Published in final edited form as:

Br J Ophthalmol. 2011 May ; 95(5): 739–754. doi:10.1136/bjo.2009.163121.

Diffuse Large B-Cell Lymphoma of the Eyelid in a Patient with Acquired Immunodeficiency Syndrome

Christopher K. Hwang, BA¹, Mark R. Melson, MD¹, and Hans E. Grossniklaus, MD, MBA^{1,2}

¹Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia

²Department of Pathology, Emory University School of Medicine, Atlanta, Georgia

Abstract

A 49-year-old man was evaluated for rapidly enlarging left lower eyelid and left neck masses. Biopsies of the masses showed diffuse large B-cell lymphoma (DLBCL). He tested positive for Human Immunodeficiency Virus (HIV). The patient was treated with chemotherapy and antiretroviral therapy, and the masses reduced in size.

Keywords

Acquired Immunodeficiency Syndrome; Diffuse Large B-Cell Lymphoma; Rituximab; c-Myc Gene; Eyelids; Orbit

Case Report

A 49-year-old man was evaluated for left jaw pain and swelling. He had a left neck mass that he noticed a week prior to presentation, which had rapidly enlarged and become painful. The patient also had a two-month history of an enlarging left lower eyelid mass (Figure 1). The patient denied fevers, chills, or weight loss, but admitted to having night sweats. He had no recent history of oral abscesses or dental procedures and denied having any ocular pain, dysphagia, dyspnea, or difficulty breathing. He denied having a history of Human Immunodeficiency Virus (HIV).

Computed tomography (CT) of the head and neck revealed a large soft tissue mass in the left lower eyelid, measuring 5×4cm. The mass extended into the superomedial orbit, compressing and displacing the globe laterally. Additionally, the CT revealed a 5×5cm neck mass with central necrosis as well as enlarged submental and bilateral jugular lymph nodes. The findings were suspicious for an abscess, and the patient underwent biopsy with incision and drainage of the neck mass and biopsy of the left lower eyelid mass. Cultures from the neck mass were negative. The patient gave permission for a laboratory testing for HIV, and it showed that he was positive with a CD4 count of 187/mm³ and a viral load of 131,000 copies/mL.

Correspondence to: Hans E. Grossniklaus MD, MBA, L.F. Montgomery Ophthalmic Pathology Laboratory, BT 428 Emory Eye Center, 1365 Clifton Road, Atlanta, GA 30322; ophtheg@emory.edu.

Competing Interest: None declared.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its licencees, to permit this article (if accepted) to be published in BJO and any other BMJ Group products and to exploit all subsidiary rights, as set out in our licence (<http://bjo.bmjournals.com/fora/licence.pdf>).

Microscopic examination of the eyelid specimen was performed (Figure 2A,B). Special stains for fungi and bacteria including acid-fast bacilli were negative. Immunohistochemical stains were positive for CD45, CD68, and Ki-67 in many cells with Ki-67 cell fraction of 50% (Figure 2D), CD20 in the small round cells (Figure 2C), and CD3 in scattered cells, but negative for Human Herpes Virus 8 (HHV8), Epstein-Barr Virus (EBV), and CD30, which excluded the possibility of a CD30+ lymphoproliferative lesion. Fluorescence in situ hybridization on formalin-fixed tissue showed no rearrangement involving the c-MYC gene. The histopathologic findings in the neck mass specimen were similar to those in the eyelid mass. (The neck mass was actually an enlarged lymph node in the neck). Taken together, both were classified as diffuse large B-cell lymphoma (DLBCL).

Following the diagnosis, the patient underwent a bone marrow biopsy and lumbar puncture, which showed no lymphoma cells, and the lymphoma was determined to be at least Stage 3. The patient was treated with chemotherapy utilizing the CHOP regimen (cyclophosphamide, hydroxydoxorubicin, oncovin, prednisone) and started on anti-retroviral therapy along with prophylactic bactrim. At the four-week follow-up examination, both the eyelid and neck masses were significantly reduced in size. However, the patient has since been lost to subsequent follow-up, and the hospital staff has not been able to contact the patient.

Questions

1. What type of cell is shown at a, b, and c in Figure 2B?
2. How does testing for c-MYC gene rearrangement help to reach the diagnosis?
3. Why did the patient not receive rituximab?

