Review

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Isolated hypoglossal nerve palsy as a presenting symptom of metastatic peripheral T-cell lymphoma – not otherwise specified (PTCL–NOS): a unique case & a review of the literature

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Practice points

- Lymphomas are a diverse group of neoplasms with varying genotypes, presentation, behavior and treatment responsiveness.
- The diagnosis of lymphoma requires biopsy and immunophenotype as defined by flow cytometry and/or immunohistochemistry.
- Tissue histology differentiates Hodgkin lymphoma from non-Hodgkin lymphoma.
- Lymphoma prognosis is evaluated by a variety of scoring systems, some of which incorporate age, lactate dehydrogenase, platelet count, Eastern Cooperative Oncology Group, extranodal and bone marrow involvement, and the Ki-67.
- Lymphoma treatment is guided by prognosis and stage of disease.
- Treatment of Hodgkin lymphoma typically includes a variation of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) and radiation.
- Treatment of non-Hodgkin lymphoma traditionally involves cyclophosphamide, doxorubicin, prednisone, and vincristine (CHOP) or rituximab-CHOP (R-CHOP) and may be supplemented by radiation, surgery and/or stem cell therapy.
- The development of immunotherapy in the form of monoclonal antibodies, antibody–drug conjugates, and chimeric antigen receptor T-cell therapy allow for more tumor-specific therapeutics.

Extensive and significant technological advancements have enhanced the sensitivity and accuracy of the pathologic classification, diagnosis, and therapeutics of lymphoma. These advances have prompted a more comprehensive understanding of neoplastic behavior and have led to improvements in both treatment and prognosis. This paper presents a comprehensive review of lymphoma and features a case report of a unique presentation of peripheral T-cell lymphoma – not otherwise specified that presented with isolated hypoglossal nerve dysfunction.

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Peripheral T-cell lymphoma-not otherwise specified (PTCL–NOS), also recognized as peripheral T-cell lymphoma of the unspecified variant (PTCL-U), is a highly aggressive subtype of T-cell non-Hodgkin lymphoma. The PTCL–NOS subtype of PTCL incorporates a heterogeneous group of T-cell lymphomas that do not meet inclusionary criteria for other subtypes and likely represent not yet identified subtypes of PTCL. Consequently, PTCL–NOS is a diagnosis of exclusion and lacks precise clinical, immunophenotypic and genetic inclusionary criteria. The featured case describes a young man who presented to the emergency department with symptoms suggestive for cranial

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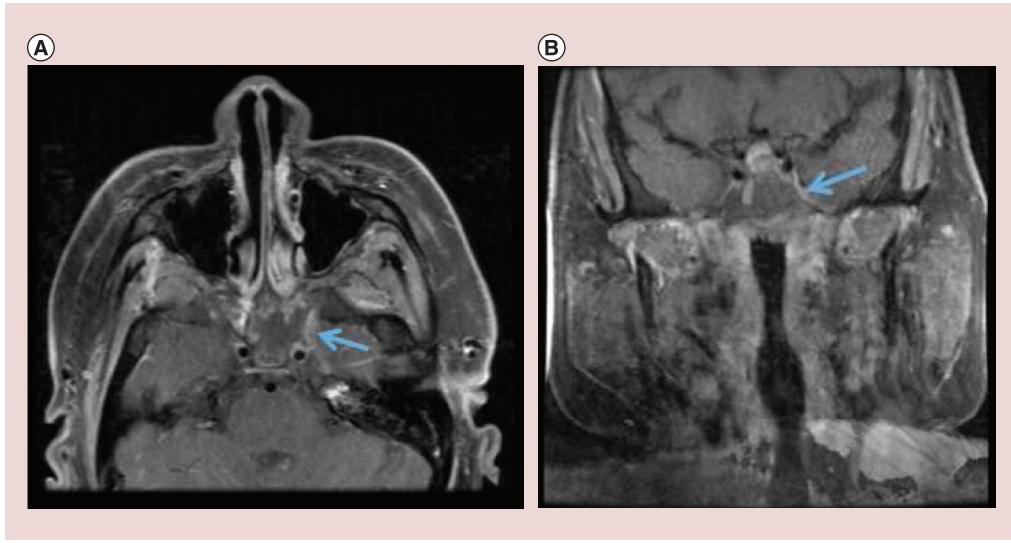

Figure 1. MRI head: intracranial dural involvement – postcontrast T1-weighted images show asymmetric dural thickening in inferomedial left middle cranial fossa, adjacent to cavernous sinus and Meckel's cave.

nerve XII palsy. Further diagnostic investigation revealed a diagnosis of PTCL–NOS with meningeal involvement resulting in isolated cranial nerve disruption. This case report and accompanying review of lymphoma highlight a unique presentation and immunophenotype of PTCL–NOS not previously described in the literature.

Case report

A 25-year-old Hispanic male presented to the emergency room with a 2.5-week history of dysarthria, inability to protrude the tongue, and worsening right knee and back pain for 4–6 months duration. Patient additionally reported temporal headaches, fevers (T_{max} 101°F), and chills for the past 2 weeks prior to presentation. Past medical history was unremarkable and family history significant only for hypertension. Medications at time of presentation included naproxen and prednisolone. Social history was notable for tobacco and alcohol use.

Vital signs on admission: temperature 98°F, blood pressure 130/76 mmHg, heart rate 94 bpm, respiratory rate 18, SpO_2 98%, BMI 32.89 kg/m^2. Physical examination was notable for inability to protrude the tongue, limited bilateral lateral tongue deviation, and decreased right palate elevation. Examination was otherwise unremarkable and there was no evidence of lymphadenopathy or other neurologic deficits. Laboratory tests revealed hemoglobin 9.4, leukocytes 19.4 thousand/µl, platelets 108, lactate 3.5 mmol/l, C-reactive protein > 160 mg/l, erythrocyte sedimentation rate 125 mm/h, ferritin 3389 ng/ml and lactate dehydrogenase (LDH) 963 U/l. Renal function parameters and liver enzymes were normal. Serology for cytomegalovirus IgG was positive at 1.5 mg/dl. Blood cultures were sterile, as well as serology for Lyme disease, Epstein-Barr virus (EBV), HIV, HSV, human T-lymphotropic virus type 1 (HTLV1) and HTLV2.

