Case Report

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

Pouya Jamshidi, James Y. Chen1,2, Huan-You Wang3, Clark C. Chen4

Center for Theoretical and Applied Neuro-Oncology, Moores Cancer Center, La Jolla, CA, 92093-0815, 1Department of Radiology, Veterans Affairs Medical Center, 3350 La Jolla Village Drive, San Diego, CA, 92161, 3Department of Radiology, Division of Neuroradiology, 4Pathology, and 5Division of Neurosurgery, University of California San Diego Health System, 3855 Health Science Drive, La Jolla, CA, 92093-0987, USA

E-mail: Pouya Jamshidi - pjamshidi@ucsd.edu; James Y. Chen - jyc042@ucsd.edu; Huan-You Wang - huw003@ucsd.edu; *Clark C. Chen - clarkchen@ucsd.edu
*Corresponding author

Received: 04 December 12 Accepted: 12 March 13 Published: 18 April 13

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 cribiform 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

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)12. Awareness of these pathologies is important to a neurosurgeon since these lesions...
tend to be exquisitely sensitive to chemotherapy and radiation. 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. 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 cribiform 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 cribiform plates and through the clivus into the preponine 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, Hydroxydaunorubicin (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...
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
Prognostic significance of anaplastic lymphoma kinase (ALK) 

Radiation therapy

CHOP-based gene to produce

Relapses are not

ALK is normally not expressed in lymphoid cells. \[8\] ALK has been reported to be an independent prognostic factor. An ALC below 1000/\muL 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. \[11,13\] 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.

ACKNOWLEDGMENT

The authors would like to thank Dr. Bob S. Carter for his constructive comments on the manuscript, UCSD healthcare providers involved in the care of this patient, including Drs. Erik Curtis, Jacob Husseman, and Dr. Ke Li for his contribution in preparing the Immunohistochemistry Table.

REFERENCES

1. Bearman RM, Pangalis GA, Rappaport H. Acute ("malignant") myelosclerosis. Cancer 1979;43:279-93.
2. Benharroch D, Meguerian-Bedoyan Z, Lamant L, Amin C, Brugieres L, Terrier-Lacombe MJ et al. ALK-positive lymphoma: A single disease with a broad spectrum of morphology. Blood 1998;91:2076-84.
3. Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peeters C et al. ALK+lymphoma: Clinico-pathological findings and outcome. Blood 1999;93:2697-706.
4. Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913-21.
5. Iwahara T, Fujimoto J, Wen D, Cupples R, Bucay N, Arakawa T et al. Molecular characterization of ALK, a receptor tyrosine kinase expressed specifically in the nervous system. Oncogene 1997;14:439-49.
6. Liso A, Tiacci E, Binazzi R, Fulford K, Benedetti R, Carotti A et al. Haploidentical peripheral-blood stem-cell transplantation for ALK-positive anaplastic large-cell lymphoma. Lancet Oncol 2004;5:127-8.
7. Lopez-Guillermo A, Cid J, Salar A, Lopez A, Montalban C, Castrillo JM et al.
Peripheral T-cell lymphomas: Initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann Oncol 1998;9:849-55.

8. Morris SV, Kirstein MN, Valentine MB, Ditzner KG, Shapiro DN, Saltman DL, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 1994;263:1281-4.

9. Porrata LF, Ristow K, Witzig TE, Tuinistra N, Habermann TM, Inwards DJ, et al. Absolute lymphocyte count predicts therapeutic efficacy and survival at the time of radioimmunotherapy in patients with relapsed follicular lymphomas. Leukemia 2007;21:2554-6.

10. Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, et al. ALK-anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: Report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496-504.

11. Stein H, Foss HD, Durkop H, Marafioti T, Delsol G, Pulford K, et al. CD30(+) anaplastic large cell lymphoma: A review of its histopathologic, genetic, and clinical features. Blood 2000;96:3681-95.

12. Swerdlow SH, International Agency for Research on C, World Health O. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: International Agency for Research on Cancer; 2008.