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Case report

A case of primary extranodal natural killer/T-cell lymphoma in the orbit and intraocular tissues with cerebrospinal fluid involvement

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ABSTRACT

Purpose: To report a rare case of primary orbital natural killer (NK)/T-cell lymphoma without nasal lesions but with cerebrospinal fluid involvement.

Observations: A 73-year-old woman was referred to the uveitis clinic with suspected unilateral acute uveitis in her right eye and a right orbital tumor. Epstein–Barr virus DNA was detected in the aqueous humor in her right eye, and orbital biopsy revealed the presence of extranodal NK/T-cell lymphoma (ENKTL), nasal type. Positron emission tomography showed significant ^{18}F-fluorodeoxyglucose uptake in the right orbit, with no other signs of systemic involvement. Cerebrospinal fluid analysis demonstrated lymphoma cell infiltration. She was diagnosed with stage IV ENKTL and treated with orbital radiotherapy and systemic chemotherapy, with subsequent remission. However, the lymphoma relapsed in her left vitreous at 10 months after therapy, suggesting metastasis of lymphoma cells to the contralateral eye via the vitreous and cerebrospinal fluid.

Conclusions and importance: A few cases of ocular-tissue ENKTL have been reported, mostly involving invasion or dissemination of primary nasal lesions; in contrast, primary orbital and intraocular ENKTL has rarely been reported. To the best of our knowledge, this is the first report of a primary orbital ENKTL metastasizing to the vitreous of the contralateral eye. Although ENKTL is rare in the orbit and intraocular tissues, it should be considered as a possible differential diagnosis in patients with orbital tumors or intraocular inflammation resistant to steroid therapy because ENKTL has a very poor prognosis in the advanced stage.

1. Introduction

Lymphomas are the most common type of primary orbital malignant tumors. Most orbital lymphomas are non-Hodgkin's lymphomas, such as mucosa-associated lymphoid tissue lymphomas, which have a relatively good prognosis, while T-cell and natural killer (NK)/T-cell lymphomas are extremely rare.[1,2]

Extranodal NK/T-cell lymphoma (ENKTL), nasal type, formerly known as lethal midline granuloma, angiocentric T-cell lymphoma, or polymorphic reticulosis, is an uncommon disease that typically arises from the nasal cavity and paranasal sinuses.[2,3] While most NK/T-cell lymphomas in ocular tissues occur as an invasion or dissemination of nasal ENKTL, a few cases of primary orbital or intraocular ENKTL have been reported.[3,4]

Here we report an extremely rare case of primary orbital NKTCL that metastasized to the contralateral eye during the follow-up period, presumably via the vitreous and cerebrospinal fluid.

2. Case report

A 73-year-old woman noted blurred vision and swelling of her right eyelid. She was initially diagnosed with unilateral anterior uveitis and treated with topical steroids (0.1% fluorometron), with no improvement of her symptoms. She was then referred to our clinic 1 month after starting local steroid therapy. Her vision was 20/100 in the right eye and 20/15 in the left eye, and the intraocular pressure was 30 mmHg in the right eye and 14 mmHg in the left. The right conjunctiva showed injection and chemosis. Her right cornea had 50–100 pigmented keratic precipitations and 2 + cells in her right anterior chamber, but there was no evidence of inflammation in her right vitreous, retina, or choroid. There was no evidence of inflammation in her left eye. She had no history of weight loss or night sweats and her body temperature was within the normal range. Magnetic resonance imaging (MRI) showed a poorly marginated large mass surrounding her right eyeball, with no evidence of extraorbital tumor, suspected to be an inflammatory

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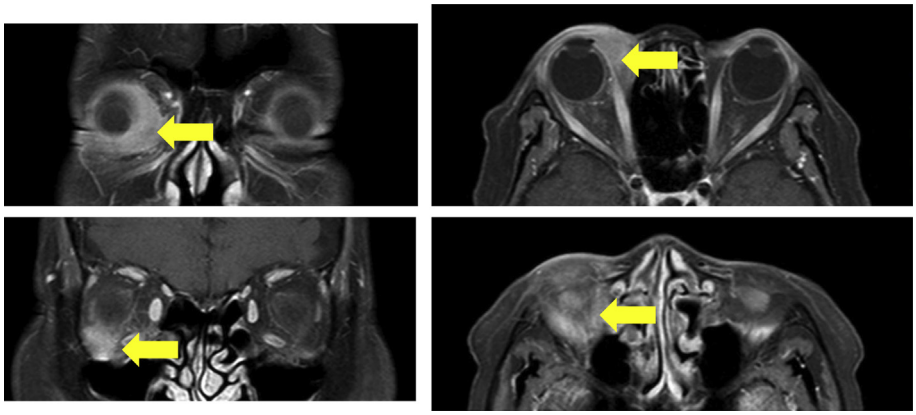

Fig. 1. Magnetic resonance imaging showed a poorly marginated large mass surrounding the right eyeball (arrow). There was no obvious intraocular invasion and no extraorbital tumors, such as nasal or brain tumors.