MRI demonstrated diffuse dural thickening with enhancement and nonspecific diffuse marrow hypointensity without evidence of ischemic disease or mass effect (Figure 1). Lumbar puncture was performed to rule out infection. Cerebrospinal fluid (CSF) analysis displayed elevated protein (121 mg/dl), decreased glucose (31 mg/dl) and leukocytosis (317 per microliter), 90% of which were atypical cells suggestive of large cell lymphoma. MRI of the right femur demonstrated a dominant right anterior thigh soft tissue mass measuring up to 8.5 cm × 8.3 cm × 16.2 cm that encircled the femoral shaft and invaded the medullary cavity as well as anterior focal cortical destruction (impending pathologic fracture) and an enhancing soft tissue masses in the left obturator musculature, underlying acetabulum, right ischiopubic ramus and along the distal right femur. Biopsy of right femoral soft tissue mass yielded a diagnosis of lymphoma (Figure 2). Immunohistochemical stains showed neoplastic large cells positive for CD4, CD43 and CD30 (subset) and negative for CD3, CD5, CD20, CD138, BCL-2 and BCL-6. EBER (EBV-encoded RNA) was negative. The Ki-67 index was approximately 60%. Immunohistochemical stains confirmed a $CD4^+$ T-cell lymphoma with abnormal phenotype ($CD3^-/CD5^-$), consistent with the diagnosis of PTCL–NOS. Further investigation revealed metastatic involvement of lung pleura and multiple cortically destructive lytic lesions within

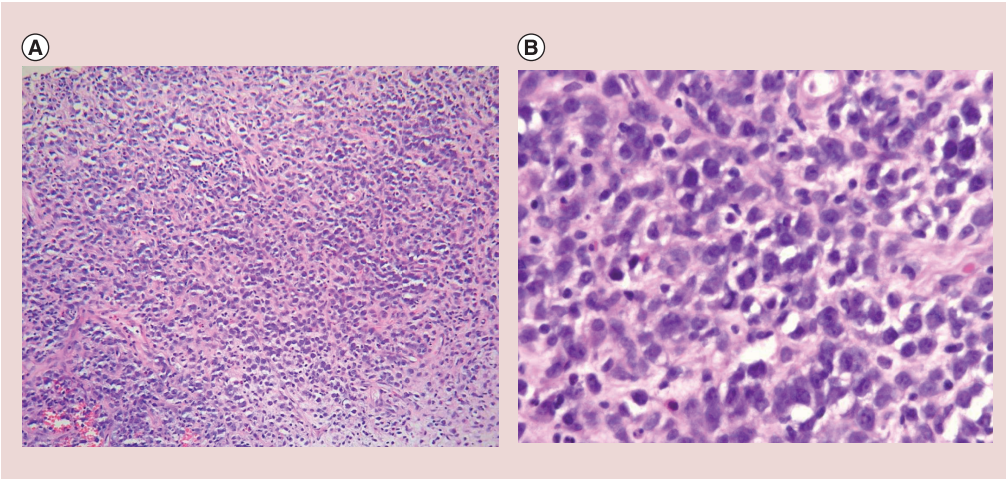

Figure 2. Hematoxylin and eosin-stained tissue displaying diffuse sheets of lymphoid cells within fibrotic stroma (20×). Foci of large cells with neoplastic features (irregular, pleomorphic, hyperchromatic, vesicular nuclei, prominent nucleoli, frequent mitoses) are present (40×) morphologically consistent with lymphoma.

the spine consistent with malignant involvement. The patient's clinical presentation of dysarthria was thought to be secondary to meningeal thickening leading to compression of the hypoglossal nerve.

Chemotherapy was initiated and consisted of four cycles of intravenous EPOCH, consisting of etoposide, prednisone, doxorubicin, vincristine and cyclophosphamide followed by three cycles of gemcitabine and oxaliplatin. The patient also received intrathecal methotrexate and cytarabine for CNS involvement. With poor response to the above regimen and, in the setting of initial neoplastic overexpression of CD30, the patient was trialed on brentuximab vedotin without adequate response. The patient was evaluated for, but did not receive, stem cell transplant.

Five months after initial presentation, the patient developed metastases to his thoracic vertebrae, ribs, femur, facial bones, and lymph nodes. Immunohistochemical stains obtained from a repeat bone marrow biopsy 7 months after presentation revealed neoplastic cells positive for CD45, CD4 (BCL-2 [subset] and c-MYC [subset]), while negative for CD3, CD5, CD79a, TdT and CD20. CD43 staining was suboptimal and equivocal. CD30 weakly stained a small subset of large cells. Overall, the second bone marrow biopsy displayed approximately 60% necrotic material.

The patient expired soon after 7 months following initial presentation.

Literature review

The 2008 WHO's designation of lymphoid neoplasms remains the current standard for lymphoma classification [1]. While the 2008 guidelines are currently in revision with update expected later this year, they are widely accepted by hematopathologists and clinicians to categorize lymphomas [2]. The WHO guidelines classify an incredibly diverse group of hematogenous malignancies by categorizing them into one of three main subsets – myeloid neoplasms, lymphoid neoplasms and histiocytic/dendritic neoplasms [1]. Lymphoid neoplasms, also referred to as lymphomas, represent a heterogeneous class of hematogenous malignancy that originates from lymphoid precursors, progenitor cells and mature lymphocytes. The WHO guidelines organize lymphomas according to the following: type of lymphocyte, microscopic pathology, chromosomal features of the lymphoma cells and the presence of specific proteins on the cell surface [4,5].

