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Case Report

Presentation of extranodal NK/T-cell lymphoma as a pituitary mass: A case report and review of the literature

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ABSTRACT

Background: Primary pituitary lymphomas are uncommon neoplasms that are typically derived from a B-cell lineage. Extranodal natural killer (NK)/T-cell lymphoma is distinct from B- and T-cell lymphomas and is associated with Epstein–Barr virus infection. Primary central nervous system (CNS) presentations of this neoplasm are exceptionally rare. Here, we report the case of extranodal NK/T-cell lymphoma presenting as a pituitary mass and review the literature related to this rare clinical entity.

Case Description: A 31-year-old previously healthy male presented with 2 weeks of progressive headaches and ophthalmoplegia. Imaging revealed a large intrasellar mass with retroclival extension and involvement of the sphenoid and cavernous sinuses. An endoscopic biopsy of the sphenoidal mucosa was performed, and pathological examination was consistent with extranodal NK/T-cell lymphoma. Despite treatment with chemo- and radiotherapy, the patient died approximately 8 months after initial presentation due to systemic disease progression with multiorgan failure.

Conclusion: The presentation of extranodal NK/T-cell lymphoma as a pituitary lesion is very rare, having been reported only twice in the previous literature. Patients with primary CNS extranodal NK/T-cell lymphoma typically experience an aggressive clinical course with a poor prognosis, as in our case.

Keywords: Biopsy, Headache, Neoplasms, Ophthalmoplegia, T-lymphocytes

INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphomas are rare, aggressive neoplasms related to Epstein–Barr virus (EBV) infection.[7,14] It is estimated that they account for approximately 1.5% of all lymphomas in the United States, though they are more common in some Asian and Latin American countries.[10,13] As an extranodal lymphoma, these neoplasms involve sites other than lymph nodes, spleen, thymus, and the pharyngeal lymphatic ring.[8] They most commonly affect the upper aerodigestive structures, presenting with nasal obstruction or epistaxis, but sometimes involve extranasal locations such as skin, gastrointestinal tract, and testes.[17] Primary central nervous system lymphoma (PCNSL) isolated to the sellar or parasellar region, or primary pituitary

lymphoma (PPL), represents a very uncommon malignancy, with only 45 cases described in immunocompetent patients to date. Most are of B-cell origin and cases in the literature report various clinical presentations but most commonly headache and hypopituitarism.[2] In the present article, we report a case of extranodal NK/T-cell lymphoma presenting as a pituitary mass, and we conduct a comprehensive review of the literature related to this unusual clinical entity.

CASE DESCRIPTION

A 31-year-old Filipino male with no significant past medical history presented to us with approximately 10 days of diplopia, progressive headache, and nausea. The patient sought medical attention at an outside hospital when his diplopia began, endorsing a sudden onset of impaired left eye movement. He was reportedly found to have a pituitary mass at that time and was subsequently discharged with a scheduled outpatient ophthalmology appointment. During this appointment, he was noted to have bilateral cranial nerve IV palsies and was directed to the emergency department at our institution. Further history from the patient was notable for 1 year of gradually escalating headaches and night sweats. He also endorsed approximately 2 weeks of decreased libido, absence of morning erections, and fatigue. On physical examination, he had moderate left ptosis with impaired left abduction and adduction consistent with third and sixth cranial nerve palsies, in addition to a right sixth cranial nerve palsy.

The patient's prolactin level was normal, but laboratory analysis revealed low luteinizing hormone and thyroid-stimulating hormone, consistent with hypopituitarism. A head computed tomography scan was obtained, which demonstrated a complex and partially erosive mass involving the sphenoid sinus, sella, and clivus [Figure 1]. Magnetic resonance imaging (MRI) demonstrated an intrasellar mass with bilateral cavernous sinus invasion encasing the cavernous internal carotid arteries and retroclival extension with pontine mass effect and displacement of the basilar artery [Figure 1]. The lesion was contrast-enhancing, isointense on T1 and T2-weighted images, and demonstrated diffusion restriction with overall imaging findings concerning lymphoma. Due to the patient's accelerating clinical course of neurological deficits, our multidisciplinary tumor board recommended an urgent biopsy of the lesion to guide further treatment. Based on the imaging, it was felt that tumor involvement of the sphenoid mucosa was extremely likely in addition to the sellar region, and a biopsy of this mucosa would achieve a tissue diagnosis with minimal associated risk.