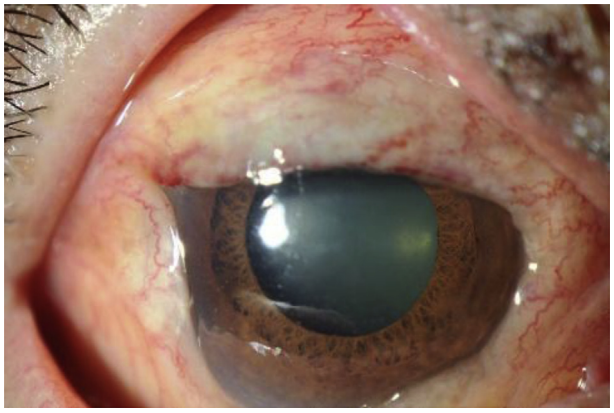

Fig. 2. Slit-lamp photomicrographs. Her swollen eyelid worsened dramatically 2 days after starting steroid pulse therapy with intravenous acyclovir.

pseudotumor (Fig. 1). A sample of aqueous humor from her right eye was subjected to multiplex polymerase chain reaction (PCR) to detect possible bacterial, fungal, parasitic, or viral infections.[5] PCR analysis was positive for Epstein–Barr virus (EBV) DNA (8.5×10^4 copies/ml). She was therefore tentatively diagnosed with EBV-associated anterior uveitis with inflammatory pseudotumor. She was initially treated with 30 mg/day oral prednisolone, which unexpectedly worsened her eyelid swelling. She was then treated with high-dose steroid pulse therapy (1 g methylprednisolone for 3 days) and intravenous acyclovir, which have previously been shown to be effective for EBV-associated ocular inflammation.[6,7] However, her swollen eyelid further worsened after starting steroid pulse therapy (Fig. 2). Therefore, she underwent biopsy of the orbital mass 4 days after starting steroid pulse therapy. Pathological examination of the tumor revealed small-to-medium-sized mononuclear cells and irregular cells, strongly suggesting the presence of orbital malignant lymphoma. Orbital radiotherapy was initiated prior to immunohistochemical evaluation, because of the risk of vision loss in her right eye as a result of the elevated intraocular pressure cause by the tumor surrounding her right eye. The tumor responded well to radiotherapy. Immunohistochemically, the tumor cells were positive for CD3ε, CD2, CD56, CD8, and TIA-1, and negative for CD4, CD7, and CD20. The Ki-67 index was > 90%. The tumor cells were also positive for EBV-encoded mRNA by in situ hybridization (Fig. 3). These results were consistent with a diagnosis of ENKTL. A positron emission tomography (PET) scan demonstrated significant ^{18}F-fluorodeoxyglucose uptake by the right orbit, with no other systemic involvement. The patient was also seen by an otolaryngologist to confirm that there was no nasal involvement. A bone marrow biopsy was negative, but cerebrospinal fluid examination revealed lymphoma cell infiltration although MRI of the brain and spinal cord showed no extraorbital lesions. In accordance with the Ann Arbor staging system,[8] she was then diagnosed with stage IV ENKTL with meningeal involvement. She was treated with three cycles of 2/3DeVIC regimen (dexamethasone, ifosfamide, carboplatin, and etoposide) plus orbital radiotherapy (total dose of 50 Gy). She also received intrathecal infusions of 15 mg methotrexate and 20 mg prednisolone three times, and three courses of high-dose methotrexate (3.5 mg/m^2), as a treatment for CNS lesions. She subsequently achieved complete remission. However, she complained of blurred vision in her left eye 10 months after completing her therapy. Visual acuity was decreased to 10/20 in her left eye. She had 2 + anterior chamber cells with keratic precipitate and 2 + vitreous cells in her left eye. A PET scan showed significant ^{18}F-fluorodexoxyglucose uptake in the left eye (Fig. 4A). Pars plana vitrectomy was performed to obtain vitreous cells. The presence of malignancy could not be proven pathologically. However, CD3 (−) CD 56 (+) cells, characteristic for ENKTL, were detected in the left eye by flow cytometry, although T lymphocytes are reported to be predominant in normal vitreous.[9] Since significant ^{18}F-fluorodeoxyglucose uptake was also seen in the left ocular appendix, MRI was performed. However, there was no evidence of extraocular involvement in her left eye (Fig. 4B). In the context of the combined results of a PET scan, flow cytometry from vitreous cells, and MRI, she was diagnosed with relapse of ENKTL in the left eye without extraocular involvement (Fig. 4B). She was treated with the SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide),[10] and intravitreal methotrexate injection in her left eye. After treatment, her left visual acuity recovered to 20/20, and anterior and vitreous cells resolved without any structural damage in the retina or choroid. The patient remained alive 14 months after her diagnosis.