Lymphomas are diagnosed with tissue biopsy and classified by histologic morphology into one of two categories: Hodgkin and non-Hodgkin. The presence of Reed-Sternberg cells identifies a lymphoma as Hodgkin and, conversely, the absence of these specific cells distinguishes a lymphoma of the non-Hodgkin variety. While Hodgkin lymphomas are typically of B-lymphocyte origin, non-Hodgkin lymphomas can stem from B-lymphocytes, T-lymphocytes or natural killer (NK cells). Although both Hodgkin and non-Hodgkin lymphomas are hematogenous malignancies that stem from lymphocytes, in addition to having distinct pathologic diagnostic criteria, they can display unique progenitor cell types and immunophenotypes with corresponding treatment responsiveness.

Genetic and molecular data contribute to the classification of neoplastic processes, improving the accuracy of lymphoma diagnoses. The immunophenotype of a cell is the combination of proteins/markers (such as CD20, CD3 and TdT) expressed by cells. Immunophenotype is evaluated by immunohistochemistry and/or flow cytometry, which help to determine the proportion of lymphoid cells that express a certain marker and their location and intensity within the cells [6]. Additionally, the immunophenotype can differentiate between lymphoid cells that are reactive versus those that are neoplastic in which growth and division are dependent on dysfunctional or abnormal cellular signaling.

Immunophenotype analysis identifies the neoplastic cell of origin (B-, T- or NK) and, as a result, flow cytometry and fluorescence *in situ* hybridization studies have been incorporated into the diagnostic standard. Microscopic examination of specific cellular morphology including size, nuclear shape, chromatin configuration, nucleoli, and amount and hue of cytoplasm are also critical components of lymphoma diagnosis and classification [5]. The incorporation of morphologic, immunophenotypic and cytogenetic data, in addition to aiding in the diagnosis of the specific type of lymphoma, allows for more personalized and effective treatments that target specific culprit cells and receptors.

Hodgkin lymphoma

Hodgkin lymphoma represents about 10% of lymphomas and is much less common than non-Hodgkin lymphoma [7]. Within Hodgkin lymphoma, age distribution is bimodal (peaking at ages 20 and 65 years) with an incidence dependent largely on geographic location and relative to the degree of industrial development; the younger age group is associated with transitional economies [8–10].

The cells that compose Hodgkin lymphoma originate from the germinal center or postgerminal center in B cells. They feature pathognomonic Reed–Sternberg cells – large basophilic cells with bilobed/multilobed nuclei in the background of inflammatory cells [7]. Hodgkin lymphoma is further subdivided into both classical and nonclassical variants. Diagnosis of classical Hodgkin lymphoma by an excisional lymph node biopsy with immunophenotyping revealing minimal resemblance of their B-cell immunophenotype (as evidenced by dim expression of PAX5, but absence of most other pan B-cell antigens), expression of CD30, variable expression of CD15, and loss of CD45 [6].

Classical Hodgkin lymphoma typically presents as painless peripheral cervical lymphadenopathy and is further subdivided into nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted [7]. The mixed-cellularity and lymphocyte-depleted subtypes carry an association with EBV/human herpesvirus 4. EBV was the first virus identified to influence cancer pathogenesis and an infection with EBV in the setting of Hodgkin lymphoma is a poor prognostic factor [11]. The poor prognosis of an EBV^+ neoplasm is due in part to the virus's ability to infect a cell and generate antiapoptotic effects. Some of the postulated mechanisms by which EBV contributes to a poor prognosis in patients with Hodgkin lymphoma include methylation of tumor-suppressor proteins and alteration of host chromosome structures (i.e., telomeres, chromatin) that are directly involved with cellular division and reproduction [12].

Treatment of Hodgkin lymphoma is dependent on both prognosis and stage of disease. Favorable prognosis of Hodgkin lymphoma is defined by the European Organization for the Research and Treatment of Cancer as the following: age greater than 50; lack of mediastinal adenopathy and B-symptoms (or with an erythrocyte sedimentation rate of less than 30 with B-symptoms); or the absence of B symptoms in addition to disease limited to three or fewer anatomic regions [13]. B-symptoms are associated with both Hodgkin and non-Hodgkin lymphoma and include fever with temperature greater than 38°C, unexplained weight loss greater than 10% body weight over the past 6 months and the presence of drenching night sweats [3]. Stage of disease is classified by the Lugano classification – Stage I defined as involvement of a single lymph node, Stage II defined as involvement of two or more lymph nodes on the same side of the diaphragm, Stage III involvement of two or more lymph nodes on opposite sides of the diaphragm, Stage IV is diffuse and/or disseminated involvement with or without lymph node involvement [14].

Patients with Stages I–II Hodgkin lymphoma are typically treated with radiation and ABVD therapy (doxorubicin, bleomycin, vinblastine and dacarbazine). Advanced Hodgkin lymphoma treatment involves either ABVD or escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone). In patients with advanced disease receiving BEACOPP, the addition of radiation to chemotherapy has shown advantages in freedom from progression, but not overall survival [15]. A third treatment variation for advanced Hodgkin lymphoma, the Stanford V, includes radiation along with doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide and prednisone [15].

Non-Hodgkin lymphoma

Non-Hodgkin lymphoma is exceedingly more common than Hodgkin lymphoma in the USA, accounting for about 90% of all new cases [1,15]. It is associated with a variety of factors including personal or family history of lymphoma, obesity, exposure to pesticides or other chemical agents in addition to autoimmune and immunodeficiency disorders [3]. Non-Hodgkin lymphoma is also associated with the following infections: HIV, HTLV-I, EBV, *Borrelia burgdorferi* (*B. afzelii* species), *Chlamydia psittaci* and Hepatitis B and C [17,18].

