Multiple Cranial Nerve Palsies as the Initial Presentation of Peripheral T-Cell Lymphoma

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Introduction

Primary non-Hodgkin lymphoma (NHL) rarely affects the sinonasal tract and represents approximately 1.5% of all lymphomas, with a higher incidence in Asia and South America.[1-3] In the United States, sinonasal lymphomas are more prevalent in elderly men and are located in the paranasal sinuses. In addition, they are usually of the B-cell subtype,[1-2,4-5] in contrast to the T-cell subtype that is more common in Asia.[6-10]

Most patients present with nasal obstruction, facial swelling, or pain. Central nervous system (CNS) involvement has mainly been reported prior to the initiation of intrathecal chemoprophylaxis and likely results from the invasive nature of the tumor and its proximity to the CNS.[4,11] Neurologic manifestations that were described with sinonasal lymphomas include diplopia, visual impairment, and hearing loss.[12] To the best of our knowledge, there are no reported cases of concurrent second, third, fourth, fifth, sixth, seventh, or eighth cranial nerve palsies at presentation secondary to sinonasal peripheral T-cell lymphoma not otherwise specified (PTCL-NOS).

Case Presentation

A 56-year-old white man with no significant medical history presented to the emergency department with right-sided facial weakness that had persisted for 1 day. His initial symptoms began 2 months prior to admission and consisted of upper respiratory tract infection, which was associated with mild frontal headache, facial discomfort, and postnasal drip. All of these symptoms had resolved within a week. Following the resolution of these initial symptoms, the patient developed blurry vision, mainly in the right eye, followed by ipsilateral hearing loss. The patient resided in Western New York. He denied recent history of travel or exposure to sick contacts. There was no other significant familial or environmental history. He worked as a landscaper, but he did not recall any injuries or bites from ticks or other insects. His vital signs were stable, and general physical examination was notable for multiple subcutaneous nontender nodular scaly lesions on his torso and lower extremities, each ranging in size up to 10 cm × 10 cm. No lymphadenopathy or hepatosplenomegaly were noted.

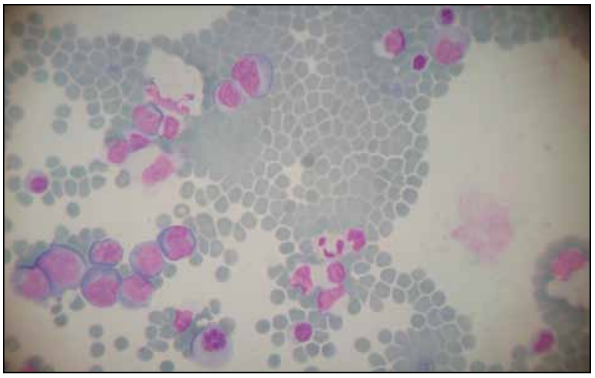

Figure 1. Cerebrospinal fluid cytology demonstrating malignant cells (Diff-Quik staining).

On ophthalmologic examination, the patient was found to have bilateral ptosis along with fixed pupils that were nonreactive to light, measuring 7 mm and 4 mm on the right and left, respectively. Movement of the right eye was limited to abduction only. Visual acuity was 20/200 in both eyes. Intraocular pressure was normal bilaterally, and confrontational visual fields were full in both eyes. Fundoscopy showed bilateral vitritis.

Neurologic examination showed right-sided facial loss of sensation, droop, and neurosensory hearing loss. The rest of the neurologic examination was normal.

