers at 5 feet OD and 20/30 OS. There was no relative afferent pupillary defect. On external examination, the right eye was 6 mm proptotic, extraocular motility was severely restricted in all fields of gaze, and the right upper and lower lids were mildly edematous (Fig. 1). On slit-lamp examination, the right eye had significant chemosis and injection, which prevented eyelid closure. Intraocular pressure by applanation was 34 mm Hg OD and 16 mm Hg OS. Dilated fundus examination was unremarkable OU. CT scan revealed a large mass in the inferior orbit and superior maxillary sinus without bony erosion (Fig. 2). Calcification was present within the maxillary sinus component of the lesion. The patient was brought to the operating room for functional endoscopic sinus surgery and incisional biopsy of the mass in the maxillary sinus.

Microscopic examination showed medium to large atypical lymphoid cells with prominent nucleoli consistent with a high grade lymphoma. The tumor contained tingible body macrophages with

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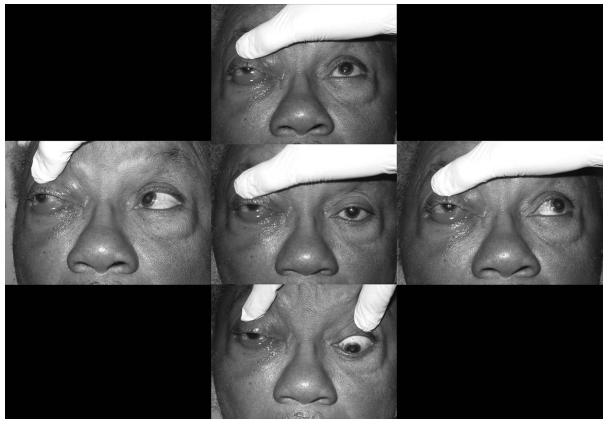

FIG. 1. Clinical appearance demonstrating chemosis, proptosis, and external ophthalmoplegia.

cellular debris, both free and within the macrophages, which imparted a characteristic starry sky appearance (Fig. 3). The tumor cells showed positive immunoreactivity for B-cell markers CD10, CD20, and BCL6, and positive staining for Ki-67 was 95%, consistent with high mitotic activity. Fluorescent in situ hybridization analysis revealed a characteristic translocation of the c-myc oncogene from chromosome 8 to the immunoglobulin (Ig) heavy-chain region on chromosome 14 [t(8;14)], confirming the diagnosis of BL.

CT of the chest, abdomen, and pelvis was performed for staging, which revealed no signs of systemic lymphoma. Cerebral spinal fluid analysis and bone marrow biopsy showed no evidence of malignancy. HIV testing by Western Blot was negative. The patient's BL was classified as stage IE (single, extranodal tumor with the exclusion of mediastinum or abdomen), and chemotherapy was initiated. He received the CODOX-M regimen (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate) and radiation therapy to the orbit.[9] He responded to treatment. At 13 months after initial presentation, he is alive, although he has developed skull metastases.

Case 2. A 63-year-old black woman presented with 5 days of nausea and abdominal pain and distention. She also reported 1 week of progressive right eye pain, redness, decreased vision, and swollen eyelids. Her vision in both eyes was poor secondary to cataracts, but she noticed further deterioration in her right eye. The patient had no recent viral syndrome, fever, sore throat, weight loss, or trauma. Her medical and surgical history was significant for insulin-dependent diabetes mellitus, inferior vena cava filter placement for deep venous thrombosis, meningioma, appendectomy, and tubal ligation. Her medications included insulin, metformin, furosemide, and simvastatin. She had a 50 pack-year history of smoking and occasional alcohol intake.

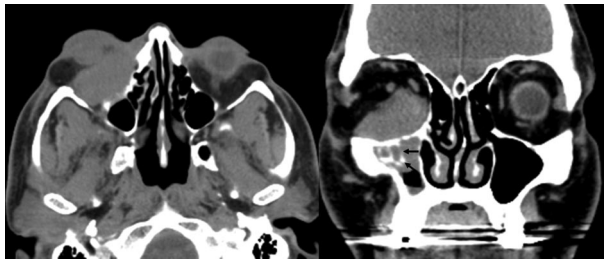

FIG. 2. Axial (left) and coronal (right) CT. Coronal image demonstrates calcification (arrows) within the maxillary sinus component of the lesion.