Non-Hodgkin lymphomas are a diverse group of neoplasms with varying symptomatology, organ involvement, laboratory findings, virulence and prognosis. Aggressive non-Hodgkin lymphomas typically present acutely or subacutely with up to 40% reporting constitutional B-symptoms [19]. Tissue or lymph node biopsy provides data on classification of lymphoid neoplasms, with 85% of non-Hodgkin lymphomas classified as B-cell in origin and the remaining 15% of T-cell origin [4,5]. In addition to tissue or lymph node biopsy and appropriate imaging, patients with non-Hodgkin lymphoma classically have a bone marrow aspiration or biopsy to most accurately stage their disease before treatment is initiated [3]. Bone marrow involvement is estimated in 30–50% of patients with non-Hodgkin lymphoma and is more commonly observed in patients with indolent lymphomas [20,21]. If leptomeningeal metastases are suspected with likelihood of CNS involvement, lumbar punctures are performed with CSF analysis that typically reveals elevated protein and a lymphocyte-predominant pleocytosis [3].

An estimated 50% of patients with non-Hodgkin lymphoma develop extranodal disease and 10–35% have evidence of extranodal lymphoma on initial presentation [3,19]. When present, primary extranodal sites of non-Hodgkin lymphoma are most commonly gastrointestinal and cutaneous [3]. Non-Hodgkin lymphoma with bone involvement usually represents disseminated disease and presents as a painful solitary lesion with swelling or pathologic fracture [3].

Aggressive non-Hodgkin lymphoma subsets include diffuse large B-cell lymphoma, Burkitt lymphoma, adult T-cell leukemia-lymphoma and precursor B and T lymphoblastic leukemia/lymphoma [3]. The most common T-cell lymphomas are further subdivided into anaplastic large cell lymphoma, angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, and PTCL–NOS also referred to PTCL-U. Patients with highly aggressive and fast growing non-Hodgkin lymphoma may present with, or develop, an elevated LDH (suspected due to high tumor burden), hepatic infiltration, and concomitant immune hemolytic anemia [3]. An elevated LDH, especially if greater than two- to three-times the upper limit of normal, is a poor prognostic factor [3].

While some non-Hodgkin lymphomas are quite aggressive, others are more indolent in nature and present more chronically as opposed to acutely. Indolent lymphomas may manifest as the gradual development of lymphadenopathy, hepatomegaly, splenomegaly or cytopenias [3]. Some common indolent non-Hodgkin lymphomas include follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma and splenic marginal zone lymphoma [3].

Similar to Hodgkin lymphoma, treatment of non-Hodgkin lymphoma depends upon disease stage and corresponding prognosis. Treatment may involve chemotherapy, immunotherapy, radiation therapy, stem cell transplant or surgery. The most common chemotherapeutic regimen for the initial treatment of aggressive non-Hodgkin lymphoma is CHOP, a multidrug regimen consisting of cyclophosphamide, doxorubicin, prednisone and vincristine.

Patients with non-Hodgkin lymphoma are treated with an alternate version of CHOP, R-CHOP. R-CHOP includes the addition of rituximab – a monoclonal antibody for the CD20 cell protein expressed by mature B cells. Rituximab can be used as monotherapy or as part of a multidrug regimen to treat lymphoma. Patients with diffuse large B-cell lymphoma treated with R-CHOP have a lower incidence of progression, relapse and death when compared with those treated with CHOP alone [22]. The addition of rituximab to the CHOP regimen in patients with diffuse large B-cell lymphoma was found to significantly affect outcomes independent of both disease severity (as determined by International Prognostic Index [IPI] score) and age [22]. The mechanisms of monoclonal antibody-mediated cellular destruction include activation of the complement pathway as well as direct antibody-dependent cellular toxicity. Rituximab was the first therapeutic monoclonal antibody used in cancer therapy. In addition to its role in induction therapy of B-cell malignancies, many patients continue to receive rituximab as maintenance therapy to further suppress malignant activity. The use of rituximab as maintenance therapy has been associated with significantly prolonged progression-free survival [23]. Other immunotherapeutic drugs used in non-Hodgkin lymphoma include two other CD20 monoclonal antibodies – obinutuzumab and ofatumumab – as well as a distinct class of drugs including monoclonal drug–antibody conjugates.

Brentuximab vedotin

Brentuximab vedotin is an antibody–drug conjugate that targets $CD30^+$ cancer cells [24]. This antibody–drug conjugate is approved by the US FDA for patients with Hodgkin lymphoma following failure of autologous stem cell transplant or following failure of at least two multidrug chemotherapeutic regimens who are not candidates for autologous stem cell transplant. Brentuximab vedotin is also approved for patients with systemic anaplastic large-cell lymphoma after failure of at least one multidrug chemotherapeutic regimen.

Treatment with the traditional CHOP regimen of PTCL has yielded an overall survival rate ranging from 12 to 49% [25]. In response to the bleak outcomes of CHOP in PTCL, and with prior demonstrated efficacy of brentuximab vedotin in Hodgkin and anaplastic large cell lymphoma, research has been directed to evaluate its efficacy in populations with PTCL [24]. An open-label Phase I international study published in 2014 involving 11 centers examined the efficacy of brentuximab vedotin in patients with PTCL that expressed CD30. The sample of 39 patients received brentuximab therapy either in sequence following CHOP therapy or in combination with cyclophosphamide, doxorubicin, prednisone (with the omission of vincristine from CHOP regimen) as initial treatment. 85% of the patients who received sequential therapy with brentuximab obtained a complete remission rate of 62% with an estimated 1-year progression-free survival rate of 71%. 88% of the combination group achieved complete remission with a 1-year progression-free survival rate of 71% [26]. While the total sample size for this study was 39, the rarity of PTCL makes it difficult to study, and only two of these patients had PTCL–NOS. Alternative therapeutic regimens that have been approved by the FDA for relapsed and refractory PTCL include pralatrexate, romidepsin and bleinostat [27].

