Multiple cranial nerve palsies in immunodeficiency subtype of Burkitt lymphoma

Abbas Ali and Abhishek Kalla

1. Introduction

Nervous system involvement in Burkitt Lymphoma is reported to be between 20–60%[1]. Burkitt Lymphoma is a late complication of HIV, and bilateral cranial nerve palsies are extremely rare in patients with AIDS [2]. We present what we believe is the first reported case of Burkitt Lymphoma presenting with bilateral facial, vestibulocochlear, left abducens, and mandibular nerve palsies.

2. Case report

A twenty year old Caucasian male with known congenital HIV who had been non-adherent with antiretroviral therapy presented with multiple cranial nerve palsies and was eventually diagnosed with Burkitt lymphoma. Before chemotherapy, he was started on radiation therapy to the brain, meninges, and base of skull with the intent of improving cranial nerve palsies and preventing further neurological sequelae since the cranial nerve palsies were dense and there was concern that intrathecal chemotherapy would have less penetration than radiation. He eventually died due to overall disease burden. We hereby present what we believe is the first reported case of Burkitt lymphoma presenting with bilateral cranial nerve palsies. Recognition of different presentations of Burkitt lymphoma is extremely important as it would aid in early diagnosis and initiation of both chemotherapy and anti-retroviral therapy potentially leading to improved outcomes.
cranial nerve functions and gross nervous exam were within normal limits. Cardiac and pulmonary exams were normal as well.

One month before this presentation his absolute CD4 cell count was 97 cells/μL and his HIV viral load was 130,000 copies/ml. His white cell count was 6.9 K/μL with an ANC of 2010, hemoglobin was 6.3g/dL, hematocrit was 19.3%, and platelet count was 125,000/μL. Electrolyte abnormalities included a potassium of 3.0 mEq/L, chloride of 89 mEq/L, and magnesium of 1.5 mg/dL. Liver function tests were normal except for a slight elevation of AST up to 48U/L. Coagulation profile was normal. Lactic acid was elevated at 9 mmol/L. LDH was elevated at 3755 U/L. ESR was 95 mm/hour. Uric Acid level was 13.6 mg/dL.

CT scan of the head showed bilateral middle ear and mastoid opacification with sphenoid and frontal sinus mucosal thickening along with fluid. Head MRI showed a 2–3 mm hyperintense focus within the left frontal cortex on FLAIR images, underpneumatization and an air fluid level in the right frontal sinus, opacification of the left frontal sinus, mild old orbital floor deformity with herniation of the intra-orbital fat content into the left maxillary sinus, complete opacification of the right mastoid air cells with fluid in the right middle ear cavity, partial opacification of the left mastoid air cells along with fluid in the left middle ear cavity.

CT scan of the chest, abdomen, and pelvis identified bulky axillary and iliac adenopathy bilaterally, enlarged spleen measuring 17 cm in length, and some scattered low-density abnormalities in the liver and kidneys.

Lumbar Puncture was done and CSF was hazy in appearance with 9 WBCs/μL with 100% mononuclear cells, 402 RBCs/μL, glucose 55 mg/dL, and protein 87 mg/dL. PCRs for Enterovirus, HSV, CMV, and EBV DNA were negative on the CSF sample. Cryptococcus antigen, VDRL, and RPR assays were non-reactive. CSF cytology showed atypical lymphocytes with open chromatin and distinct nucleoli along with cytoplasmic vacuoles. Some cells were positive for CD10/Kappa immunophenotype. CSF flow cytometry also revealed B cells positive for CD10/Kappa light chains. Lymph node core biopsy showed lymphocytes with fine chromatin and distinct nucleoli.

Peripheral smear also revealed the presence of B cells that were CD10 and kappa positive with intermediate staining intensity for CD19 and CD20 antigen. He underwent an axillary lymph node biopsy that showed atypical lymphocytes with fine chromatin and distinct nucleoli. Fluorescence in situ hybridization of B lymphocytes showed a t(8;14) translocation (c-myc/IgH), which confirmed the diagnosis of Burkitt Lymphoma. A bone marrow biopsy also identified infiltration by lymphoma.