The patient underwent an endoscopic transnasal transsphenoidal biopsy, and an extremely abnormal appearing sphenoid mucosa was noted intraoperatively. Multiple biopsies of the intrasphenoidal tissue were obtained and sent for the frozen section. Upon review of the frozen specimens, it was clear that this was an invasive tumor highly consistent with lymphoma. Additional intrasphenoidal specimens were obtained for further analyses. We elected not to obtain biopsies from the intrasellar space as our collected specimens were felt to be adequate for tissue diagnosis. The exposure was closed, and the patient tolerated the procedure without complications. Histologic sections demonstrated sinonasal mucosa involved by a diffuse lymphocytic infiltrate consisting of medium-to-large monomorphic cells with round to irregular nuclei with numerous apoptotic bodies and foci of necrosis. As shown in Figure 2, immunohistochemistry demonstrated neoplastic cells positive for cytoplasmic CD3 and CD56 (NK cell marker) and negative for CD20 (B-cell marker). *In situ* hybridization for EBV was positive. Based on these findings, the pathologic diagnosis was determined to be extranodal NK/T-cell lymphoma. The neoplastic cells were also positive for CD4, CD5, CD7, CD8 (small subset), CD30 (approximately 40%) and negative for AE1/AE3, CD23, CD10, BCL-6, and MUM-1.The patient's serology was positive for EBV and negative for human immunodeficiency virus and hepatitis.

Oncologic treatment with the modified steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) protocol was initiated, consisting of dexamethasone, methotrexate, ifosfamide, peg-asparaginase, and etoposide given every 3 weeks.[5] A repeat MRI 3 weeks after his first cycle demonstrated a decrease in tumor size. He completed four cycles of this protocol over approximately 3 months. However, 2 months after receiving his fourth chemotherapy cycle, he developed a progressive left facial droop. An MRI obtained at the time of this presentation revealed enlargement of the tumor and enhancement of multiple cranial nerves suggestive of disease progression. Flow cytometry of cerebrospinal fluid (CSF) was negative for NK/T cell lymphoma, but CSF EBV was positive and intrathecal methotrexate was administered. Over the next 2 days, he had continued progression of his left facial droop and began to develop right-sided facial weakness as well. Whole brain radiation therapy was then initiated the next day. The patient received whole brain radiation therapy 5 days/week for 6 weeks for a total of 54 Gy. Pembrolizumab was initiated, and he completed two cycles of this given 3 weeks apart. Unfortunately, the patient died approximately 8 months after initial presentation due to systemic disease progression with multi-organ failure.

DISCUSSION

Pituitary neoplasms are highly prevalent and commonly benign, with adenomas accounting for approximately 90% of all pituitary tumors.[21] Most pituitary tumors are asymptomatic and discovered incidentally, though they can