Chimeric antigen receptor T-cell therapy

Despite the encouraging role of monoclonal antibodies and drug–antibody conjugates in cancer treatment, some lymphomas remain either refractory to treatment or relapse following therapy; these limitations prompted the development of chimeric antigen receptor (CAR) therapy. CAR therapy is an emerging type of immunotherapy utilizing autologous or allogeneic T-cells that are genetically engineered to target malignant cells. CAR therapy involves modulating T-cells with artificial receptors to target specific tumor cell surface antigen, activate T-cells and thereby augment T-cell function. CD19, a cell-surface protein exclusively expressed by B-lymphocytes, is one target that has been investigated with CAR therapy. Patients with refractory B-cell lymphoma who received CD19 T-cells had improved clinical outcomes in comparison with those who received chemotherapy alone [28]. While CD19-redirected CAR targets a specific cellular protein on B-cells similar to the way rituximab targets CD20, this type of immunotherapy is unique in that it utilizes genetically modified T-cells to target receptors as opposed to the mechanism of a generic antibody. Unlike monoclonal antibody treatment, CAR therapy involves the manipulation of lymphocytes and requires immunosuppression in the form of lymphodepletion prior to receipt of genetically modified cells. Sources of variation with current investigations of CD19-redirected CAR therapy in non-Hodgkin lymphoma include the type and duration of immunosuppressant therapy as well as the time between immunosuppressive therapy and receipt of CAR T-cells.

Immunophenotype

Mature T-cell lymphomas tend to display either a T-helper ($CD4^+$) or cytotoxic ($CD8^+$) immunophenotype and may show loss of markers expressed by most normal T-cells such as CD5 and CD7 [6]. Other cell markers implicated in lymphoma include *c-MYC*, a proto-oncogene present on chromosome 8, which regulates the expression of 15% of genes in the human genome [29]. In the setting of an aggressive lymphoma, *c-MYC* induces cell proliferation and promotes both genomic instability and apoptosis [30]. *BCL-2*, another cellular marker, is a potent inhibitor of apoptosis, therefore potentiating cell survival [31]. Genetic instability and DNA damage in *MYC*-induced lymphomas is due in part to the expression of proapoptotic proteins that, in the absence of *BCL-2*, bind to effector proteins such as *BAX* or *BAK* and initiate mitochondrial depolarization and subsequent cell death [32].

The coexpression of both *c-MYC* and *BCL-2* prompts a synergistic and potentially hazardous genomic backdrop for catastrophic cellular signaling and division. The immunophenotypic expression of both *BCL-2* and *c-MYC* is a phenomenon observed in B-cell lymphomas, specifically diffuse large B-cell lymphoma and referred to as 'double-hit lymphoma' [33]. Despite controlling for clinical and molecular prognostic factors such as germinal center genotype, patients with double-hit diffuse B-cell lymphoma have inferior overall survival [33].

Table 1. Lymphoma prognostic indices.

Variables	Patient X	IPI	PIT	m-PIT	ITCLP
Age (>60)		X	X	X	X
ECOG (>1)	X (3)	X	X	X	X
Elevated LDH	X (963)	X	X	X	
Ann Arbor stage (III–IV)	X (IV)	X			
Extranodal involvement (≥ two sites)	X	X			
Bone marrow involvement	X		X		
Platelet count (<150,000/mmc)	X (108)				X
Ki-67 (≥ 80%)				X	

ECOG: Eastern Cooperative Oncology Group; IPI: International prognostic index; ITCLP: International T-cell lymphoma project; LDH: Lactate dehydrogenase; m-PIT: Modified-prognostic index for PTCL–NOS; Patient X: Current patient under review; PIT: Prognostic index for PTCL–NOS; PTCL–NOS: Peripheral T-cell lymphoma–not otherwise specified. Adapted with permission from [27].

Lymphoma prognostic data

Multiple prognostic indicator scores have been developed that incorporate an expanding breadth of factors that help providers to estimate outcomes. Some of these lymphoma-specific prognostic scores include the International Prognostic Index, the International T-cell Lymphoma Project as well as well as other prognostic scores specific to PTCL–NOS, which is the focus of this case, such as the Prognostic Index for PTCL–NOS and the modified-Prognostic Index for PTCL–NOS (Table 1). These scores incorporate data regarding age, LDH, platelet count, Eastern Cooperative Oncology Group, the presence of extranodal and bone marrow involvement, and the Ki-67 to catalog the behavior of the lymphoma and estimate its virulence.

Peripheral T-cell lymphoma-not otherwise specified

Mature T-cell neoplasms are known as PTCLs, a heterogeneous group of lymphoid disorders classified by morphology, immunophenotype, genetics, and clinical features. PTCL–NOS is a subtype of this category that encompasses all T-cell lymphomas that cannot be classified by specific features. It accounts for an estimated 25% of PTCL and makes up approximately 4% of all non-Hodgkin lymphomas [3,27]. PTCL–NOS occurs in older patients and usually presents in advanced stages with extremely variable symptomatology. While constitutional B-symptoms are the presenting symptom for 35% of patients with PTCL–NOS, presentation usually also includes generalized lymphadenopathy with or without extra-nodal involvement [34]. Only approximately 13% have extranodal involvement without evidence of nodal involvement [34]. The two most common sites for extranodal disease are cutaneous and gastrointestinal [3]. CNS involvement is only observed in approximately 4–6% of patients with PTCL. There are limited published studies that have specifically addressed the risk of CNS disease and relapse in PTCL.

Unfavorable PTCL–NOS prognostic factors include those that compose the IPI (Table 1), B-symptoms, bulky disease as defined by tumor ≥10 cm, elevated serum C-reactive protein, circulating tumor cells, and platelet count less than 150×10^9. The aforementioned unfavorable prognostic factors are predictive of both overall survival and failure-free survival [34]. Notably, hypergammaglobulinemia was a favorable prognostic indicator of both overall survival and failure-free survival [34].

Hypoglossal nerve palsy

Cranial nerve XII, the hypoglossal nerve, is a purely motor nerve responsible for the innervation of the styloglossus, hyoglossus and genioglossus, muscles recruited for tongue protrusion. Isolated optic nerve, oculomotor nerve and trigeminal nerve involvement are the most common cranial nerve deficits observed with lymphoma [35]. Isolated palsy of the hypoglossal nerve is extremely atypical [36].

