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SHORT COMMUNICATION

Epstein-Barr positive T-cell lymphoma in the ocular region

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PURPOSE. *To present two cases of rapidly growing tumors in the ocular adnexa. Both tumors were Epstein-Barr virus (EBV) positive peripheral T-cell lymphoma.*
METHODS. *Case 1 was a 60-year-old man with a non-tender ulcerating tumor involving the lateral third of both upper and lower right eyelid. Case 2 was a 55-year-old man with a swelling of the left eyelid expanding cranially and dislocating the left eye, resulting in proptosis and diplopia. Both patients underwent incisional biopsy that did not disclose the malignant nature of the tumors. Clinical evaluation resulted in suspicion of malignancy and surgical excision was performed.*
RESULTS. *The tumors were found to be consistent with EBV-positive peripheral T-cell lymphoma.*
CONCLUSIONS. *Peripheral T-cell lymphoma is uncommon but a diagnosis to be considered in a patient with a tumorous lesion in the eye region. Furthermore, peripheral T-cell lymphoma may be EBV-positive. (Eur J Ophthalmol 2006; 15: 181-5)*

KEY WORDS. *Epstein-Barr virus, Eyelid, Necrotizing tumor, Ocular adnexa, Swelling, T-cell lymphoma*

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INTRODUCTION

Malignant tumors of the eyelid are a common but often challenging clinical problem. The evaluation and subsequent treatment depend upon the tentative diagnosis and the histopathologic findings. The tentative diagnosis is important when planning the surgical treatment since the required surgical margins depend upon the tumor to be excised (1). Necrotizing lesions of the eyelid may disclose either a neoplasia (2) or an infectious lesion like necrotizing fasciitis (3). Lymphomas comprise 10–15% of malignant ocular adnexal tumors and develop primarily in older adults (4). Between one-third and one-half of patients with ocular adnexal lymphoma develop systemic lymphoma and there is an increased risk of extraocular disease when the lesion is localized in the eyelid compared with lymphomas arising in the remaining ocular adnexa (5). Lymphoma of the ocular adnexa is almost invariably a small cell B-cell lymphoma, MALT-lymphoma being the most common (5-7).

Epstein-Barr virus (EBV) is a member of the human herpesvirus family. It is found worldwide and EBV is recognized to be the causative agent of self-limiting infectious mononucleosis. After a primary infection, EBV usually remains latent with a possibility of inducing various lymphomatoid malignancies (8).

We present two cases of rapidly developing invasive necrotizing tumors of the eye region, which both proved to be EBV-positive T-cell lymphoma.

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METHODS

Case 1

A 60-year-old man presented with a 2-week history of an enlarging, non-tender, ulcerating tumor involving the lateral third of both upper and lower right eyelid (Fig. 1A). The tumor was 2.0 x 2.0 x 1.0 cm at presentation and had been treated with topical antibiotics for 2 weeks with no effect. Medical history included a 6-years history of diabetes type 2 and excessive alcohol consumption through many years with resulting hepatomegalia. The ophthalmologic examination was otherwise normal, as was the systemic examination; in particular, no other skin lesions were observed.

Histopathologic examination of an incisional biopsy revealed necrotic epidermis and dermis with Gram-positive and Gram-negative cocci. The patient was treated with systemic and topical antibiotics. Despite this treatment the tumor enlarged. Surgical excision was performed on suspicion of malignancy or infection with unknown microorganisms. The lesion healed within a few days after surgery and a subsequent complete examination including magnetic resonance and positron emission tomographic scanning revealed no systemic disease. The patient received no other treatment and has not shown any signs of recurrence during a follow-up period of 2.5 years.