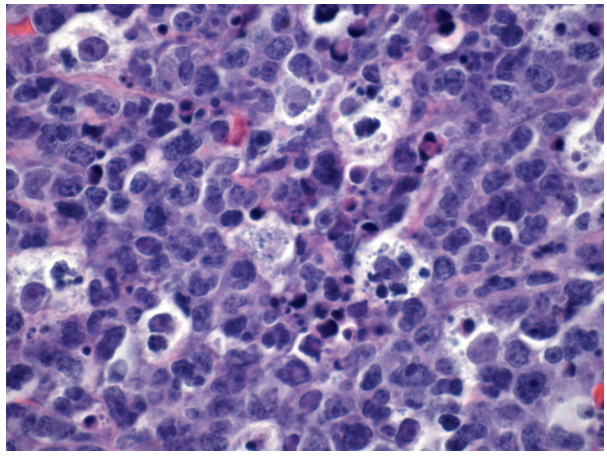

FIG. 3. Histopathology demonstrates medium to large atypical lymphocytes and a "starry sky" appearance of tingible-body macrophages (hemotoxylin-eosin, ×400).

On ocular examination, uncorrected visual acuity was bare hand motion OD and 20/400 OS, with a prominent right relative afferent pupillary defect. External examination of the right eye revealed complete external ophthalmoplegia, ptosis, eyelid edema, chemosis, injection, and proptosis with a tight orbit. Intraocular pressure by tonometry was 70 mm Hg OD and 17 mm Hg OS. An urgent lateral canthotomy and inferior cantholysis were performed in the emergency room, which lowered the intraocular pressure to 32 mm Hg. A view of the fundi was not possible secondary to bilateral, dense cataracts. Oral and endoscopic intranasal examination showed no evidence of eschar, ischemic mucosa, or purulence. CT showed diffuse, right orbital infiltration with significant ethmoid sinus disease and adjacent bony erosion (Fig. 4). CT of the abdomen and pelvis was also performed, which revealed lesions in the spleen and left groin suggestive of a possible malignancy. The patient was also found to suffering from lactic acidosis. Given her diabetes, ketoacidosis, and rapid progression with profound visual loss, mucormycosis was the greatest acute concern. The patient was brought to the operating room for an emergent, right orbitotomy for exploration and frozen section biopsy.

Microscopic examination showed medium-sized atypical lymphocytes with round nuclei, prominent nucleoli, and many mitotic and apoptotic figures. The presence of scattered tingible body macrophages gave a starry sky appearance. Immunohisochemistry performed on tumor cells were positive for CD10, CD20, CD45, and BCL6. Positive staining for Ki-67 was greater than 90%. Although cytogenetic studies were not specific for BL, this was the final diagnosis based on histologic figures and immunophenotyping. Biopsies of left inguinal mass and lymph nodes were also consistent with BL. Her disease was labeled stage IV, and she underwent chemotherapy with a regimen including cyclophosphamide, vincristine, rituxan, adriamycin, and

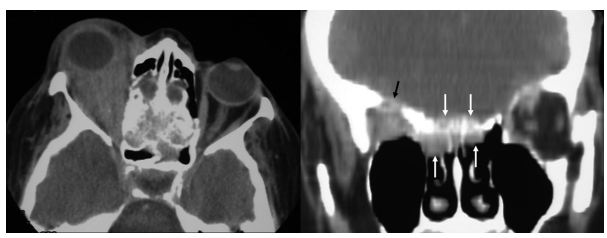

FIG. 4. Axial and coronal CT. Bone erosion is present along the right orbital roof (black arrow) and infiltration of the skull base and ethmoid sinuses (white arrows).