In both nuclear (medullary) and peripheral lesions, the clinical signs of hypoglossal nerve dysfunction are ipsilateral atrophy, fasciculation, dysarthria and tongue palsy with deviation toward the side of the lesion with tongue protrusion. Bilateral affection of the hypoglossal nerve manifests as a complete tongue palsy with consecutive oral dysphagia and dysarthria [37,27]. A 2016 review of 245 cases of hypoglossal nerve palsies revealed 14.2% to be primary neoplastic and 13% due to metastatic malignancy, with the remainder postoperative, inflammatory, and secondary to radiation and trauma [39]. Male gender and a personal history of malignancy are hypothesized to predict a neoplastic source of cranial nerve XII palsy [39].

Reported etiologies of hypoglossal nerve palsy without further neurologic manifestations include tumor, Chiari malformation, dural arteriovenous fistula of the transverse sinus, and idiopathic [36,40]. Other causes of isolated cranial nerve XII palsy include infectious sequelae from dengue fever, mononucleosis, and tuberculosis [41–43]. Autoimmune, vascular conditions, and mechanical compression secondary to osteophyte projection of the atlanto-occipital joint have also resulted in cranial nerve XII palsy [44].

Beyond the scope of PTCL–NOS, a review of B-cell and T-cell lymphomas and the cranial nerves emphasizes the rarity of cranial and peripheral nerve involvement by lymphoma [35]. Although rare, when lymphoma does lead to isolated cranial nerve involvement, it is typically associated with a lymphoma of B-cell origin [35]. While leptomeningeal spread is possible if there is enlargement of cranial nerves within the leptomeningeal space, dural involvement is rare [35].

A case published in Clinical Neurology in 2012 describes a patient with dysarthria, headaches and bilateral tongue atrophy found to have cranial nerve (CN) XII enlargement on MRI (Table 2). In contrast to the current T-cell lymphoma with isolated hypoglossal nerve palsy, this case is a B-cell lymphoma with hypoglossal nerve palsy along with both oculomotor nerve palsy and leg weakness [45].

Case discussion

Why this case is unique for PTCL–NOS

PTCL–NOS metastatic on presentation with isolated CN XII involvement, extension into the dura, and an immunophenotype positive for *BCL-2*/*c-MYC* in a 25-year-old Hispanic male without EBV seropositivity or lymphadenopathy. Of the ten previously reported key prognostic factors of PTCL–NOS, the patient under review manifested seven with the exclusion of circulating tumor cells, bulky disease greater than 10 cm, and age more than 60 years [34].

Age/BMI

PTCL–NOS typically affects patients with a median age of 60 years and is twice as common in men than in women [34]. A review of the current case, in conjunction with the previously reported five other cases of PTCL–NOS with cranial nerve involvement, demonstrates a bimodal age distribution with peaks at ages 23–25 [46,47] and 56–60 years [48–50]. The patient in the current case study had a BMI of 32.89, which, per National Institute of Health standards, quantifies Class I obesity [51]. Per the Cancer Prevention Study II, the relative risk of mortality in patients with non-Hodgkin's lymphoma and a BMI between 29.9 and 39.9 is 1.50 [52].

Ethnicity

The patient under review is the only reported patient with PTCL–NOS and CNS involvement that is of Hispanic ethnicity. Two of the other five other documented cases of PTCL–NOS with CNS involvement did not report race, however, the patients in the remaining three studies were Caucasian [46,48] and Japanese [49]. According to data from the National Cancer Institute pooled from 2012 to 2014, Hispanic patients in their 20s have a 0.02% chance of being diagnosed with non-Hodgkin lymphoma in their 20s and an overall lifetime risk of 2.16% with an estimated death from cancer estimated at 0.77% [53]. Hispanics were reported to have the second to lowest risk of non-Hodgkin lymphoma diagnosis in their 20s, second to American Indians/Alaskan Natives, yet the second to the highest risk of death from non-Hodgkin lymphoma, following Caucasians [53].

Isolated extranodal involvement

This presentation of PTCL–NOS is unique, representing the only reported case to date with isolated extranodal involvement lacking intrinsic nodal lymphadenopathy on initial presentation. Furthermore, while extranodal disease without intrinsic lymphadenopathy is a rarity in PTCL–NOS, when present it has been reported as primarily gastrointestinal and cutaneous [3]. Divergent from these previously reported sites of extranodal lymphadenopathy, the patient under review presented with lesions of the right femur, hypoglossal nerve, and dura.

Isolated hypoglossal nerve involvement

The patient under review presented with a history of new-onset dysarthria with limited tongue protrusion, indicators of a bilateral hypoglossal nerve deficit, which retrospectively are presumed secondary to lymphoma. While there are five total reported cases of neurologic and cranial nerve involvement secondary to PTLC-NOS to our knowledge (Table 2), the present case characterizes the only presentation of isolated hypoglossal nerve involvement reported

Table 2. Peripheral T-cell lymphoma-not otherwise specified, and the CNS involvement to date.

