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Case Report

Anaplastic lymphoma kinase-positive large cell lymphoma of the anterior skull base: Report of an unusual case and review of the literature

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Abstract

Background: Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) is a rare peripheral T-cell lymphoma, accounting for approximately 3% of adult non-Hodgkin lymphomas (NHL). In this report we describe an unusual case of an ALK(+) ALCL, which presented as an aggressive mass involving upper nasal cavity and anterior skull base. The pathogenesis, histopathology with radiologic correlations, and management of this case are reviewed.

Case Description: A 28-year-old Asian female presented with a 3-month history of nasal congestion culminating in epistaxis. Physical examination was notable for a tissue mass obstructing nasal cavity and the sphenoid sinus. Computed tomography (CT) and magnetic resonance (MR) imaging revealed a lesion primarily involving the upper nasal cavity extending intracranially through the cribriform plates into the anterior cranial fossa. Histologic and immunohistochemical analysis of the specimen obtained through a transnasal biopsy revealed an ALK(+) ALCL. The patient underwent two cycles of chemotherapy and focal radiation therapy, achieving minimal residual disease. The patient remained neurologically unchanged with stable minimal residual disease at the 1-year follow-up.

Conclusions: To the best of our knowledge, this is the first case of an ALK(+) ALCL that presented as an aggressive upper nasal cavity and anterior skull base lesion. This case report highlights the importance of multi-modality approaches including preoperative imaging and tissue biopsy for definitive diagnosis.

Key Words: Anaplastic large cell lymphoma, anaplastic lymphoma kinase, anterior skull base, lymphoma, upper nasal cavity

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INTRODUCTION

Lymphoma exclusively involving the nasal sinus or the anterior cranial fossa is rare in Western populations. It is, however, more common among Asian populations, constituting 3-8% of non-Hodgkin lymphoma (NHL).[1,2,12] Awareness of these pathologies is important to a neurosurgeon since these lesions

tend to be exquisitely sensitive to chemotherapy and radiation.[3,12] This sensitivity mitigates the need to surgery in most instances.

Peripheral T-cell lymphoma including anaplastic lymphoma kinase (ALK)(+) anaplastic large cell lymphoma (ALCL) is primarily nodal disease, although extranodal sites such as skin, gastrointestinal tract, bone marrow, liver, peripheral blood, head and neck region, and central nervous system can be involved.[7] However, sinonasal involvement by ALK(+) ALCL has not been previously reported. Here we describe an unusual case where an ALK(+) ALCL presents as an aggressive lesion of upper nasal cavity and anterior skull base. The tumor eroded from the nasal cavity into the skull base, and extended intracranially through the cribriform plates into the anterior cranial fossa.

In this report the pathogenesis, correlations of histopathology with radiologic imaging, and management of ALK(+) ALCL are reviewed and discussed.

CASE REPORT

A 28-year-old Asian female presented with a 3-month history of nasal congestion culminating in epistaxis. Her medical history was otherwise unremarkable. Physical examination was notable for a tissue mass obstructing nasal cavity and compromised visual acuity (OS: No light perception, OD: 20/20). The patient gave a poor history regarding her visual loss but denied acute changes in vision over the weeks preceding admissions. No cutaneous lesions were identified. The absolute lymphocyte count (ALC) was 900/μL. Other laboratory values, including a detailed endocrinology panel, were within normal limits. Computed tomography (CT) and magnetic resonance (MR) imaging were obtained.

MR imaging of the orbital and nasal region demonstrated a homogenous and well-circumscribed mass, with mild homogenous enhancement [Figure 1] and mild restricted diffusion [Figure 2a]. The lesion expands both nasal cavities and extends intracranially through the cribriform plates and through the clivus into the prepontine cistern. The mass encased the right cavernous carotid artery and exert mass effect on the optic nerve and chiasm. Enlarged retropharyngeal lymph nodes [Figure 2b] and upper level IB/II lymph nodes were observed. Maxillofacial CT scan confirmed the MR imaging findings and bony erosion of the anterior clivus, bilateral medial sphenoid bones, and left clinoid process. A staging positron emission tomography (PET)-CT showed hypermetabolism in the tumor tissue. Endonasal biopsy of the mass yielded specimens that showed histologic and immunohistochemical findings diagnostic of an ALK(+) ALCL [Figure 3 and Table 1].