Case 2

A 55-year-old man with no prior medical history presented with a 4-week history of a swelling of the left upper eyelid. The swelling presented after a common cold and expanded rapidly cranially via the orbit, dislocating the left eye. The patient was not febrile. Sus-

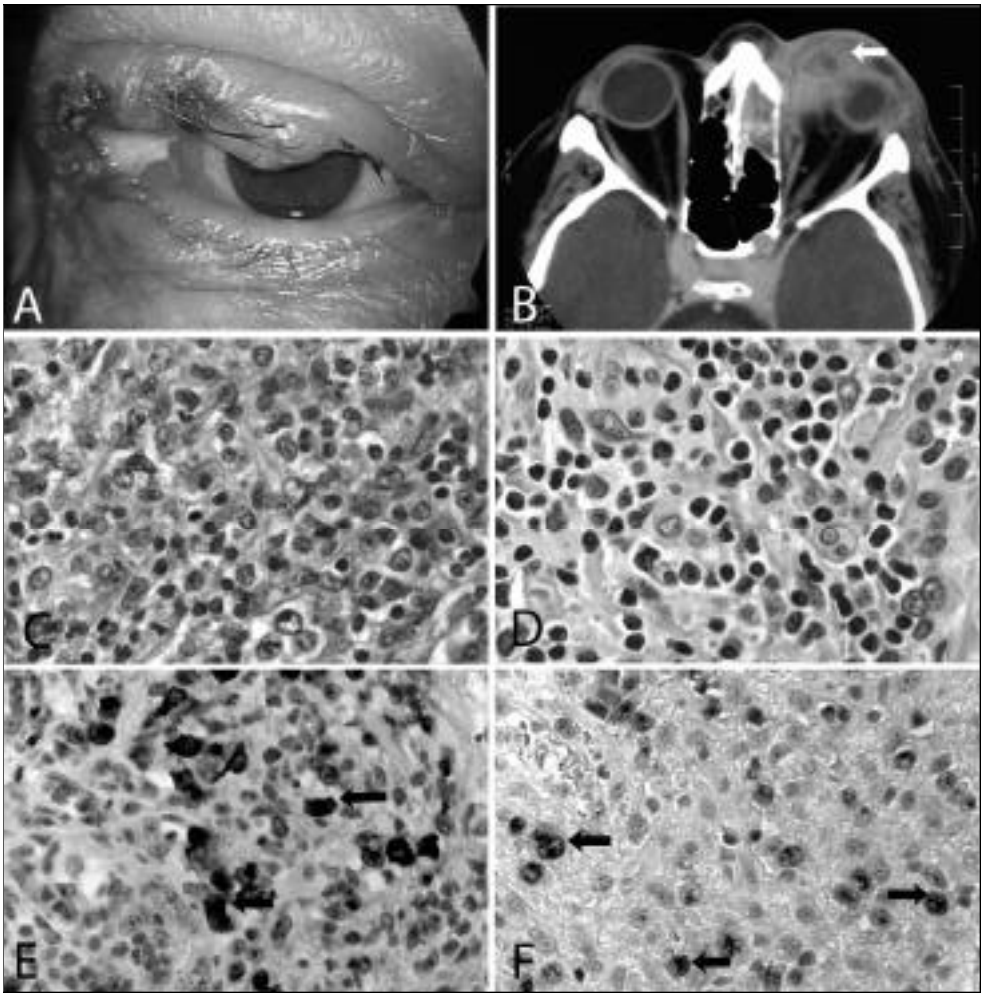

Fig. 1 - (A) *Case 1: The ulcerating tumor involving the lateral part of both upper and lower right eyelid.* **(B)** *Case 2: Computed tomographic scanning of the patient showing a tumor medially in the left orbit (arrow) spreading cranially.* **(C)** *Case 1: The tumor cells are characterized by an abundant pale cytoplasm, large polymorphic, hyperchromatic nuclei, and prominent nucleoli (hematoxylin-eosin x400).* **(D)** *Case 2: Pleomorphic, large tumor cells often with multiple nucleoli are seen (hematoxylin-eosin, x400).* **(E)** *Case 1: Epstein-Barr virus (EBV) expression is evident throughout the specimen as a nuclear staining (arrows) (EBER, x400).* **(F)** *Case 2: The EBV expression is not as prominent as in Case 1, but multiple tumor cells are seen reacting with EBV-antibodies (arrows) (EBER, x400).*

pecting sinusitis, the patient was treated with antibiotics and detumescent nasal drops. However, the swelling continued to grow and a computed tomographic (CT) scan showed a soft tissue tumor medially in the left orbit spreading cranially (Fig. 1B). The ophthalmic examination revealed a subcutaneous immobile tumor measuring 6 x 5 x 4 cm beneath the left supercilium. The eye could not be opened voluntarily and the eyeball was dislocated inferiorly and laterally resulting in proptosis and diplopia. The skin was tense but without signs of inflammation.