Characteristics	Patient X	Fragou *et al.*, 2009 [46]	Weiss *et al.*, 2012 [48]	Matano *et al.*, 2006 [49]	Wang *et al.*, 2016 [47]	Grau *et al.*, 2010 [50]
Age (gender) at dx	25 (male)	23 (female)	56 (male)	57 (male)	23 (male)	60 (female)
Race	Hispanic	Caucasian	Caucasian	Japanese	Not reported	Not reported
Presenting symptom	Two-week history of fevers and temporal headaches; 2.5-week history of dysarthria, inability to protrude the tongue, 4–6 months of worsening right knee and back pain	Ischemic stroke (fever 39°C and hemiplegia)	Right-sided facial weakness for 1 day (history of 2 months URI symptoms with frontal headache and postnasal drip), blurry vision, ipsilateral hearing loss	Subcutaneous tumor on back. Complete remission after chemotherapy then relapsed. One year later developed diplopia, dysarthria, dysphagia	One-month history of intermittent high fever (T_{max} 40°C) and low back pain, night sweats, progressive weight loss	Intermittent diplopia for 1 day that then persisted the following day
Lymphadenopathy on presentation	Absent	Present (inguinal)	Absent	Present (axillary, inguinal)	Absent	Absent
LDH	963	356	Not reported	CSF LDH 631, serum LDH not reported	WNL	Not reported
Ann Arbor stage	IV	IV	IV	IV	'IE'	I
Extranodal involvement	Right femur mass dural extension	Retroperitoneal mass	Mass in left lower lung	Subcutaneous back and leg tumors	Lumbar lesions	Extra-axial mass at caudal clivus
Bone marrow involvement	Present	Absent	Absent	Present	Absent	Absent
Platelet count	28	Not reported	Not reported	Not reported	Not reported	Not reported
Ki-67	60%	8–10%	Not reported	Not reported	60%	40%
Flow cytometry	Initial: CD4, CD43, CD30 (subset); Repeat 7 months after diagnosis: CD45, CD4 (BCL-2 [subset] and c-MYC [subset])	CD3, CD5	CD45, CD8, CD2, CD7	CD2, CD3, HLA-DR5, CD5, CD8, CD38, CD45RO, TCR-α	CD45RO, CD3, CD2, CD45, CD43, Vim, CD38, Mum-1	CD3, CD8, CD1a, CD20, focal signal for CD23
Neurologic involvement	CN XII	Sylvian infarction associated with cerebral edema	CN III, IV, V, VI, VII, VIII	CN III, V, VII, VIII, X, XI, XII	Primary spinal lymphoma with lesions in L3–L5 vertebrae	CN VI
CSF analysis	Protein (121 mg/dl), glucose (31 mg/dl), white cell count (317 per microliter), 90% of which were atypical cells with oval nuclei and prominent nucleoli suggestive for large-cell lymphoma	Reported as 'negative'	Glucose 19 mg/dl, protein 272 mg/dl, RBCs 530/mm^3 nucleated cells of 73/mm^3, sterile cultures, cytology: blast cells with azurophilic cytoplasmic granules	560 mononuclear cells/l; protein 540 mg/dl, glucose 8 mg/dl (plasma glucose, 84 mg/dl); and LDH, 631 IU/l, cytology: proliferation of atypical lymphocytes	'Free of lymphoma cells'	Secondary meningiosis following removal of tumor
Viral serologies: EBV, CMV, HTLV1, and HTLV2 IgG	Serum CMV^+	Negative	Serum EBV^+, HTLV not reported	HTLV negative, EBV testing not reported	Not reported	Not reported
Neurologic imaging	MRI: diffuse dural thickening with enhancement and nonspecific diffuse marrow hypointensity CT: moderate partial opacification of bilateral mastoid air cells, moderate mucosal thickening of sphenoid sinuses	CT: massive sylvian infarction associated with severe cerebral edema	MRI: bilateral leptomeningeal asymmetric enhancement of III, IV, V, VI, VII and VIII, and right sphenoid polypoid lesion and polypoid lesions in right nasal cavity	MRI: multiple cranial nerve thickenings with gadolinium enhancement without intraparenchymal lymphomatous lesions	CT and MRI of lumbar spine with contrast: mass lesions at right of L3–L5 vertebra and in epidural space at L4 with resultant spinal stenosis	CT: extra-axial mass mediolaterally on the caudal clivus without osseous infiltration MRI: homogeneously enhancing, well-circumscribed, extra-axial lesion with moderate displacement of the pontomedullary junction and close proximity to the jugular foramen

CHOP: Cyclophosphamide, doxorubicin, prednisone, and vincristine; CMV: Cytomegalovirus; CN: Cranial nerve; CSF: Cerebrospinal fluid; CT: Computed tomography; Dx: Diagnosis; EBV: Epstein-Barr virus; EPOCH: Etoposide, prednisone, doxorubicin, vincristine and cyclophosphamide; HTLV: Human T-lymphotropic virus type; IE: Single extranodal organ; LDH: Lactate dehydrogenase; Patient X: The current patient under review; RBC: Red blood cells; WNL: Within normal limits.

Table 2. Peripheral T-cell lymphoma-not otherwise specified, and the CNS involvement to date (cont.).

Characteristics	Patient X	Fragou *et al.*, 2009 [46]	Weiss *et al.*, 2012 [48]	Matano *et al.*, 2006 [49]	Wang *et al.*, 2016 [47]	Grau *et al.*, 2010 [50]
Treatment	Four cycles of EPOCH followed by three cycles of gemcitabine and oxaliplatin. He also received intrathecal methotrexate and cytarabine (Ommaya reservoir) for CNS involvement. Trial of brentuximab vedotin	CHOP cyclophosphamide, doxorubicin, vincristine, prednisone	Ommaya reservoir for intrathecal chemotherapy with methotrexate, cytarabine (Ara-C) and hydrocortisone. Two cycles of systemic treatment with etoposide, methylprednisolone, high-dose Ara-C and cisplatin (ESHAP)	Six courses cyclophosphamide, doxorubicin, vincristine, prednisolone → complete remission → subcutaneous tumor relapsed 2002. 2003 neuro involvement intrathecal methotrexate, cytarabine and prednisolone	Spinal surgery for tumor excision followed by local radiotherapy and chemotherapy with cyclophosphamide, adriamycin, vincristine and prednisolone	Preoperative dexamethasone followed by surgical excision of extra-axial mass at caudal clivus
Prognosis	Died 7 months after presentation	Died 26 days after treatment initiation from multiple organ failure; autopsy revealed small periventricular and intraparenchymal mass infiltrations that caused multifocal occlusion of blood vessels	Died 2 months after presentation	Died 2 years after presentation	Died 1 year after presentation	Surgical removal of the lesion relieved the presenting symptoms but presumably also caused CSF dissemination of tumor cells resulting in secondary meningiosis with 'possible poor prognosis'