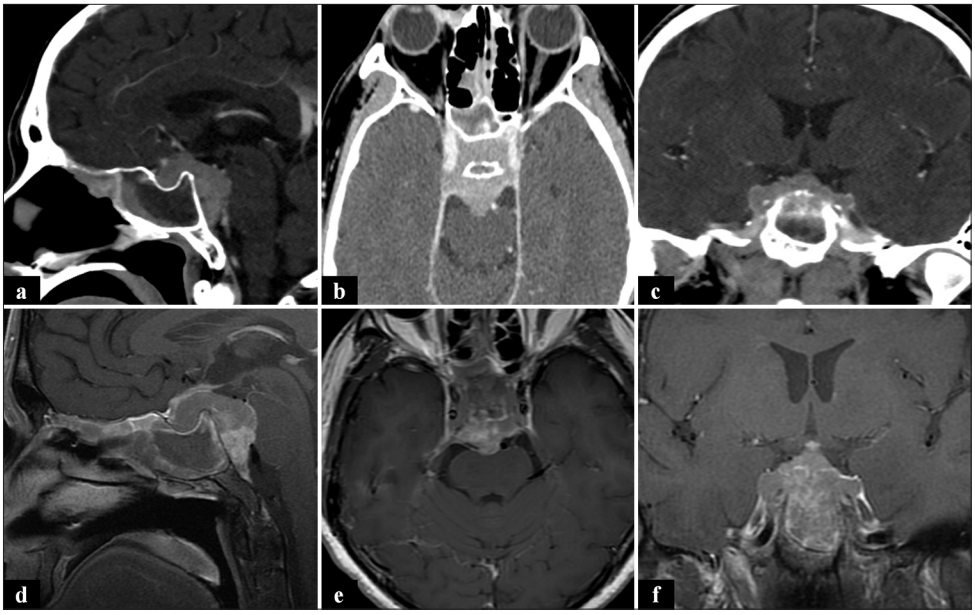

Figure 1: (a-c) Head computed tomography with contrast demonstrating an enhancing mass in the sellar/suprasellar region and additional multifocal areas of mucosal thickening and enhancement along the walls of the sphenoid sinus. (d-f) T1-weighted contrast-enhanced magnetic resonance imaging demonstrating a contrast-enhancing mass centered on the sella and cavernous sinuses.

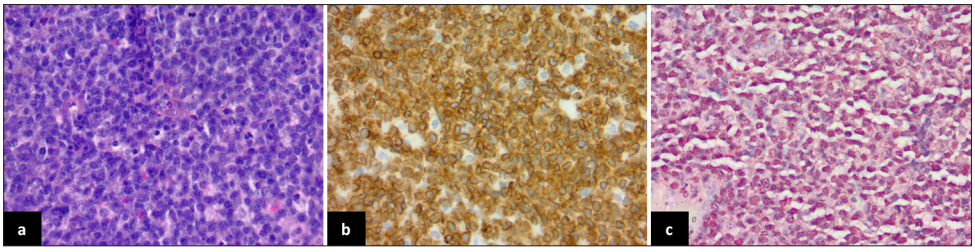

Figure 2: Tumor histology: (a) High-powered field, hematoxylin and eosin stain; 40×, (b) cytoplasmic CD3, CD3 immunohistochemical stain; 40×, (c) Epstein–Barr virus-encoded small RNAs, Epstein-Barr virus in situ hybridization stain; 40×.

present with variable symptoms depending on cell type, hormone secretion, and growth behavior.[3,12] Functional pituitary adenomas are hormone-secreting and associated with endocrine-related clinical presentations. Nonfunctional pituitary adenomas typically produce symptoms secondary to mass effect, which may include hypopituitarism from compression of pituitary structures in addition to other symptoms such as headache and visual disturbances.[4] PCNSL is a subtype of non-Hodgkin lymphoma that is confined to the brain, spinal cord, meninges, CSF, cranial nerves, or intraocular compartments. It is rare in immunocompetent patients but has had an increasing incidence in recent years, now representing about 5% of all extranodal lymphomas and 3% of intracranial neoplasms in this population.[6] Almost all cases of PCNSL are diffuse large B-cell lymphoma and while the pathogenesis is still unclear, it is associated with a poor prognosis compared to lymphomas outside of the central nervous system (CNS).[15] PCNSL typically arises in the frontal lobe and basal ganglia.[3] PPL, with lymphoma involvement limited to the sellar or parasellar region, is a rare entity with less than 50 cases described in the literature to date. As is the case with PCNSL, PPLs are most commonly of B-cell origin.[2] NK/T-cell pituitary lymphoma is a largely unknown neoplasm.

In our review of the literature, we identified only two cases of extranodal NK/T-cell lymphoma manifesting as a primary pituitary tumor. The first case, published in 2007, reports a 26-year-old male who presented with headache, diplopia, nausea, vomiting, and fever. Laboratory analysis revealed hypocortisolism, hypothyroidism, and hypotestosteronemia.[10] Imaging demonstrated compression of the optic chiasm by an enhancing sellar mass with suprasellar extension and involvement of planum sphenoidale, anterior clinoid process, infundibulum, clivus, and cavernous sinus. Pathology of the mass was consistent with extranodal NK/T-cell lymphoma, and the

tumoral cells were EBV positive. The patient was treated with fractionated intensity-modulated radiotherapy plus six cycles of hyper-CVAD chemotherapy (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), intrathecal methotrexate, and cytarabine. However, he ultimately died due to the systemic progression of the disease 6 months after his initial presentation. The second case, published in 2018, describes a 23-year-old male with a pituitary tumor initially thought to be a macroadenoma.[20] The patient in this report presented with headache, diminution of vision, fatigue, nausea, vomiting, and episodes of hypoglycemia. Imaging demonstrated a large, heterogeneously enhancing mass in the sellar/suprasellar region, which was biopsied and determined to be NK/T-cell lymphoma. The authors report that the patient was treated with chemoradiotherapy and was doing well at 1-year follow-up. No further details were provided about the patient's treatment regimen or follow-up beyond this time.

