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CASE REPORT

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Multiple cranial nerve palsies in immunodeficiency subtype of Burkitt lymphoma

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ABSTRACT

Burkitt lymphoma is a late complication of HIV, and bilateral cranial nerve palsies are extremely rare in patients with AIDS. A twenty year old Caucasian male with known congenital HIV who had been non-adherent with anti-retroviral 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 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 anti-retroviral therapy potentially leading to improved outcomes.

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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 a two week history of difficulty hearing bilaterally with a 'wooshing' sound in the left ear, facial weakness, progressive slurring of speech, and numbness of the chin. He denied fever, chills, rash, headache, dizziness, or light-headedness. He also denied any recent sick contacts, head trauma, or aminoglycoside use. History was limited by the patient's hearing difficulty and unwillingness to answer questions due to frustration secondary to health issues.

A review of systems was positive for night sweats, generalized weakness, fatigue, unquantifiable and unexplained weight loss, and sore throat.

Past medical history was significant for congenital HIV, non-adherence with antiretroviral therapy, and a recent hospitalization during which he was treated for community acquired pneumonia in the setting of neutropenia. Of note, he had an interim emergency department visit for vague left ear discomfort. Past surgical history was non-contributory. Family history was positive for HIV in both parents; his father initially acquired it and later died from complications related to AIDS, and his mother had acquired HIV from his father.

The patient admitted to smoking a half pack of cigarettes a day, occasionally smoking marijuana, and drinking alcohol. He was living with his mother and had just finished high school.

On presentation he had stable vital signs, was cachectic-appearing, and was irritable. Examination was negative for Kernig's and Brudzinski's signs. External auditory canals were hyperemic. Tympanic membranes were normal with intact light reflexes. There was poor oral hygiene and poor dentition. He complained of tenderness with palpation of suboccipital, posterior auricular, and cervical lymph nodes. Also palpable were axillary and inguinal lymphadenopathy.

Neurological exam revealed left ptosis, inability to frown forehead and puff cheeks bilaterally, purse lips, and flattening of the left nasolabial furrow indicating bilateral asymmetrical facial palsy that was graded at 3/6 on the House-Brackmann scale. There was incomplete sensorineural deafness bilaterally with a pulsatile tinnitus in the left ear. Mild weakness in abduction of left eye was noted indicating left abducens nerve palsy. There was diminished sensation on the chin indicating involvement of the mandibular division of the trigeminal nerve. Remainder of the

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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/uL and his HIV viral load was 130,000 copies/ml. His white cell count was 6.9 K/uL with an ANC of 2010, hemoglobin was 6.3g/dL, hematocrit was19.3%, and platelet count was 125,000/uL. 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 d showed a 2–3 mm hyperintense focus within the left frontal cortex on FLAIR images, under-pneumatization 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 WBC's/UL with 100% mononuclear cells, 402 RBC's/UL, 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 dual 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 Pneumocustis 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 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 is seen in HIV/AIDS. Patient's typically present with disseminated disease, bulky intra-abdominal adenopathy, elevated LDH, and CD4 count more 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.

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