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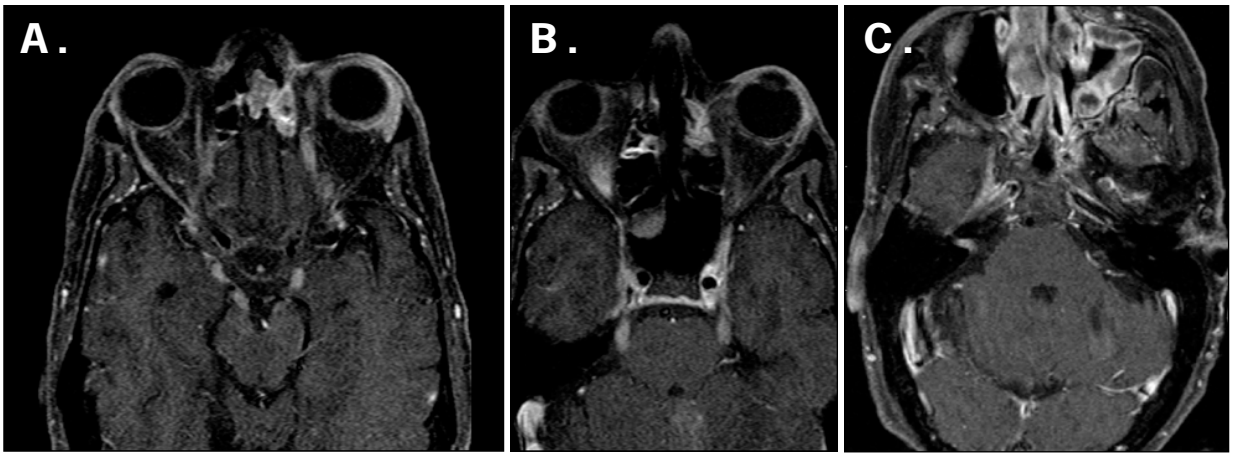

Figure 2. Gadolinium-enhanced magnetic resonance imaging of the brain and orbit axial image showing leptomeningeal involvement of multiple cranial nerves. (A) Enhancement of the cranial nerve III, bilaterally. (B) Enhancement of the cranial nerve V (cisternal segment), bilaterally. (C) Enhancement of the cranial nerves VII and VIII, at the right internal auditory canal.

Laboratory analysis showed monocytosis (21.4% of 7.1 × 109/L white blood cells) and C-reactive protein of 9.7 mg/dL. Tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 27-29, were all within normal limits. Serum Epstein-Barr virus (EBV) DNA polymerase chain reaction (PCR) was found to be positive. Cerebrospinal fluid (CSF) examination revealed a glucose level of 19 mg/dL, protein of 272 mg/dL, red blood cells of 530/mm^3, nucleated cells of 73/mm^3, sterile cultures, and negative herpes simplex virus PCR. Interestingly, the cytology showed blast cells with azurophilic cytoplasmic granules (Figure 1).

Additional autoimmune, infectious, and toxic work-ups were negative. Urinalysis, an electrocardiogram, and chest x-ray were all normal.

Computed tomography of the head and orbit demonstrated chronic paranasal sinus disease. Magnetic resonance imaging of the brain and orbit with contrast showed bilateral leptomeningeal asymmetric enhancement of cranial nerves III, IV, V, VI, VII, and VIII (Figure 2), in addition to a right sphenoid polypoid lesion measuring 1.2 cm in size and polypoid lesions in the right nasal cavity with peripheral rim contrast enhancement along with restricted diffusion (Figure 3). Electromyography and a nerve conduction study showed evidence of chronic inflammatory demyelinating polyneuropathy.

Skin biopsy from an abdominal lesion showed spongiotic dermatitis with a neoplastic cell population consistent with secondary involvement by T-cell lymphoma. Sinoscopy was performed to obtain samples of the sphenoid sinus polyp and right turbinate, as found in the imaging studies. The biopsy showed extensive infiltrate by large lymphoma cells with marked necrosis and angiocentric/destruction distribution. Immunohistochemical studies found that the lymphoma cells were strongly diffusely positive for CD45 and were otherwise negative for CD56. Highly proliferative T-cell lymphoma, not otherwise specified, was diagnosed (CD3-/CD5-/BF1-/CD8+/CD2+/CD7+/CD30-) (Figure 4). It was confirmed by T-cell gene rearrangement studies, with a monoclonal peak similar to that found in the skin biopsy. In situ hybridization staining for EBV encoded–RNA (EBER) was negative. Bone marrow biopsy demonstrated cellular marrow with trilineage hematopoiesis and no definite morphologic evidence of lymphoma.

For further evaluation, computed tomography of the neck, chest, abdomen, and pelvis was performed and demonstrated a 4.4-cm mass in the left lower lobe of the lung, with no lymphadenopathy. Bronchoscopic biopsy of the mass showed T-cell lymphoma with pathologic findings similar to those seen in the sinonasal cavity.

