JAMA Ophthalmology Clinical Challenge

Progressive Eyelid Lesions in a Woman With Essential Thrombocythemia

Akshara R. Legala, BS; Marissa K. Shoji, MD; Don O. Kikkawa, MD

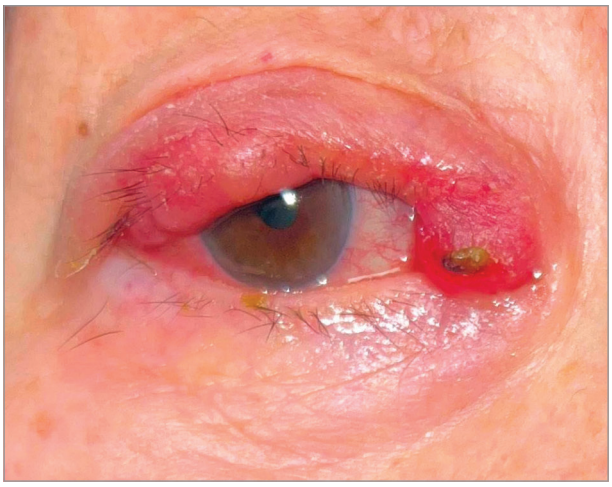

Figure 1. External photograph of right upper eyelid lesions. Examination of the patient's right upper eyelid on presentation demonstrated a central lesion with thickening of the margin and an ulcerated and erythematous nodule near the medial canthus.

A 75-year-old woman presented with a history of enlarging, erythematous right upper eyelid lesions. She reported approximately 3 months of symptoms, with initial development of a single erythematous lesion along the eyelid margin. The lesion had previously been evaluated by another practitioner who diagnosed a hordeolum and prescribed erythromycin ointment and warm compresses. However, the lesion became progressively larger with development of a second medial lesion over the ensuing 2 months, prompting referral. She denied pain, trauma, and prior skin cancer. Her medical history was notable for essential thrombocythemia (ET) with calreticulin (*CALR*) gene variation. Her ocular history was notable for an upper eyelid blepharoplasty 20 years prior but was otherwise unremarkable.

Examination of the right upper eyelid demonstrated a central lesion with a thickened eyelid margin, madarosis, and inspissated glands, and a medial nodular and erythematous lesion with overlying ulceration (**Figure 1**). There was minimal tenderness to palpation. There was no proptosis, and her extraocular muscle movements were full. There was mild conjunctival injection of the right eye without any conjunctival lesions. The remainder of her ocular examination was unremarkable.

WHAT WOULD YOU DO NEXT?

A. Intralesional corticosteroid injection

B. Biopsy of eyelid lesions

C. Oral antibiotics

D. Oral corticosteroids

CME Quiz at jamacmelookup.com

Diagnosis

ALK− anaplastic large cell lymphoma

What to Do Next

B. Biopsy of eyelid lesions

Discussion

Despite initial treatment for suspected hordeolum, the patient's eyelid lesions progressively enlarged with new madarosis and ulceration. This raised concern for malignancy including sebaceous cell carcinoma, lymphoma, and squamous cell carcinoma, prompting biopsy (option B) as the next step. Intralesional corticosteroid injection for acute chalazion (option A), oral antibiotics for preseptal cellulitis (option C), and oral corticosteroids for inflammatory disease (option D) were not indicated given the clinical presentation and concern for malignancy.

Histopathology demonstrated medium cells with horseshoe nuclei, abundant cytoplasm, and mitotic figures that were CD30+, Ki67+, and ALK−, consistent with ALK− anaplastic large cell lymphoma (ALCL) (**Figure 2**). Initial systemic imaging showed no systemic involvement, leading to a diagnosis of primary cutaneous ALCL.

Primary cutaneous ALCL is a CD30+ T-cell lymphoproliferative disorder that may present as rapidly growing localized lesions in the face, trunk, or extremities.[1] It may be classified as ALK+ and ALK− based on presence of ALK-fusion proteins, with ALK− ALCL typically having worse prognosis due to delayed diagnosis or poor response to treatment.[2,3] Treatment options include CHOP chemotherapy (ie, cyclophosphamide, doxorubicin, vincristine, and prednisolone), radiotherapy, or surgical resection.[1]

Eyelid lymphoma is overall rare, composing 5% of ocular adnexal lymphomas, and tends to be of B-cell origin.[4,5] ALCL involv-

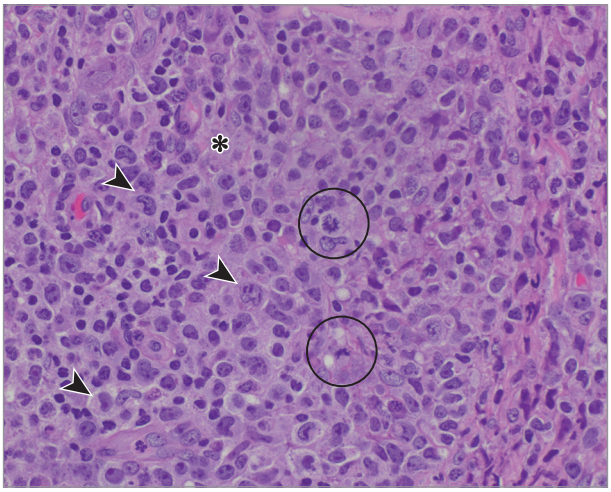

Figure 2. Histopathology of right upper eyelid lesion. Histopathology of the biopsied eyelid lesion demonstrates medium-sized atypical lymphoid cells with irregular to horseshoelike nuclear contours (black arrowheads) and relatively abundant pale cytoplasm (asterisk). Scattered atypical mitotic figures (circled) are noted. (hematoxylin-eosin, original magnification ×40).

ing the eyelid is very uncommon, with fewer than 25 reported cases.[5,6] Its infrequent presentation often leads to misdiagnosis as other periorbital pathology, such as chalazion or squamous cell carcinoma, potentially delaying diagnosis and treatment.[6] Concerning features of progression despite treatment, development of new lesions, madarosis, or ulceration warrant biopsy.