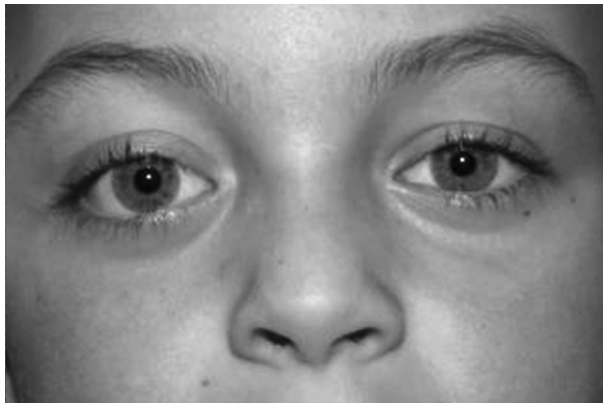

FIG. 5. External appearance with minimal external signs, but obvious exophthalmos if noted on the right.

prednisone, and orbital radiation. There was no evidence of immunosuppression on clinical workup.

Five months after initial presentation, the patient presented with fevers and an ulcerated, infected left groin mass. Progression of systemic disease was noted on imaging. Despite debridement and systemic antibiotic therapy, the patient died of sepsis.

Case 3. An 8-year-old white boy presented with a 2-days history of right-sided facial swelling and rapidly progressive right eye proptosis. He reported no pain, headache, blurry vision, diplopia, fever, weight loss, trauma, or recent illness. He had no significant medical history.

On ocular examination, visual acuity was 20/20 OU without correction. On external examination, there was 4 mm of right proptosis, extraocular motility was full in all fields of gaze, and eyelids were within normal limits (Fig. 5). There was no relative afferent pupillary defect and slit-lamp examination was normal. Intraocular pressure by applanation was 13 mm Hg OD and 14 mm Hg OS. Dilated fundus examination was normal. CT and MRI revealed a mass centered in the right lateral orbital wall and greater wing of the sphenoid with bony destruction (Fig. 6). The mass extended in the right orbit and temporalis fossa, and involved the skull base at the junction of the middle and anterior cranial fossae. Differential diagnosis included rhabdomyosarcoma, neuroblastoma, lymphoma, and leukemia. The patient was brought to the operating room for incisional biopsy of the mass in the temporalis fossa.

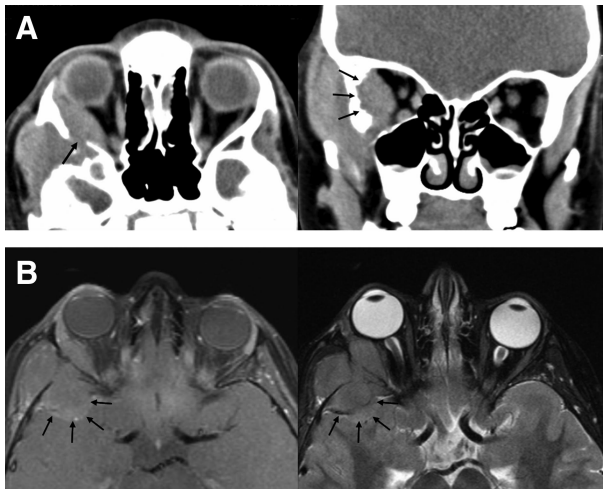

FIG. 6. **A,** Axial and coronal CT. The lesion involves the right lateral orbit and temporalis fossa with intracranial extension (arrows). **B,** T_1-weighted, post contrast (left) and T_2-weighted (right) axial MR images with a homogenous signal and intracranial extension (arrows). Note the poor enhancement of the mass with gadolinium.

Microscopic examination showed skeletal muscle densely infiltrated by intermediate sized lymphocytes with irregular nuclei, scant cytoplasm, and numerous mitotic and apoptotic figures. The presence of scattered tingible body macrophages gave a starry sky appearance. Flow cytometry demonstrated predominantly B-cell lymphocytes with the following immunophenotype: $CD9^+$, $CD10^+$, $CD19^+$, $CD20^+$, $CD24^+$, $CD38^+$, $CD79a^+$, $HLA\text{-}DR^+$. Fluorescent in situ hybridization analysis demonstrated a fusion of the c-myc and Ig heavy-chain loci in 20% of the cells. These results were consistent with a mature large B-cell lymphoma and the t(8;14) associated with BL.