An Ommaya reservoir was placed, and the patient received intrathecal chemotherapy with methotrexate, cytarabine (Ara-C), and hydrocortisone. Later, a port was placed, and 2 cycles of systemic treatment were completed with a combination of etoposide, methylprednisolone, high-dose Ara-C, and cisplatin (ESHAP). Unfortunately, the patient died 2 months following his initial presentation, and no postmortem examination was performed.

Discussion

The patient presented with gradual development of multiple cranial nerve palsies and diffuse nodular scaly rash. He underwent extensive evaluation to explore the cause of his neurologic findings. The initial differential diagnoses included neurologic causes (eg, multiple sclerosis, myasthenia gravis, Miller-Fisher syndrome, Wernicke

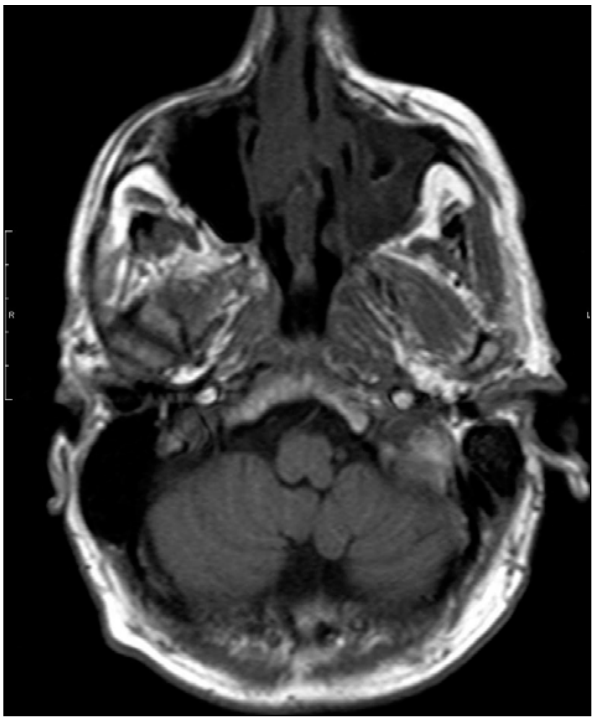

Figure 3. Gadolinium-enhanced magnetic resonance imaging of the brain and orbit. This precontrast T1-weighted axial image demonstrates left maxillary sinus fullness and mucosal thickening with polypoid lesions in the right nasal cavity.

encephalopathy, Ramsay Hunt syndrome, and heavy metal intoxication), autoimmune and vascular causes (eg, CNS vasculitis, cavernous sinus thrombosis, Wegener's granulomatosis, systemic lupus erythematosus, polyarteritis nodosa, and sarcoidosis), infectious causes (eg, viral [human immunodeficiency virus, progressive multifocal leukoencephalopathy, herpes simplex virus, cytomegalovirus, EBV], bacterial [Lyme, botulism, tuberculosis, nocardia, actinomyces, syphilis], and fungal [cryptococcus, aspergillosis, mucor]), and malignant causes (eg, leptomeningeal carcinomatosis or lymphomatosis, paraneoplastic encephalitis, lymphomas, and leukemias).[13,14] Sinus and lung masses were subsequently identified. Based on the clinical presentation, along with the laboratory and imaging findings, the patient was diagnosed with sinonasal PTCL-NOS.

Sinonasal lymphoma involving the nasal cavity or paranasal sinuses is a rare primary NHL, mostly diffuse large B-cell type.[4,8,15] T-cell and natural killer–cell lymphomas are less common and are usually found in the nasal cavity with EBV-association.[12] The latter are more aggressive and are associated with a worse prognosis. The patient had a positive serum EBV DNA PCR, but his tissue was negative for EBER. Sinonasal T-cell lymphomas are extremely rare and also carry a poor prognosis in comparison to B-cell NHL.[8] PTCL-NOS is a T-cell lymphoma that does not match one of the defined entities.[16] It is the most common subtype of PTCL worldwide.[17,18] Most of the patients in this subclass are adults with generalized aggressive disease and poor prognosis.[19,20] Histologically, a range of cellular morphologies can be identified.[18,21] Involvement of the paranasal sinus and elevated serum lactate dehydrogenase level were reported to increase the risk of CNS involvement in patients with PTCL.[10,11]