CHOP: Cyclophosphamide, doxorubicin, prednisone, and vincristine; CMV: Cytomegalovirus; CN: Cranial nerve; CSF: Cerebrospinal fluid; CT: Computed tomography; Dx: Diagnosis; EBV: Epstein-Barr virus; EPOCH: Etoposide, prednisone, doxorubicin, vincristine and cyclophosphamide; HTLV: Human T-lymphotropic virus type; IE: Single extranodal organ; LDH: Lactate dehydrogenase; Patient X: The current patient under review; RBC: Red blood cells; WNL: Within normal limits.

in the literature. The only other reported case of PTCL–NOS that affected the hypoglossal nerve was observed in a 57-year-old Japanese male and also simultaneously affected CN III, V, VII, VIII, X, XI [49]. Notably that case was the only other case, in addition to this current case of PTCL–NOS, with hypoglossal nerve dysfunction that displayed bone marrow involvement.

This case manifests an even more unusual presentation of the already rare lymphomatous cranial nerve involvement. In contrast to the B-cell lymphocyte usually responsible for cranial nerve involvement, a T- cell lymphocyte was the implicated cell. Aside from lymphocyte of origin, the localization of involvement to include the dura further differentiates this case from previously reported lymphomas. Although the patient in this case manifested cranial nerve involvement, it is notably differentiated from primary CNS lymphoma because the CNS was not the sole region of disease; disease burden appreciated initially in the right femur and over the course of disease progression unfortunately involved extensive metastatic bony spread with multiple resultant bony pathologic fractures.

Bone marrow involvement & immunophenotype

As previously referenced above, bone marrow involvement in non-Hodgkin lymphoma occurs in less than 50% of cases and, when present, most commonly is observed in indolent lymphomas. In contrast to the indolent nature of non-Hodgkin lymphoma with bone marrow involvement, this case of PTCL–NOS is a highly aggressive case, classified as one of the 20% of PTCL–NOS cases with bone marrow involvement. Per a review of 340 cases of PTCL–NOS, bone marrow involvement was not a strong predictor of overall survival [34].

Of the five total reported cases of PTCL–NOS with CNS involvement, in addition to the current case, only one other displayed bone marrow involvement [49]. The current patient had two bone marrow biopsies over the course of his disease that, aside from the CD4 cell type present in both biopsies, featured the expression of different cellular markers. The first biopsy obtained during initial diagnosis revealed flow cytometry positive for CD3, CD4, CD5, CD8 and CD30. The second bone marrow biopsy obtained 1 month prior to death featured cells positive for CD4, CD45, *BCL-2* and *c-MYC*.

The patient's initial bone marrow was positive for both CD4 and CD8 (markers of mature T-cell lymphomas) and CD30 (a cell surface receptor that is a member of the tumor necrosis factor family). Despite the fact that the second biopsy revealed lymphoma that did not express CD30, Brentuximab was trialed after the other treatment modalities failed to maintain remission, despite its FDA-approved use in Hodgkin lymphoma.

The second bone marrow biopsy, but not the initial biopsy, was positive for both *c-MYC* and *BCL-2*, indicating a virulent transformation. Literature review yields no other published case of human T-cell lymphoma without associated EBV infection that has an immunophenotype positive for both *c-MYC* and *BCL-2*. The only other reported case of T-cell lymphoma positive for c-MYC and BCL-2 is an extranodal NK/T-cell lymphoma nasal type associated with an EBV infection [54]. Extranodal NK/T-cell lymphoma nasal type involves the overexpression of latent membrane protein-1, which in turn stimulates expression of both *MYC* and *BCL-2* [55]. While the immunotypic presence of both *c-MYC* and *BCL-2* is observed in B-cell lymphomas and deemed a 'double-hit lymphoma,' no such phenomenon has been reported to date of a non-EBV associated T-cell lymphoma.

Conclusion

Extensive and significant technological advancements have enhanced the sensitivity and accuracy of the pathologic classification, diagnosis, and therapeutics of lymphomas. These advances have prompted a more comprehensive understanding of neoplastic behavior and have led to improvements in treatment and prognosis. The featured case report of PTCL–NOS is a unique presentation of a rare disease. The extranodal and metastatic presentation with initial femur involvement and interval development of diffuse dural enhancement with isolated hypoglossal nerve deficit and an immunophenotype remarkable for *BCL-2* and *c-MYC* without associated EBV seropositivity or initial lymphadenopathy is unprecedented in the literature. Epidemiologically, PTCL–NOS with CNS involvement has not previously been reported in a young Hispanic male. The initial presentation with evidence of metastases and resistance to systemic chemotherapy, intrathecal chemotherapy, and novel immunotherapeutic techniques emphasize the aggressive nature of the disease.

Future perspective

Innovations in biotechnology prompt the identification of cell surface receptors, cytokines, growth factors and associated genes, creating opportunities to intercept and modulate cell division. Optimistically, the aforementioned advancements and the development of immunotherapy will allow for treatment that selects solely for neoplastic tissue. Further specification and enhanced precision of immunotherapeutic targets will limit excessive cytotoxic effects on nontarget cells to achieve maximal tumor destruction with minimal effects on benign tissue growth. Prior investigations have utilized monoclonal antibodies as an adjunct to induction treatment (along with other regimens such as CHOP) as well as maintenance therapy. Further investigation is needed to deduce what effects preinduction treatment with monoclonal antibodies and/or CAR therapy would have on response to initial induction treatment, overall survival, and progression-free survival in patients with both Hodgkin and non-Hodgkin lymphoma. Clarification of optimal lymphodepletion duration and chronology for specific tumor types prior to induction of CAR therapy may improve responsiveness and lower the incidence of refractory disease.

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