CT of the chest, abdomen, and pelvis showed abnormalities in the kidneys, pancreas, and right lower lobe of the lung, which were consistent with systemic involvement and stage IV disease. Bone marrow biopsy revealed normocellular marrow with no evidence of lymphoma. HIV testing by Western Blot was negative. Because of his extensive BL, chemotherapy was initiated with COPADM regimen (cyclophosphamide, vincristine, prednisone, intrathecal methotrexate, doxorubicin, intravenous methotrexate, retuximab, cytarabine, etoposide).[10] He was not given radiation therapy. At 12 months after his original presentation, the BL has responded well to treatment, and postchemotherapy imaging has shown resolution of the skull and orbital mass, and the kidney and pancreas lesions.

RESULTS

A review of the literature revealed 13 cases of orbital Burkitt lymphoma (OBL).[11–23] Including the 3 patients presented in this report, the study population consisted of 16 total cases. Data for these patients are summarized in the Table (www.op-rs.com, Article Plus). This series consisted of 10 men and 6 women, with a mean age of 25.6 years (range 10 months to 84 years, median 12 years). The most common ocular signs at presentation were proptosis (13/16), external ophthalmoplegia (9/16), eyelid edema (7/16), ptosis (3/16), and eyelid mass (3/16). Optic neuropathy was noted in 5 of 16 patients (31%). Concomitant paranasal sinus involvement was present in 8 of 16 patients (50%). Thirteen patients (81%) had systemic involvement, of which the most common locations were central nervous system (CNS) (6/16), lymphatics (6/16), bone marrow (6/16), and liver (4/16). Survival data were available for 13 patients. Seven patients (54%) died within 12 months of presentation.

Eight cases of BL with ocular signs and no orbital involvement were found during the literature search but were excluded from the main analysis.[24–31] Of these cases, the most common ophthalmic involvement was cranial neuropathy (7/8), optic neuropathy (4/8), and cavernous sinus infiltration with ophthalmoplegia (3/8). Four patients had lymphomatous meningitis with cerebral spinal fluid infiltration. One case had intraocular disease with retino-choroidal and vitreous exudates and optic nerve edema. In total, 7 patients (88%) had CNS involvement, and 4 of the 8 patients died within 11 months of presentation. All of these cases lacked orbital tumor involvement on imaging or autopsy.

DISCUSSION

BL, classified as a mature B-cell non-Hodgkin lymphoma, is a monoclonal proliferation of B-lymphocytes that can arise from any location in the body and demonstrates the "starry sky" pattern of lymphocytes on histologic examination. Originally, it was described as a mandibular malignancy and documented in sub-Saharan Africa in a pediatric population.[1] This endemic form was found to be highly associated with EBV infection.[4,32] Later, a non-African or North American form was documented, which became known as the sporadic

form. In contrast to the endemic BL seen in Africa, which usually manifests as a tumor of the mandible, maxilla, and orbital bones, the sporadic form typically involves the abdomen, often the ileocecal region, and rarely demonstrates orbital or ocular involvement.[33] A third category of BL is an immunocompromised variant, originally described in patients with AIDS.[5,6] Sporadic BL is EBV positive in 20% of cases, and immunocompromised BL is EBV-positive in greater than 40% of cases, whereas the endemic form has reported rates as high as 95%.[34–37] The relationship of sporadic BL and EBV is controversial. Of note, one large study noted that cases with EBV antibody positivity had better outcomes.[32,38]

BL is frequently associated with the translocation of the c-myc oncogene from chromosome 8 to the Ig heavy chain region of chromosome 14, and it was noted in 2 of 3 cases we report with OBL, and 3 of the cases we reviewed.[13,16,18] Less often, there are translocations of the Ig light chains from chromosomes 2 or 22 to the c-myc region of chromosome 8; no other translocations were noted in our review of the literature on OBL.