Treatment was quickly initiated with high-dexamethasone and anti-retroviral therapy with abacavir, lamivudine, and dolutegravir along with atovaquone for Pneumocystis Jiroveci pneumonia prophylaxis. It was also decided to start the patient on radiation therapy to the brain, meninges, and base of skull with the intent of improving cranial nerve palsies and preventing further neurological sequelae since the cranial nerve palsies were dense and there was concern that intrathecal chemotherapy would have less penetration then radiation. Intravenous hydration and allopurinol were used to prevent tumor lysis syndrome. His cranial nerve palsies did not respond and after the 4th round of radiation he developed ophthalmoplegia of the left eye. MRI showed diffuse dural enhancement without leptomeningeal enhancement, and with normal visualized intracranial nerves at the base of the skull. He subsequently developed pancytopenia and tumor lysis syndrome. Intrathecal methotrexate and steroids were initiated. Rasburicase was added to the tumor lysis syndrome treatment. The patient was also started on R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) instead of R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) since it could be completed within one day. The patient went on to develop further neutropenia requiring G-CSF. He also developed bladder and bowel incontinence with MRI of the lumbosacral spine showing central canal stenosis from L5 to S1 due to soft tissue invasion into epidural space. High-dose dexamethasone was re-started, but radiation therapy was not given due to the lack of evidence of cord compression on imaging with pancytopenia and a risk of radiation in that region further suppressing the bone marrow. The patient eventually expired due to overall disease burden within a month.

3. Discussion

Burkitt Lymphoma has three subtypes: endemic, sporadic and immunodeficiency associated [3]. These are histologically identical. Epstein Barr virus plays an important role in the endemic and antibodies to it have been noted in 95% cases of endemic as opposed to 25% cases of the non-endemic variety [4] along with 40% cases of HIV associated Burkitt Lymphoma [1].

The genetic hallmark of all three subtypes is the rearrangement of the C-MYC oncogene that contributes to lymphomagenesis through dysregulation of cell cycle, cellular differentiation, apoptosis, cellular adhesion, and metabolism [5]. Histologically the tumor cells are round and uniform with multiple nucleoli and basophilic lipid-vacuole laden cytoplasm. Cells have a proliferation index of > 99% on Ki67 staining and express CD10, CD19, CD20, CD22, CD79a and surface IgM [5].
After t(8;14) translocation involving c-myc and Immunoglobulin heavy chain, the most common other translocations are t(2;8) and t(8;22) [6]. The tumor is characterized by monoclonal proliferation of non-cleaved B cells [6]. It is one of the most rapidly dividing tumors with a growth fraction (Ki67 score) of 100 percent [7].

Nervous system involvement is seen in approximately 20–60% of Burkitt Lymphoma cases [1]. Central nervous system manifestations commonly include paraplegia, hemiplegia, quadriplegia, lethargy, seizures, cranial nerve palsy, areflexia, blindness, deafness, and meningitis [8].

The pathogenesis of cranial nerve involvement and meningeal involvement is speculative. It may be caused by migratory extension to the dura along nerve or blood vessel sheaths or directly through bone and periosteum [9].

The immunodeficiency-associated subtype of Burkitt Lymphoma is frequently seen in HIV/AIDS. Patients typically present with disseminated disease, bulky intra-abdominal adenopathy, elevated LDH, and CD4 count more than 200 cells/ul [8]. Neurological complications have been found to occur in 40% of patients with AIDS. Approximately 10–20% of AIDS patients present with neurological complaints [10]. HIV infected individuals have a 10–20% lifetime risk of developing Burkitt Lymphoma; a risk that is unaffected by antiretroviral therapy since the risk is independent of CD4 cell count [11].

Compared to the general population, the higher incidence of developing Burkitt lymphoma in HIV-affected individuals is attributed to transforming properties of the virus, immunosuppression, cytokine dysregulation, and opportunistic infections with other lymphotropic viruses like human-herpes virus 8 and Epstein-barr virus [12]. In addition to these, HIV is considered a neurotropic virus and can cause intra-neural edema with fiber swelling leading to signal enhancement on MRI [13].

Cranial nerve palsies have been reported in patients with AIDS involve the third, fourth, sixth and seventh nerves [14]. Facial palsy commonly occurs at an early stage of HIV infection and is characterized by degeneration and non-suppurative inflammation. This palsy is more common in a healthy HIV carrier than in a patient with AIDS [15]. Paralysis can occur before the appearance of antibodies against HIV antigen. The etiology remains unclear, but may be due to the virus itself or it may be secondary to other infections like herpes simplex virus, adenovirus, mumps, and rubella [2].

There is one reported case of bilateral 8th nerve palsy in early HIV infection. Gremaldi et al. suggest that cranial neuropathies are preferentially bilateral in primary retroviral infections, likely due to vasculitis as evidenced by perivascular inflammation [16].

In the pre-HAART era, patients with AIDS were precluded from treatment with intensive chemotherapy due to their co-morbidities and mortality associated with chemotherapy. However, since the advent of HAART many patients have minimal opportunistic infections allowing dose intensive chemotherapy to be instituted which has improved outcomes [11].

Staging requires imaging of chest, abdomen, pelvis, and brain along with cerebrospinal fluid cytology, flow cytometry, and bone marrow biopsy [17]. Owing to rapid mutation and growth rate of Burkitt Lymphoma, moderate dose chemotherapy regimens like CHOP have shown a relapse rate of 70 percent [18].

High dose chemotherapy regimens with minimal interruptions minimize development of drug resistance and improve survival rates [19]. These survival rates have been further improved with the addition of rituximab [20].