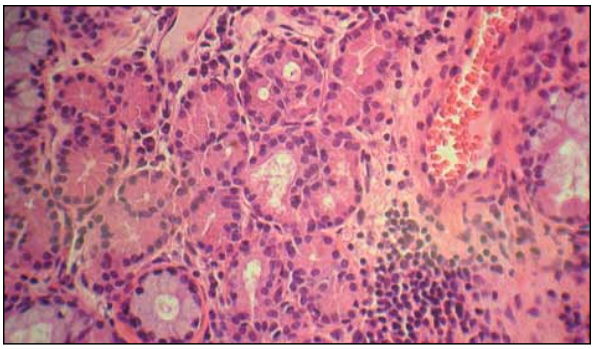

Figure 4. High-power view of the sinus-sphenoid polyp tissue sections shows respiratory mucosa and submucosa with extensive infiltrate by large lymphoma cells with marked necrosis and angiocentric distribution (hematoxylin-eosin stain).

The presenting symptoms in sinonasal lymphomas, whether B cell or T cell, seldom include neurologic involvement. There have been reports of diplopia, visual or hearing impairment, paresthesia, anosmia, trigeminal neuralgia, and ptosis at presentation,[12] but not of multiple cranial nerve involvement. This report described the rare presentation of a middle-aged man with cranial nerve palsies secondary to PTCL-NOS. Since concurrent multiple cranial nerve palsies are a neurologic complication that may be the initial manifestation of lymphoma, healthcare providers—mainly radiologists and otolaryngologists—must have a high index of suspicion to evaluate these patients and differentiate sinonasal lymphomas from other causes.

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Review

An Unusual Extranodal Presentation of Non-Hodgkin Lymphoma

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Post-thymic T-cell lymphomas represent less than 15% of all non-Hodgkin lymphomas (NHL) and can be divided into 2 subsets, peripheral T-cell lymphomas (PTCLs) or cutaneous T-cell lymphomas (CTCLs), based on their primary site of involvement and presentation. The 2008 World Health Organization (WHO) classification of PTCL and the 2005 WHO-European Organization for Research and Treatment of Cancer classification of CTCL (revised in 2008 by the WHO) includes more than 35 biologically and clinically distinct T-cell and natural killer (NK)-cell neoplasms that differ significantly in presentation, pathology, and response to therapy.[1-3] The epidemiology of T-cell lymphomas shows important geographic and racial variation, and the overall incidence of PTCL is higher in Asia and Central/South America, where it is likely secondary to infection with human lymphotropic virus type 1 and Epstein-Barr virus (EBV).[4] CTCL does not appear to have a well-identified increase in prevalence in any region in the United States, but it is more common among African Americans.[5]

The clinical presentation of NHL varies tremendously based on histologic subtype. Involvement of the central nervous system (CNS) can occur as the sole area of disease (primary CNS lymphoma) or due to secondary spread of systemic disease. Secondary involvement of the CNS is found in a minority of NHL patients at the time of diagnosis, and the exact percentage differs by subtype. In aggressive B-cell NHL, 2–10% of patients will have CNS involvement at some time during their course.[6,7] Risk factors for invasion of the CNS have been proposed and include advanced-stage disease, presence of B symptoms, more than 1 extranodal site of disease, elevated lactate dehydrogenase level, low serum albumin concentration, age older than 60 years, high- or high-intermediate–risk disease as assessed by the international prognostic score, and certain high-risk sites of disease.[6-8] High-risk sites of disease include the testes, paranasal sinuses, and retroperitoneum; the risk of other sites (eg, the bone and bone marrow, breast, mediastinum, and blood vessels) is more controversial.[8-11] Risk of CNS involvement varies according to the histologic subtype of B-cell NHL, with Burkitt lymphoma, lymphoblastic lymphoma, and mantle cell lymphoma having an incidence of CNS relapse without CNS prophylaxis

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ranging from 4–50% in some patients.[12-14] Patients with AIDS-related NHL have an increased risk of CNS involvement likely due to a high frequency of extranodal disease and more aggressive histology.[15]