In our study, the pediatric population was most frequently afflicted. Still, 4 patients (25%) over the age of 60 years have been reported with OBL, including 2 of the cases presented in this article.[22,23] The oldest patient reported was age 84 years, described by Coupland et al.[23] as an immunocompetent woman whose first symptom of BL was diplopia, and was found to have a conjunctival mass, a large parotid mass, and involvement of lymph nodes and bone marrow. Levine et al.[38] noted in their 8-year review of 421 patients from the American Burkitt Cancer Registry that under the age of 13 years, the ratio of males to females was higher (2.65:1 as compared with 1.35:1 in ages >13 years). Our data on OBL support these data, with a ratio of 3.5:1 under age 13 years and 0.75:1 in ages over 13 years.

Knowles and Jakobiec[39] noted in their 1980 review of 60 patients with orbital lymphoid neoplasms that the most common physical finding was a palpable mass at 90%, followed by proptosis at 33%. In our review of OBL, the most common ocular finding on examination was proptosis (13/16). An eyelid mass occurred in less than 20% of patients. Optic neuropathy occurred in about one third of patients. Adjacent paranasal sinus involvement was noted in 50% of patients. Concomitant cavernous sinus involvement was rare (1/16). This sole report by Huisman et al. described a 12-year-old boy who presented with external ophthalmoplegia and exophthalmos, and headache, nausea, and vomiting; CT and MRI revealed a homogenously enhancing mass in the right cavernous sinus extending in the orbital apex. Systemic evaluation revealed mediastinal involvement, and biopsy was consistent with BL.[18] Notably, 3 cases of cavernous sinus involvement without orbital involvement, which presented with ocular motility deficits, were excluded from the review.[25,27,30]

The systemic spread of sporadic BL can be extensive. In our review of OBL, more than 80% of the cases had systemic involvement (13/16). Moreover, CNS disease was one of the most common sites at 40% (6/16), along with lymph nodes and bone marrow. The rate of CNS involvement in our series of OBL was significantly higher than reports of all patients with sporadic BL. In a study of 30 American BL patients by Banks et al.,[40] the CNS was least commonly involved. In another review of the American Burkitt Lymphoma registry, Levine et al.[38] found only approximately 5% (13/256) had CNS involvement. Therefore, a high suspicion for CNS involvement should be maintained when evaluating patients with BL and orbital signs.

Mortality was high for patients with OBL, which coincides with previous reports.[22] Survival data were available for 13 patients. Seven patients (54%) died within 12 months of presentation, and only 2 patients had no evidence of systemic involvement at the latest documented follow-up. Of the 2 patients without systemic disease, survival data were available on one, who was alive at follow-up at 4 years. Neurologic involvement at presentation of BL has been associated with more rapid progression and higher mortality.[41] Our review of OBL concurred with this finding. Of the 6 patients with CNS involvement, 4 died at an average of 4 months after presentation, with the remainder alive at an average follow-up of 14 months. This is in contrast to the 7 cases without CNS involvement that have survival data; 2 patients died an average of 9 months after presentation, and 5 were alive at an average follow-up of 23 months.

In conclusion, BL should be included in the differential diagnosis of immunocompetent patients who present with orbital disease. Although BL is often associated with African and immunocompromised patients, it can occur in immunocompetent individuals with a wide age range. Two of our 3 patients had evidence of bone erosion on initial imaging. However, no specific periocular, clinical, or radiographic finding is specific for OBL. Adjacent paranasal sinus involvement was seen in 50% (8/16) of patients, and optic neuropathy occurred in 31% (5/16) of patients. Eventual systemic involvement is common. The large number of patients with CNS involvement in our review of the literature supports the role of lumbar puncture and neuroimaging in the work-up of all patients with OBL and in those with ocular signs. Prognosis remains guarded, with significant mortality within 1 year of presentation.

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