Intrathecal cytarabine and methotrexate given along with systemic therapy has been shown to reduce CNS relapses and improve outcomes. First-line chemotherapy regimens include CODOX-M plus IVAC, hyper-CVAD, or dose adjusted EPOCH [21–23].

4. Conclusion

After an extensive literature review, we believe this to be the first reported case of Burkitt Lymphoma presenting with bilateral facial, vestibulocochlear, left abducens, and mandibular nerve palsies. Recognition of different presentations of Burkitt lymphoma is extremely important as it would aid in early diagnosis and initiation of both chemotherapy and antiretroviral therapy potentially leading to improved outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Pal L, Valli ER, Santosh V, et al. Disseminated Burkitt’s lymphoma presenting as multiple cranial nerve palsies. Indian J Cancer. 1995 Sep;32(3):116–120.

[2] Sasaki M, Leite PG, Leite AG, et al. Bilateral peripheral facial palsy secondary to lymphoma in a patient with HIV/AIDS: a case report and literature review. Braz J Infect Dis.. 2002 Feb;6(1):50–54.

[3] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 May 19;127 (20):2375–2390. Epub 2016 Mar 15.

[4] Panago JC, Hunag MS, Levive P. Absence of Epstein-barr viral DNA in American Burkett’s lymphoma. N ENG J Med. 1973;289(1395):1399.

[5] Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. Blood. 2004;104:3009–3020.
[6] Burkitt D. A sarcoma involving the jaws in African children. Br J Surg. 1958 Nov;46(197):218–223.
[7] Tao Q, Robertson KD, Manns A, et al. Epstein-Barr virus (EBV) in endemic Burkitt’s lymphoma: molecular analysis of primary tumor tissue. Blood. 1998 Feb 15;91(4):1373–1381.
[8] Odeku EL, Adeloye A, Osuntokun BO. The neurological picture of Burkitt’s lymphoma in Ibadan. Afr J Med Sci. 1973 Apr;4(2):119–126.
[9] Ziegler J, Bluming A, Momtow R, et al. Central nervous system involvement in Burkitt’s lymphoma. Blood. 1970 Dec;36(6):718–728.
[10] Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. 1985. J Neurosurg. 2007 Dec;107(6):1253–1273. discussion 1251.
[11] Noy A. Controversies in the treatment of Burkitt lymphoma in AIDS. Curr Opin Oncol. 2010 Sep;22(5):443–448.
[12] Grogg KL, Miller RF, Dogan A. HIV infection and lymphoma. J Clin Pathol. 2007 Dec;60(12):1365–1372.
[13] Sattoretti-Schefer S, Wichman W, Valavanis A. Idiopathic, herpetic, and HIV-associated facial nerve palsies; abnormal MR enhancement patterns. Am J Neuroradiol. 1994;15:479–485.
[14] Karna S, Biswas J, Kumarasamy N, et al. Multiple cranial nerve palsy in an HIV-positive patient. Indian J Ophthalmol. 2001 Jun;49(2):118–120.
[15] Belec L, Georges AJ, Vuillecard E, et al. Peripheral facial paralysis indicating HIV infection. Lancet. 1988;2:1421–1422.
[16] Grimaldi LM, Luzi L, Martino GV, et al. Bilateral eighth cranial nerve neuropathy in human immunodeficiency virus infection. J Neurol. 1993 Jun;240(6):363–366.
[17] Zelenetz AD, Abramson JS, Advani RH, et al. NCCN clinical practice guidelines in oncology: non-Hodgkin’s lymphomas. Natl Compr Canc Netw. 2010 Mar;8(3):288–334.
[18] Smeland S, Blystad AK, Kvaløy SO, et al. Treatment of Burkitt’s/Burkitt-like lymphoma in adolescents and adults: a 20-year experience from the Norwegian Radium Hospital with the use of three successive regimens. Ann Oncol. 2004 Jul;15(7):1072–1078.
[19] Rodrigo JA, Hicks LK, Cheung MC, et al. HIV-associated burkitt lymphoma: good efficacy and tolerance of intensive chemotherapy including CODOX-M/IVAC with or without Rituximab in the HAART Era. Adv Hematol. 2012;2012:735392. Epub 2011 Nov 14.
[20] Barta SK, Lee JY, Kaplan LD, et al. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer. 2012 Aug 15;118(16):3977–3983. Epub 2011 Dec 16.
[21] Magrath I. Lessons from clinical trials in African Burkitt lymphoma. Curr Opin Oncol. 2009 Sep;21(5):462–468.
[22] Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. J Clin Oncol. 1996;14:925–934.
[23] Thomas D, Cortes J, O’Brien S, et al. Hyper-CVAD program in Burkitt’s type adult acute lymphoblastic leukemia. J Clin Oncol. 1999;17:2461–2470.