Answers

1. What type of cell is shown at a, b, and c in Figure 2B?

Microscopic examination of the eyelid specimen showed numerous mononuclear cells (c), including small lymphocytes (a) and larger cells with round, vesiculated nuclei, prominent nucleoli, and variable amounts of cytoplasm (b). The histomorphological features were suggestive of an inflammatory process; however, a neoplastic proliferation could not be excluded, particularly as micro-organisms could not be detected in the special stains. Subsequent immunohistochemical staining demonstrated that the above-mentioned larger pleomorphic cells were of B-cell type, and that the lesions represented a high-grade B-cell lymphoma.

2. How does testing for c-MYC gene rearrangement help to reach the diagnosis?

Burkitt's lymphoma (BL) and DLBCL have overlapping morphologic features and immunohistochemical phenotypes and are often difficult to distinguish. The presence of c-MYC gene rearrangement helps to make the distinction. Greater than 95% of cases of BL express chromosomal translocations involving the c-MYC gene locus, 8q24 (eg t(8,14)(q24;q32), t(2;8)(p11;q24), t(8;22)(q24;q11)),^{1, 2} which occurs only in 5 to 10% of the cases of DLBCL.³ Therefore, the absence of a rearrangement involving the c-MYC gene, together with morphological and immunohistochemical features (e.g. Ki-67 growth fraction <90%), strongly favors the diagnosis of DLBCL. However, it does not exclude the diagnosis of BL with absolute certainty.⁴

3. Why did the patient not receive rituximab?

Rituximab is a recombinant CD20 antibody that has revolutionized the treatment of DLBCL in HIV-negative patients. However, the role of rituximab is not clearly defined in patients with AIDS. Rituximab typically causes panhypogammaglobulinemia, which can lead to

humoral immune deficiency. When combined with preexisting deficiency in cellular immunity, rituximab can put the patient with AIDS at a much higher risk for infections. In a trial of CHOP therapy with and without rituximab, Kendall and coworkers showed nonsignificant increase in overall complete remission in patients with AIDS treated with rituximab (58 versus 47%), but no overall benefit due to a significant increase in the rate of death secondary to infection.⁵ However, an analysis of the patients with CD4 count greater than 50/mm³ showed no significant difference in the death rate caused by an infection between the patients treated with and without rituximab. Therefore, some advocate the use of rituximab with appropriate antimicrobial prophylaxis in HIV-positive patients with a relatively high CD4 count (ie greater than 100/mm³).⁶ In either case, highly active antiretroviral therapy (HAART) should be administered concomitantly with chemotherapy in all cases of AIDS-related lymphoma with undetectable blood viral load as the target.⁶

Discussion

After Kaposi sarcoma, non-Hodgkin lymphoma (NHL) is the second most common malignancy in patients with AIDS.^{7, 8} NHL occurs in patients with AIDS in a much higher prevalence than the non-AIDS population.^{7, 8} In fact, Ziegler and coworkers first described the association between NHL and AIDS and proposed that NHL be a criterion for the diagnosis of AIDS.⁹ In patients with AIDS, NHLs are usually aggressive B-cell lymphomas.⁸

There have been only two previous reports of DLBCL of the eyelid in patients with AIDS.^{10, 11} In both cases, the mass rapidly grew over a period of weeks, as it occurred in our patient. Goldberg and coworkers described a 34-year-old woman who had a DLBCL of the right lower eyelid.¹⁰ She was treated with radiation therapy, and the mass quickly reduced in size. At 18-months follow-up, the patient had no evidence of disseminated lymphoma or recurrence of the right lower eyelid lymphoma. Radiation therapy is a potentially curative local therapy in patients with a limited stage DLBCL (ie stage I or II that can be contained in one irradiation field), but like our patient, the greater majority of patients with AIDS are diagnosed at advanced stages and not eligible.¹² Tunc and coworkers reported a 36-year-old man with AIDS and DLBCL associated with diffuse Kaposi sarcoma (KS) of the left upper eyelid.¹¹ Those authors found evidence of EBV in the DLBCL and Human Herpes Virus 8 (HHV8) in the KS, supporting the role of these viruses in the pathogenesis of both malignancies. However, our patient did not have evidence of EBV or HHV8. That patient underwent surgical excision and died one month later. Despite the low number of reports of DLBCL of the eyelid in HIV-positive patients in the literature, the true prevalence is not known and is an area of future research.