Treatment course

The patient underwent Etoposide, Prednisone, Oncovin, Cyclophosphamide, Hydroxyldaunorubicin (EPOCH) chemotherapy regimen for one cycle. Because of iatrogenic anemia, the patient was switched to the Ifosfamide, Mesna, Esoposide, Cytarabine (IVAC) chemotherapy regimen for another cycle. The patient additionally underwent conformal radiation therapy to the residual lesion was added (40 Gy in 20 fractions). Repeated MR imaging 6 months after completion of the treatment regimen showed a dramatic decrease in tumor size, such that the optic nerve no longer showed signs of compression [Figure 4]. PET-CT revealed markedly reduced hypermetabolism in the skull base mass and complete resolution hypermetabolism of the retropharyngeal lymph nodes. At the 1-year follow-up, the patient's neurologic and general condition remained

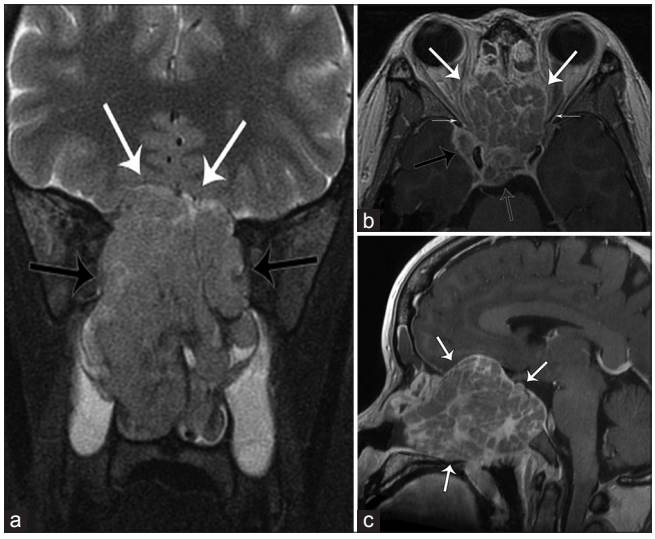

Figure 1: Pretreatment MRI: Coronal (a), axial (b) and sagittal (c) postcontrast T1demonstrate a mildly enhancing upper nasal cavity mass with extending through the cribriform plates. Associated abnormal retropharyngeal lymph nodes

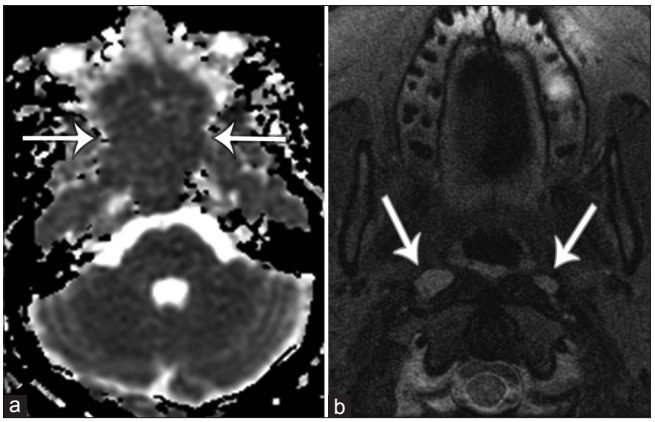

Figure 2: MR images important for the correct differential diagnosis: ADC map (a) demonstrating mild restricted-diffusion, suggesting hypercellularity. Axial T2 (b) at the level of the nasopharynx demonstrates enlarged retropharyngeal lymph nodes, suggesting either primary lymphoid-disease or typical nodal spread of esthesioneuroblastoma