3. Discussion

This is a rare case of primary ENKTL involving the uvea and orbit with leptomeningeal dissemination. Lymphomas involving the orbit are generally low-grade B-cell lymphomas, with marginal zone lymphomas accounting for > 50% of cases.[11] In contrast, ENKTL is extremely rare in the orbit, and most cases represent a direct invasion from the nose and paranasal sinuses.[1–3] Since ENKTL usually has an aggressive clinical course compared with other types of orbital lymphomas, its early diagnosis and intervention is essential for improving prognosis of the affected patients.[12]

Given that primary ENKTL is uncommon in the orbit and intraocular tissues, its early recognition may be difficult for general ophthalmologists. Indeed, the current case was initially thought to be a pseudotumor with anterior EBV infection, and thus was treated with corticosteroids. EBV has been implicated in the development of a variety of

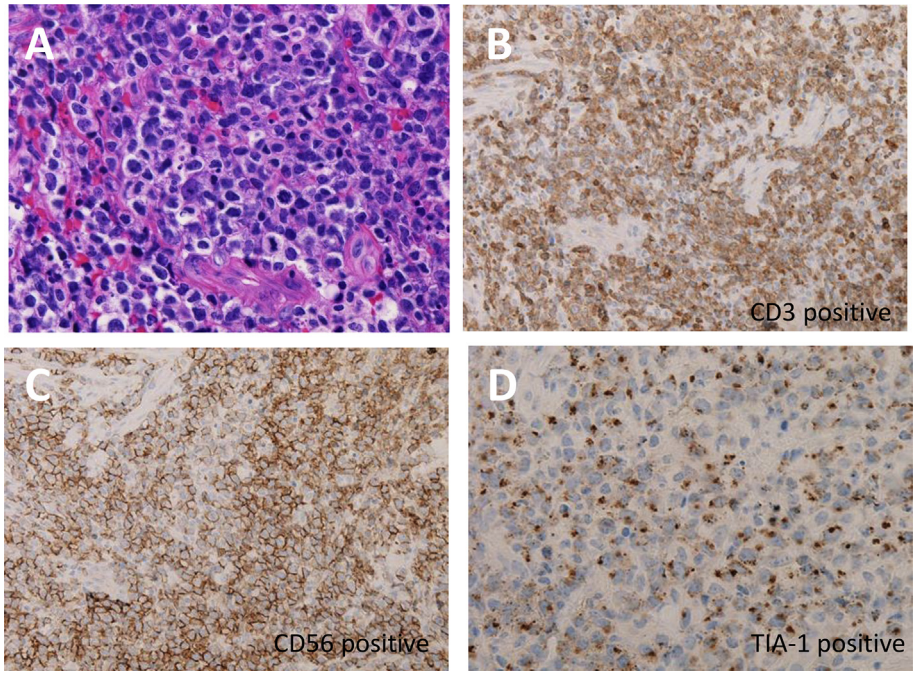

Fig. 3. Histological and immunohistochemical images of the tumor. (A) Small-to-medium-sized mononuclear cells. Immunostaining was positive (B) for CD3 epsilon, (C) CD56, and (D) TIA-1.

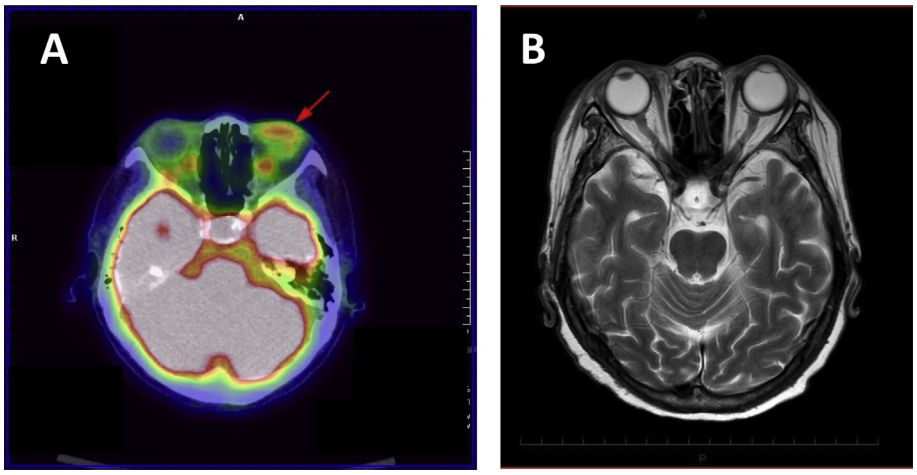

Fig. 4. A) Positron emission tomography/computed tomography showed significant ^{18}F-fluorodexoxyglucose uptake (red arrow) in the left eye at 10 months after chemoradiotherapy. B) Magnetic resonance image showed no obvious evidence of tumor in both orbits and eyes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