Immunosuppression (e.g. due to HIV) should be suspected in patients with rapidly progressing DLBCL of the eyelids. Likewise, the differential diagnosis of a rapidly enlarging eyelid mass in a patient with AIDS should include DLBCL.

Acknowledgments

Funding Supported in part by an unrestricted departmental grant from Research to Prevent Blindness, Inc., and NIH NEI P30 06360

References

1. Haralambieva E, Schuurin E, Rosati S, et al. Interphase fluorescence in situ hybridization for detection of 8q24/MYC breakpoints on routine histologic sections: validation in Burkitt lymphomas from three geographic regions. *Genes Chromosomes Cancer*. 2004; 40(1):10–8. [PubMed: 15034863]

2. Hummel M, Bentink S, Berger H, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. *N Engl J Med*. 2006; 354(23):2419–30. [PubMed: 16760442]
3. Kramer MH, Hermans J, Wijburg E, et al. Clinical relevance of BCL2, BCL6, and MYC rearrangements in diffuse large B-cell lymphoma. *Blood*. 1998; 92(9):3152–62. [PubMed: 9787151]
4. Swerdlow, SH.; Campo, E.; Harris, NL.; Jaffe, ES.; Pileri, SA.; Stein, H.; Thiele, J.; Vardiman, JW. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4 ed. IARC Press; Lyon: 2008.
5. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. *Blood*. 2005; 106(5):1538–43. [PubMed: 15914552]
6. Doweiko, J. *AIDS-related Lymphomas: Treatment of Systemic Lymphomas*. Basow, D., editor. Waltham, MA: 2009. UpToDateUpToDate
7. Bernstein WB, Little RF, Wilson WH, Yarchoan R. Acquired immunodeficiency syndrome-related malignancies in the era of highly active antiretroviral therapy. *International Journal of Hematology*. July; 2006 84(1):3–11. *International Journal of Hematology*. [PubMed: 16867895]
8. Krause J. AIDS-related non-Hodgkin's lymphomas. *Microscopy Research & Technique*. Nov; 2005 68(3-4):168–75. [PubMed: 16276515]
9. Ziegler JL, Beckstead JA, Volberding PA, Abrams DI, Levine AM, Lukes RJ, Gill PS, Burkes RL, Meyer PR, Metroka CE, et al. Non-Hodgkin's lymphoma in 90 homosexual men. Relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. *N Engl J Med*. Aug; 1984 311(9):565–70. [PubMed: 6611504]
10. Goldberg SH, Fieo A, Wolz DE. Primary eyelid non-Hodgkin's lymphoma in a patient with acquired immunodeficiency syndrome. *Am J Ophthalmol*. Feb; 1992 113(2):216–7. [PubMed: 1550198]
11. Tunc M, Simmons M, Char D, Herndier B. Non-Hodgkin lymphoma and Kaposi sarcoma in an eyelid of a patient with acquired immunodeficiency syndrome. Multiple viruses in pathogenesis. *Arch Ophthalmol*. Nov; 1997 115(11):1464–6. [PubMed: 9366682]
12. Sandler AS, Kaplan LD. Diagnosis and management of systemic non-Hodgkin's lymphoma in HIV disease. *Hematol Oncol Clin North Am*. 1996; 10(5):1111–24. [PubMed: 8880199]

Figure 1.
The rapidly enlarging mass of the left lower eyelid had a smooth surface and was moderately tender to palpation.

Figure 2.

A. The eyelid biopsy is infiltrated with numerous mononuclear cells, including large cells with round, vesiculated nuclei and prominent nucleoli with abundant cytoplasm. There are small lymphocytes also present. (hematoxylin and eosin, 100X)

B. Figure 2A at a higher magnification (hematoxylin and eosin, 250X)

C. Immunohistochemical stains are positive for CD20 in the neoplastic cells. (peroxidase anti-peroxidase, 250X)

D. Immunohistochemical stains are positive for Ki-67 in the neoplastic cells. (avidin-biotin-peroxidase complex immunohistochemical technique, 100X)