Histopathologic examination of an incisional biopsy of the left upper eyelid showed chronic inflammation and perivasculitis. On clinical suspicion of malignancy a surgical excision was performed. A hard tumor below the supercilium with infiltration of the upper eyelid muscles and the supraorbital nerve and extending into the orbital periost was identified.

Following surgery the patient gained normal vision, but CT scanning revealed metastatic spread to the mediastinal and axillary lymph nodes. Bone marrow biopsy showed no signs of infiltration. The patient was treated with six series of cyclophosphamide, Adriamycin, Oncovin, and etoposide injections combined with high-dose corticosteroid tablets. Subsequently, the patient was in full remission and autologous bone marrow transplantation was performed. CT scanning and clinical controls have shown no signs of progression of disease 8 months after transplantation.

Histopathologic examination

Specimens from both patients were fixed in 4% buffered formaldehyde and embedded in paraffin. The sections were stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), Brown and Hopps modification of the Gram stain, and Grocott. Immunohistochemistry included staining with antibodies against cytokeratin, S-100, vimentin, and CD45 as the primary immunohistochemical panel. The specific lymphoid lineages of the tumor cells were determined with the following antibodies: CD3, CD4, CD5, CD8, CD20, CD30, CD43, CD56, CD57, CD68-PGM-1, CD79a, T-cell intracytoplasmic antigen (TIA-1), granzyme B, and anaplastic large cell lymphoma kinase protein (ALK-1). Additionally, the specimens were examined for the presence of EBV using EBV latent membrane protein (EBV-LMP) and in-situ hybridization for EBV-encoded small RNA (EBER) and Bam H-fragment, lower strand frame (BHLF).

RESULTS

Case 1

Histopathologic examination showed an ulcer with necrotic masses and bacteria in the epithelial layer. The adjacent dermis was likewise necrotic in the superficial part but infiltrated with medium-sized to large tumor cells characterized by an abundant pale cytoplasm, large polymorphic, hyperchromatic nuclei, prominent nucleoli, and frequent mitoses (Fig. 1C). The infiltrate extended to subcutis and in some areas also infiltrated thrombotic vessels. The tumor did not extend to the margins of the specimen.

Immunohistochemically, the tumor cells reacted with antibodies shown in Table I. The findings are consistent with a peripheral T-cell lymphoma, unspecified (PTCL, NOS) with EBV expression (Fig. 1E).

TABLE I - REACTIONS WITH IMMUNOHISTOCHEMICAL MARKERS

Immunohistochemical marker	Case 1	Case 2
Cytokeratin	-	-
Vimentin	-	-
S-100	-	-
CD45	+	+
CD20	-	-
CD79α	-	-
CD3	+	+
CD4	+	NP
CD5	+	-
CD8	+	NP
CD30	+	+
CD43	+	-
ALK-1	-	-
CD56	-	NP
CD57	-	NP
CD68PGM-1	-	NP
TIA-1	-	+
Granzyme B	NP	+
EBV-LMP	+	NP
EBV-EBER	+	+
EBV-BHLF	-	NP

NP = Not performed; ALK-1 = Anaplastic large cell kinase protein; TIA-1 = T-cell intracytoplasmic antigen; EBV-LMP = Epstein-Barr virus latent membrane protein; EBV-EBER = Epstein-Barr virus encoded small RNA; EBV-BHLF = Epstein-Barr virus Bam H-fragment, lower strand frame

Case 2

The specimen from this patient showed connective tissue with strands of fatty and muscular tissue with infiltration of polymorphic, large tumor cells with nucleoli and frequent mitoses (Fig. 1D). Surrounding the tumor cells were acute and chronic inflammatory cells, and in areas the tissue was necrotic. The tumor cells extended throughout the whole specimen.

Immunohistochemical reactions are presented in Table I. The findings are consistent with a primary systemic ALK-1 negative anaplastic large T-cell lymphoma (ALCL) with EBV expression (Fig. 1F).