malignancies, including nasopharyngeal carcinoma, gastric cancer, and various types of lymphomas.[13–15] Thus, lymphoma should be considered differential diagnosis, along with ocular inflammatory disease, when the EBV genome is detected in the aqueous humor, vitreous, or orbital tumor. Moreover, although most types of extranodal lymphomas respond to corticosteroid therapy, the orbital tumor in the current case deteriorated under treatment with high-dose steroids, which may be a characteristic of ENKTL. Hon et al. demonstrated two distinct categories of ocular ENKTL: uveitis/vitritis and orbital infiltration.[1] In this case, the right orbital tumor was initially diagnosed as NKTCL, and NK/T-cell lymphoma cells were then detected in the vitreous of the contralateral eye 10 months after therapy. This indicates that the primary orbital-type lymphoma had led to the uveitis/vitritis-type in the ipsilateral eye, as a result of direct invasion and metastasis to the contralateral vitreous via the cerebrospinal fluid. The patient was > 70 years old with stage IV, placing her in a high-risk group. Despite the recurrent lymphoma in her left eye and subsequent need for chemotherapy, she remained alive at 14 months after her diagnosis, suggesting that early intervention may have been effective in this case.

4. Conclusions

ENKTL should be considered differential diagnosis in patients with steroid-resistant orbital tumors. In the event of anterior uveitis or vitritis with an orbital mass lesion at presentation, orbital incisional biopsy, as well as quantitative PCR for EBV-DNA using aqueous or vitreous humor samples, is essential to facilitate an early diagnosis.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Conflicts of interest

All authors have no financial disclosures.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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References

1. Hon C, Kwok AK, Shek TW, Chim JC, Au WY. Vision-threatening complications of nasal T/NK lymphoma. *Am J Ophthalmol.* 2002;134:406–410.
2. Coupland SE, Foss HD, Assaf F, et al. T-cell and T/natural killer-cell lymphomas involving ocular adnexal tissues: a clinicopathologic, immunohistochemical, and molecular study of seven cases. *Ophthalmology.* 1999;106:2109–2120.
3. Woog JJ, Kim YD, Yeatts RP, et al. Natural Killer/T-cell lymphoma with ocular and adnexal involvement. *Ophthalmology.* 2006;113(1):140–147.
4. Maruyama K, Kunikita H, Sugita S, Mochizuki M, Ichinohasama R, Nakazawa T. First case of primary intraocular natural killer t-cell lymphoma. *BMC Ophthalmol.* 2015;15:169.
5. Sugita S, Shimizu N, Watanabe K, et al. Use of multiplex PCR and real-time PCR to detect human herpes virus genome in ocular fluids of patients with uveitis. *Br J Ophthalmol.* 2008;92(7):928–932.
6. Wong KW, D'Amico DJ, Hedges 3rd TR, Soong HK, Schooley RT, Kenyon KR. Ocular involvement associated with chronic Epstein-Barr virus disease. *Arch Ophthalmol.* 1987;105(6):788–992.
7. Jin R, Zhao P, Ma X, et al. Quantification of Epstein-Barr virus DNA in patients with idiopathic orbital inflammatory pseudotumor. *PLoS One.* 2013;8(1):e50812.
8. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. *Canc Res.* 1971;31(11):1860–1861.
9. Wittenberg LA, Maberley DA, Ma PE, Wade NK, Gill H, White VA. Contribution of vitreous cytology to final clinical diagnosis fifteen-year review of vitreous cytology specimens from one institution. *Ophthalmology.* 2008;115(11):1944–1950.
10. Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. *J Clin Oncol.* 2011;29(33):4410–4416.
11. Ferry JA, Fung CY, Zukerberg L, et al. Lymphoma of the ocular adnexa: a study of 353 cases. *Am J Surg Pathol.* 2007;31(2):170–184.
12. Kim SJ, Yoon DH, Jaccard A, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-base treatment: multicenter, retrospective analysis. *Lancet Oncol.* 2016;17(3):389–400.
13. Niedobitek G. Epstein-Barr virus infection in the pathogenesis of nasopharyngeal carcinoma. *Mol Pathol.* 2000;53(3):248–254.
14. Takada K. Epstein-Barr virus and gastric carcinoma. *Mol Pathol.* 2000;53(3):255–261.
15. Flavell KJ, Murray PG. Hodgkin's disease and the Epstein-Barr virus. *Mol Pathol.* 2000;53(3):262–269.