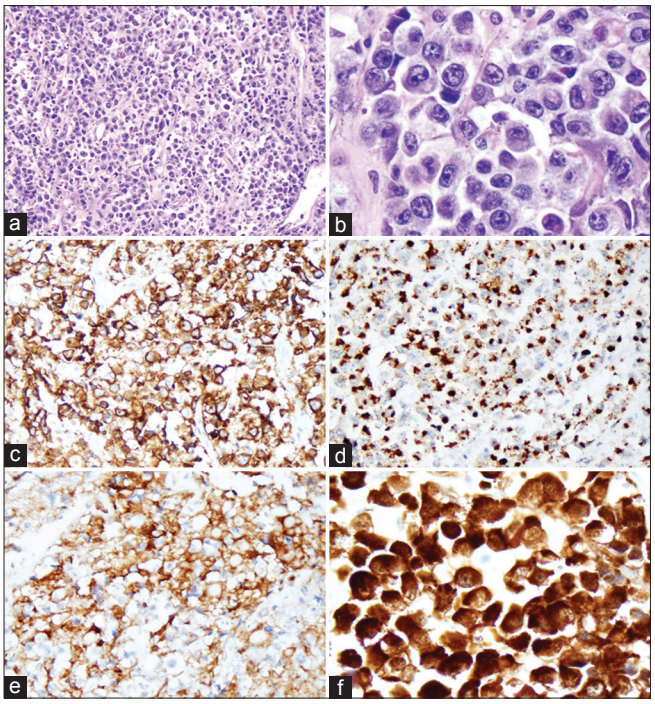

Figure 3: Microphotographs of the lymphoma cells and immunohistochemistry. Diffuse lymphoid infiltrate composed of large-sized cells (a) (H and E, ×100); "hall marker" cells (b) (H and E, ×400); lymphoma cells are positive for CD30 (c), TIA-1 (d), CD4 (e) and ALK-1 (f) (C-E, ×200; F, ×400)

stable, with unchanged visual acuity/field, stable MR imaging, and normal endocrinology labs.

Pathology

Hematoxylin and eosin (H&E) sections of the nasal cavity mass biopsy show a diffuse lymphoid infiltrate [Figure 3a] underneath the nonkeratinizing stratified squamous epithelium consistent with the nasopharyngeal location. The lymphoid infiltrate is composed of sheets of large-sized markedly pleomorphic cells with abundant amphophilic cytoplasm, eccentrically located nuclei with vesicular chromatin, and prominent nucleoli. Occasional nuclei demonstrate horseshoe-like shape, consistent with the so-called "hallmark cells" [Figure 3b].

To further delineate the nature of this lymphoma, a panel of immunohistochemistry was performed [Figure 3c-f]. Immunohistochemistry demonstrates that the neoplastic cells are strongly and diffusely positive for CD30 [Figure 3c], epithelial membrane antigen (EMA) [Table 1], and T-cell intracellular antigen-1 (TIA-1) [Figure 3d]. The majority of the neoplastic cells are also positive for CD4 [Figure 3e] and CD5, partially positive for CD45, and rarely positive for CD2 [Table 1]. The neoplastic cells show diffuse nuclear and cytoplasmic staining of ALK-1 [Figure 3f]. Epstein–Barr virus (EBV) by *in-situ* hybridization is negative. These findings were consistent with the diagnosis of ALK(+) ALCL.

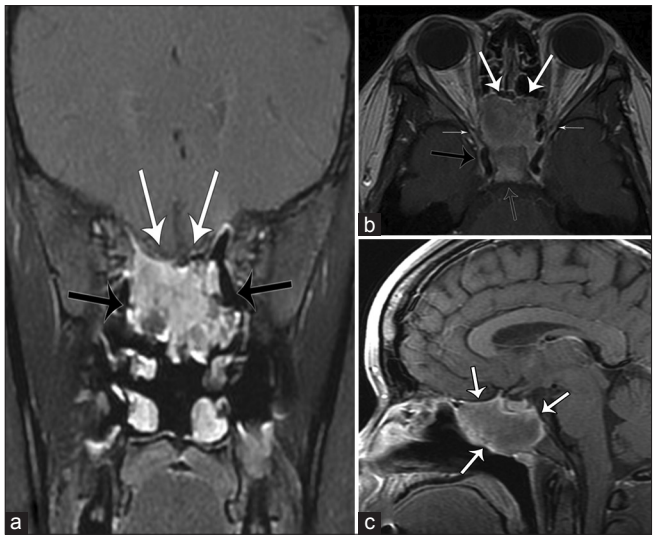

Figure 4: Four month post treatment coronal (a), axial (b), and sagittal (c) postcontrast T1 MR images, demonstrate decreased size of the lymphoma mass in the nasal cavity, along the cribriform plates, and prepontine cistern

Additionally, the negative CD3, CD7, and CD56 rule out NK-cell lymphoma; the negative CD138 rules out plasma cell neoplasia; the negative pan-keratin rules out a metastatic carcinoma; furthermore, the negative GFAP, chromogranin, synaptophysin, neuron-specific enolase, and S100 rule out tumors from the central nervous system and melanoma. The detailed immunohistochemistry of all the markers used and their results are listed in Table 1.