The patient's history of ET, a chronic myeloproliferative neoplasm, may have increased the risk of ALCL. ET is associated with increased risk of secondary hematological malignancies and solid tumors.[7] ALK– ALCL associated with ET is rare, with only 1 prior report of central nervous system ALK– ALCL occurring in a patient with ET without skin or eyelid involvement.[8] ET may potentially increase the risk of developing ALCL due to abnormalities of the JAK-STAT pathway.[9] This patient had a variant in the *CALR* gene, which is involved in this pathway and may deregulate hematopoietic stem cell clonal expansion while disrupting natural immunosurveillance.[9] Physicians should consider malignancy in persistent or enlarging eyelid lesions, especially in patients with hematological conditions such as ET. Prompt biopsy may lead to earlier diagnosis and treatment, potentially improving prognosis in patients with ALK– ALCL.

Patient Outcome

In subsequent oncology visits, the patient developed new skin lesions along her face and body, with repeat biopsy confirming the same ALK– ALCL. She received orbital radiation for her eyelid lesions and started weekly methotrexate, with resolution of her eyelid lesions and marginal improvement of her other lesions. However, further testing revealed central nervous system involvement, suggesting systemic ALCL for which she began systemic and intrathecal chemotherapy. Her eyelid lesions represented the first manifestation of systemic disease, highlighting the importance of vigilance and a high index of suspicion as well as prompt biopsy to facilitate timely diagnosis and treatment.

ARTICLE INFORMATION

Author Affiliations: University of California San Diego School of Medicine, La Jolla (Legala); Shiley Eye Institute, Division of Oculofacial Plastic and Reconstructive Surgery, University of California San Diego, La Jolla (Shoji, Kikkawa).

Corresponding Author: Don O. Kikkawa, MD, Shiley Eye Institute, Division of Oculofacial Plastic and Reconstructive Surgery, University of California San Diego, 9415 Campus Point Dr, La Jolla, CA 92093-0946 (dkikkawa@health.ucsd.edu).

Published Online: December 12, 2024. doi:10.1001/jamaophthalmol.2024.5304

Conflict of Interest Disclosures: Dr Kikkawa reported receiving consultant fees from Amgen, Acerylrin, Lassen, and Immunovant outside the submitted work. No other disclosures were reported.

Additional Contributions: We thank Cole Ferguson, MD, PhD, and Kari Hird, MD, both from the University of California San Diego, for their help with obtaining and reviewing histopathology for this patient. We thank the patient and her family for granting permission to publish this information.

REFERENCES

1. Ortiz-Hidalgo C, Pina-Oviedo S. Primary cutaneous anaplastic large cell lymphoma—a review of clinical, morphological, immunohistochemical, and molecular features. *Cancers (Basel)*. 2023;15(16):4098. doi:10.3390/cancers15164098

2. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood*. 2014;124(9):1473-1480. doi:10.1182/blood-2014-04-571091

3. Rafizadeh SM, Ghahvehchian H, Rajabi MT, Heidari M, Rahmanikhah E. Anaplastic large cell lymphoma with intraocular or ocular adnexal involvement: a case report and systematic review. *Ophthalmic Plast Reconstr Surg*. 2024;40(3):235-244. doi:10.1097/IOP.0000000000002520

4. Porcar Plana CA, Rico Santos E, Losa García JL, Campos Mollo E. Primary cutaneous anaplasic large-cell lymphoma involving medial canthus of the eyelid. *Arch Soc Esp Oftalmol (Engl Ed)*. 2020;95(9):459-462. doi:10.1016/j.oftal.2020.04.007

5. Svendsen FH, Heegaard S. Lymphoma of the eyelid. *Surv Ophthalmol*. 2017;62(3):312-331. doi:10.1016/j.survophthal.2016.11.009

6. Iuliano A, Fossataro F, Laezza MP, et al. Primary cutaneous anaplastic large-cell lymphoma of the eyelid: report of 2 cases and review of the literature. *Orbit*. 2021;40(6):481-487. doi:10.1080/01676830.2020.1826543

7. Frederiksen H, Farkas DK, Christiansen CF, Hasselbalch HC, Sørensen HT. Chronic myeloproliferative neoplasms and subsequent cancer risk: a Danish population-based cohort study. *Blood*. 2011;118(25):6515-6520. doi:10.1182/blood-2011-04-348755

8. Tajima Y, Miyazaki Y, Higashi T, et al. Primary CD30/Ki-1–positive anaplastic large cell lymphoma of the central nervous system occurring in a patient with a 17-year history of essential thrombocythemia. *Leuk Lymphoma*. 2003;44(7):1243-1245. doi:10.1080/1042819031000077106

9. Fucikova J, Spisek R, Kroemer G, Galluzzi L. Calreticulin and cancer. *Cell Res*. 2021;31(1):5-16. doi:10.1038/s41422-020-0383-9