In the present article, we report the third published case of extranodal NK/T-cell pituitary lymphoma. Our patient similarly presented with headache, visual changes, and hypopituitarism and experienced a clinical course much like the first patient reported by Liu *et al*.[10] In a systematic review including 40 patients with PPL, Duan *et al*. report headache and hypopituitarism as the most common presenting symptoms.[2] Presumably due to the mass effect on surrounding structures, this presentation is similar to that of many nonfunctional pituitary adenomas, which are exceptionally more common. They also report sphenoidal involvement in 13 of their included patients but note that most cases did not involve pathological examination of the sphenoid mucosa. Thus, the true frequency of sphenoidal involvement in PPL could be higher. Multiple patients had histologically confirmed sphenoidal involvement but with no radiographic evidence.[9] Although they are typically histologically benign, pituitary adenomas sometimes demonstrate local invasion. However, extension inferiorly and invasion of the sphenoid sinus is less common.[11,16] In our case, the patient's imaging was suggestive of sphenoidal involvement, and a tissue diagnosis was made through a biopsy of the sphenoid mucosa. Most cases of PPL were diagnosed with a pituitary biopsy, but a biopsy of the sphenoid mucosa may yield a diagnosis with lower surgical risk and should be considered in appropriate cases.[2]

PPL is regarded as a subtype of PCNSL, but it has been argued that it may be a distinct entity considering the difference in embryologic origins between the pituitary gland and the CNS parenchyma.[5,18] NK/T-cell lymphoma is also a distinct clinical entity from B- and T-cell non-Hodgkin lymphomas, commonly of a NK cell origin, but a minority of cases are derived from the T-cell lineage.[19] NK/T-cell lymphomas arise almost exclusively in extranodal sites. Approximately 80% of extranodal NK/T-cell lymphomas occur in the nasal cavity, paranasal sinuses, nasopharynx, oropharynx, and upper aerodigestive tract, classically causing midface, destructive lesions. Less common sites include the gastrointestinal tract, skin, testes, and salivary glands.[19] According to the most recent World Health Organization classification, extranodal NK/T-cell lymphomas are considered a subtype of EBV-positive NK/T-cell lymphomas.[1] The other subtype in this group, EBV-positive nodal T- and NK-cell lymphoma, involves the lymph nodes and often the spleen, liver, and bone marrow as well.[14] EBV-positive nodal T- and NK-cell lymphoma classically lack the angioinvasiveness and necrosis that are distinguishing pathologic features in most cases of extranodal NK/T-cell lymphoma.[14] Primary CNS extranodal NK/T-cell lymphoma is rare, with only 25 cases described in the literature to date.[23,24] It is associated with a poor prognosis, with a median overall survival of 6 months based on a systematic review of 23 primary CNS extranodal NK/T-cell lymphoma.[15] Due to the rarity of this lymphoma, no standard treatment has been established. Most cases have been treated with intrathecal and systemic chemotherapy (typically L-asparaginase or peg-asparaginase regimens) and radiation.[5] Pembrolizumab, an anti-programmed death 1 antibody, has shown efficacy in some cases of relapsed/refractory NK/T-cell lymphoma.[19] However, an aggressive clinical course often still manifests, as in our case.[22]

CONCLUSION

Extranodal NK/T-cell lymphoma is an uncommon neoplasm that is distinct from B- and T-cell lymphomas. Primary CNS presentations are exceptionally rare, and only three cases, including ours, have described the presentation of extranodal NK/T-cell lymphoma as a pituitary mass. Patients with primary CNS extranodal NK/T-cell lymphoma typically experience an aggressive clinical course with a poor prognosis. PPLs, though also rare tumors, are typically of B-cell origin and commonly involve the sphenoid sinus. Biopsy of sphenoid mucosa may be a safer alternative to pituitary biopsy for diagnosis and should be considered in appropriate cases.

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