DISCUSSION

Clinically, the two cases presented with a history of eyelid swelling and an infection as the primary diagnosis. Incisional biopsies revealed infection, inflammation, perivasculitis, and necrosis, but no infiltration of tumor cells. A non-malignant diagnosis such as bacterial infection (among these periorbital necrotizing fasciitis), mycotic infection, or even Wegener's granulomatosis are relevant differential diagnoses (9). During close clinical follow-up the processes enlarged despite antibacterial treatment and prompt surgical excisions revealed the correct malignant diagnosis. The cases emphasize the limitations of incisional biopsies and the necessity to evaluate the results critically and with much attention to the clinical development.

Among malignancies in the eye region malignant lymphoma is relatively uncommon (4) and specifically peripheral T-cell lymphoma (PTCL) is rare (10, 11). T-cell lymphoma is clinically aggressive compared with B-cell lymphoma and Hodgkin lymphoma. Adding to the poor prognosis is the fact that many cases of T-cell lymphoma present in an advanced stage (12).

PTCL, NOS accounts for approximately 4% of adult non-Hodgkin lymphomas (13). Most patients with PTCL, NOS present with nodal involvement, but any site may be affected, including the skin (14). Generalized disease is seen in most cases, with infiltration of bone marrow, liver, spleen, and peripheral blood (14). Once systemic spread has occurred, response to treatment is poor, with frequent relapses, and the overall 5-year survival rate is as low as 20–30% (14, 15). Anaplastic large cell lymphoma (ALCL) accounts for approximately 3% of adult non-Hodgkin lymphoma (16). As for PTCL, NOS, most patients present with advanced stage disease, with involvement of the bone marrow (16). Anaplastic large cell lymphoma kinase (ALK) expression is caused by chromosomal translocations, and the majority of ALCLs are positive for ALK (17, 18). Most studies show that ALK-positive ALCL affects younger patients and has a favorable treatment response compared to ALK-negative ALCL, the overall 5-year survival rate being close to 80% in ALK-positive ALCL in contrast to only 40% in ALK-negative ALCL (17, 18).

Both presented tumors showed positive reaction with EBER by in situ hybridization and Case 1 reacted with EBV-LMP antibodies. Bam H-fragment, lower strand frame (BHLF) was negative in Case 1, implying that the EBV-infected lymphoma cells were not in the lytic cycle leading to cell death (19). EBV is known to be causally associated with Burkitt's lymphoma, Hodgkin's disease, and nasal/nasal type NK/T cell lymphoma (8). In peripheral T-cell lymphoma the tumor cells are frequently EBV-negative (18, 20). However, in EBV endemic areas EBV is detected in up to 62% of peripheral T-cell lymphomas, particularly in extranodal lymphomas involving the nasopharynx (21). It has been suggested that the presence of EBV genome in PTCL is associated with CD30 expression (22) and several studies indicate that EBV is a predictor of poor outcome in PTCL (19-21, 23, 24). The risk of EBV associated disease is low in Denmark (25). The EBV expression in the tumor cells was highly evident in both cases (Fig. 1, E and F) and we therefore consider that EBV might be the causative agent of the two presented cases of PTCL located in the eye region.

In conclusion, malignant lymphoma of T-cell origin is an uncommon but important differential diagnosis when investigating a patient with a tumorous lesion in the eye region. Furthermore, peripheral T-cell lymphoma may be EBV positive.