T-cell receptor (TCR) gene rearrangement studies performed by ARUP Laboratory (Salt Lake City, Utah) showed monoclonal TCR gamma gene rearrangement. Chromosomal analysis of the rearrangements suggest that the positive ALK expression was most likely due to the translocation of ALK located on chromosome 2p23 and nucleophosmin located on 5q35 namely t(2;5)(p23;q35), based on the both nuclear and cytoplasmic granular staining pattern [Figure 3f].

DISCUSSION

Lesions in the upper nasal cavity and skull base constitute a diverse group of pathologic conditions that present unique management challenges. Therapeutic strategies are largely dictated by the radiation sensitivity of the lesion and local anatomy. Cyto-reduction through surgery or neo-adjuvent chemotherapy is warranted for radiation resistant tumors in close proximity to the optic apparatus. In the case presented here, the decision to proceed with chemotherapy and radiation is grounded on the well-known sensitivity of ALK(+) ALCL to these agents.[3,4,12] It is important to note that patients afflicted with lesions with involvement of the anterior skull base and intracranial extension are at elevated risk

Table 1: Summary of immunohistochemistry

Antigen	Result
ALK-1	+(nuclear and cytoplasmic)
CD2	-
CD3	-
CD4	+
CD5	+
CD7	-
CD8	-
CD15	-
CD20	-
CD30	+
CD45	+(partial)
CD56	-
CD138	-
Chromogranin	-
EBV (*in situ* hybridization for EBER)	-
EBV (immunohistochemistry for LMP)	-
EMA	+
GFAP	-
NSE	-
Pan-cytokeratin	-
Synaptophysin	-
S-100	-
TIA-1	+

ALK-1: Anaplastic lymphoma kinase 1; "−": Negative; "+": Positive; EBV: Epstein-Barr virus; EBER: EBV encoded early RNA; LMP: Latent membrane protein; EMA: Epithelial membrane antigen; GFAP: Glial fibrillary acidic protein; NSE: Neuron specific enolase; TIA-1: T-cell intracellular antigen 1

for developing CSF rhinorrhea and should be carefully monitored in this regard.

While there are lymphomas of NK/T- and B-cell origin that present in the nasal cavity or anterior skull base, ALK(+) ALCL of T-cell origin has not been reported in this anatomical location. In the current World Health Organization (WHO) classification, ALCL is divided into cutaneous and systemic types, with the latter further delineated by the presence or absence of ALK protein expression. ALK gene encodes a tyrosine kinase receptor belonging to the insulin receptor superfamily, which is expressed within the central nervous system in the early stage of embryogenesis.[5] ALK is normally not expressed in lymphoid cells.[8]

The presence of ALK protein defines a group of T-cell ALK(+) ALCL with favorable prognosis when treated with standard chemotherapy.[3,4,12] CHOP-based chemotherapy regimen is often the preferred first line of treatment in case of NHL. The overall 5-year survival rate in ALK(+) ALCL approaches 80% in contrast to only 48% in ALK(-) ALCL.[10] ALC has been reported to be an independent prognostic factor. An ALC below 1000/μL correlates with shorter survival and lower complete remission rate.[9] Relapses are not uncommon (30% of cases), but often remain sensitive to chemotherapy; allogeneic bone marrow transplants may be effective in refractory cases.[6] Radiation therapy may be necessary after completion of chemotherapy to eliminate residual sites of disease.

At molecular genetic level, all ALK(+) ALCL harbor ALK translocation at chromosome 2p23 locus but with different partner genes, the most frequent of which is nucleoplasmin (*NPM*) gene on chromosome 5q35 locus.[8] Variant translocations involving other partner genes on chromosomes 1, 2, 3, 17, 19, 22, and X also occur.[3,11] All of these translocations result in up-regulation of ALK, but the subcellular distribution of the staining varies depending on the involved partner gene. For example, the t(2;5) (p23;q35) involving the *NPM* gene, a house-keeping gene, fuses the *ALK* gene to produce a chimeric protein in which the N-terminal protein of *NPM* is fused to the intracytoplasmic portion of *ALK*,[8] so that a unique nuclear and cytoplasmic staining pattern is observed such as in this case.

In sum, we report an unusual case of ALK(+) ALCL that presented as an aggressive neoplasm involving upper nasal cavity and anterior skull base. To the best of our knowledge, this is the first report of an ALK(+) ALCL in this anatomical location. This case illustrates the importance of multi-modality approaches in the diagnosis and management of neurologic malignancies.

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