Except for sporadic case reports, little is known about CNS involvement by T-cell lymphoma. These patients commonly have a number of the noted risk factors outlined above. A single-institution retrospective review of 250 patients with peripheral T-cell NHL from the United States reported a CNS relapse rate of 2.4%.[16] In comparison, a second retrospective study of 228 patients from Korea with primary NK/T-cell lymphoma reported a rate of CNS involvement of 8.8%.[17] The higher rate in this population likely reflects the predilection of NK/T-cell lymphoma for involvement of the hard palate and nose, with venous drainage to the cavernous sinuses. Retrospective series from Japan and the United States also report high rates of CNS involvement in the human T-cell lymphotropic virus-1 (HTLV-1)-related adult T-cell leukemia/lymphoma (ATLL), ranging from 10% to as much as 30%. According to the National Comprehensive Cancer Network guidelines, ATLL is the only PTCL entity in which prophylaxis with intrathecal chemotherapy is recommended. Lastly, although the indolent CTCL mycosis fungoides primarily involves the skin, autopsy and clinical studies have demonstrated CNS involvement similar to that in other systemic NHLs.[18-22]

The mechanisms by which lymphoma cells enter the CNS are poorly defined. Hypotheses include hematogenous spread, direct extension from adjacent metastases, and centripetal growth along neurovascular bundles. Neural cell adhesion molecule (NCAM, also known as CD56)—a homophilic binding glycoprotein expressed on the surface of neurons, glia, skeletal muscle, and NK cells—has also been implicated, and tumor cells expressing CD56 may interact with cells in the CNS and facilitate the trafficking across the blood-brain barrier.[23] In a series of 46 patients with T-cell lymphoma, 24% were NCAM-positive, and of these, 36% had CNS involvement, compared with 3% of NCAM-negative tumors.[24] NCAM-positive tumors also had a predilection for widespread extranodal involvement, and patients with NCAM-positive tumors had a median survival of less than half that of patients with NCAM-negative tumors. A study of T-cell trafficking into the subarachnoid space of healthy individuals found that P- and E-selectin expression on endothelial cells in the CNS may also be a contributing factor.[25]

The case of multiple cranial nerve palsies as the initial presentation of PTCL reported by Weiss and colleagues contributes to the growing literature of CNS involvement in T-cell NHL.[26] The patient was a middle-aged white man whose T-cell lymphoma was diagnosed after he presented with multiple cranial nerve palsies and skin rash. Imaging revealed likely involvement of the leptomeninges, multiple cranial nerves, the nasal cavity, and the lung, and tissue sampling confirmed disease in the skin, nasal cavity, lung, and cerebrospinal fluid. Notably, EBV was isolated from the peripheral blood but not in the tissue biopsy sample, CD56 was negative on immunostain from the nasal specimen, and a similar monoclonal T-cell receptor rearrangement was detected in the skin and nasal cavity.

A prominent feature of this presentation is the multiple sites of extranodal involvement with a lack of nodal disease. This finding is not uncommon, as between 10% and 35% of patients with NHL will have primary extranodal disease at diagnosis, and this likely predisposed the patient to secondary CNS involvement.[27] The diagnosis in this case was PTCL-NOS, however NK/T-cell lymphoma may have been considered. This case had several features that were inconsistent with NK/T-cell lymphoma: the patient was not from a geographic area associated with high risk, the large majority of patients with NK/T-cell lymphoma present with localized nasal obstruction (although extranodal disease may occur), most tumor cells express the NK cell marker CD56, T-cell receptor rearrangements are usually germline, and in situ hybridization for EBV-encoded small nuclear RNAs is virtually always present.[28] Interestingly, EBV was detected in the peripheral blood but not in the tumor cells of this patient. Approximately 90–95% of the adult human population carries EBV as a chronic latent infection, and healthy adults experience episodes of EBV viremia with EBV DNA levels in the whole blood of less than 2,000 copies/mL.[29] Persistent and high-titer viremia may reflect an underlying immunocompromised state and predisposition to NHL, although the exact role in the pathogenesis of PTCL-NOS is not clear.[30]

PTCL-NOS is an aggressive neoplasm, and there is no general consensus on the optimal treatment regimen. Anthracycline-based combination chemotherapy regimens are commonly used. Even with therapy, however, only approximately 30% of patients are alive and free of disease at 5 years.[4] Therapy of CNS involvement could include craniospinal irradiation, high-dose systemic therapy, high-dose corticosteroids, and/or intrathecal chemotherapy. However, prognosis is poor, and survival rates are similar regardless of the treatment used.[31,32] The reported patient highlights the unusual extranodal presentation of NHL and the extremely poor prognosis of patients with PTCL, particularly when the CNS is involved.

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