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REFERENCES

1. Augsburger JJ, Schneider S. Tumors of conjunctiva and cornea. In: Yanoff M, Duker JS, eds. Ophthalmology, 2nd ed. St. Louis: CV Mosby; 2004: 535-45.
2. Alyahya GA, Heegaard S, Prause JU. Malignant changes in a giant orbital keratoacanthoma developing over 25 years. Acta Ophthalmol Scand 2000; 78: 223-5.
3. Shayegani A, MacFarlane D, Kazim M, Grossman ME. Streptococcal gangrene of the eyelids and orbit. Am J Ophthalmol 1995; 120: 784-92.
4. Knowles DM, Jakobiec FA. Ocular adnexal lymphoid neoplasms: clinical, histopathologic, electron microscopic and immunologic characteristics. Hum Pathol 1982; 13: 148-62.
5. McKelvie PA, McNab A, Francis IC, Fox R, O'Day J. Ocular adnexal lymphoproliferative disease: a series of 73 cases. Clin Exp Ophthalmol 2001; 29: 387-93.
6. Knowles DM, Jakobiec FA, McNally L, Burke JS. Lymphoid hyperplasia and malignant lymphoma occurring in the ocular adnexa (orbit, conjunctiva and eyelids): a prospective multiparametric analysis of 108 cases during 1977 to 1987. Hum Pathol 1990; 21: 959-73.
7. White WL, Ferry JA, Harris NL, Grove AS Jr. Ocular adnexal lymphoma. A clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Ophthalmology 1995; 102: 1994-2006.
8. Osata T, Takada K, Tokunaga M. Epstein-Barr virus infection and oncogenesis. In: Osata T, ed. Epstein-Barr Virus and Human Cancer. Tokyo; 1998: 3-16.
9. Kronish JW, McLeish WM. Eyelid necrosis and periorbital necrotizing fasciitis. Report of a case and review of the literature. Ophthalmology 1991; 98: 92-8.
10. Auw-Haedrich C, Coupland SE, Kapp A, Schmitt-Graff A, Buchen R, Witschel H. Long term outcome of ocular adnexal lymphoma subtyped according to the REAL classification. Revised European and American Lymphoma. Br J Ophthalmol 2001; 85: 63-9.
11. Coupland SE, Hellmich M, Auw-Haedrich C, Lee WR, Stein H. Prognostic value of cell-cycle markers in ocular adnexal lymphoma: an assessment of 230 cases. Graefes Arch Clin Exp Ophthalmol 2004; 242: 130-45.
12. Ascani S, Zinzani PL, Gherlinzoni F, et al. Peripheral T-cell lymphomas. Clinico-pathologic study of 168 cases diagnosed according to the R.E.A.L. Classification. Ann Oncol 1997; 8: 583-92.
13. Ralfkiaer E, Müller-Hermelink HK, Jaffe ES. Peripheral T-cell lymphoma, unspecified. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001: 227-9.
14. Lopez-Guillermo A, Cid J, Salar A, 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.
15. Rudiger T, Weisenburger DD, Anderson JR, et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 2002; 13: 140-9.
16. Delsol G, Ralfkiaer E, Stein H, Wright D, Jaffe ES. Anaplastic large cell lymphoma. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001: 230-5.
17. ten Berge RL, Oudejans JJ, Ossenkoppele GJ, Meijer CJ. ALK-negative systemic anaplastic large cell lymphoma: differential diagnostic and prognostic aspects - a review. J Pathol 2003; 200: 4-15.
18. Stein H, Foss HD, Durkop H, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000; 96: 3681-95.
19. Huh J, Cho K, Heo DS, Kim JE, Kim CW. Detection of Epstein-Barr virus in Korean peripheral T-cell lymphoma. Am J Hematol 1999; 60: 205-14.
20. d'Amore F, Johansen P, Houmand A, Weisenburger DD, Mortensen LS. Epstein-Barr virus genome in non-Hodgkin's lymphomas occurring in immunocompetent patients: highest prevalence in nonlymphoblastic T-cell lymphoma and correlation with a poor prognosis. Danish Lymphoma Study Group, LYFO. Blood 1996; 87: 1045-55.
21. Zhou XG, Hamilton-Dutoit SJ, Yan QH, Pallesen G. High frequency of Epstein-Barr virus in Chinese peripheral T-cell lymphoma. Histopathology 1994; 24: 115-22.
22. Kanavaros P, Jiwa NM, de Bruin PC, et al. High incidence of EBV genome in CD30-positive non-Hodgkin's lymphomas. J Pathol 1992; 168: 307-15.
23. Cheng AL, Su IJ, Chen YC, Uen WC, Wang CH. Characteristic clinicopathologic features of Epstein-Barr virus-associated peripheral T-cell lymphoma. Cancer 1993; 72: 909-16.
24. Su IJ, Hsieh HC, Lin KH, et al. Aggressive peripheral T-cell lymphomas containing Epstein-Barr viral DNA: a clinicopathologic and molecular analysis. Blood 1991; 77: 799-808.
25. Melbye M, Ebbesen P, Levine PH, Bennike T. Early primary infection and high Epstein-Barr virus antibody titers in Greenland Eskimos at high risk for nasopharyngeal carcinoma. Int J Cancer 1984; 34: 619-23.