Editorial

Additional clinical insights into subtype-specific orbital lymphomas

Anna M. Stagner, Lawrence R. Zukerberg

The James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston, MA, USA

Correspondence to: Lawrence R. Zukerberg, MD. Department of Pathology, Massachusetts General Hospital, 55 Fruit St., Warren 219, Boston, MA 02114, USA. Email: LZUKERBERG@mgh.harvard.edu.

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Ocular adnexal (OA) lymphoproliferative disorders are a heterogeneous group of diseases that for many years were lumped together by clinical ophthalmologists for prognostication purposes (1). The majority are extranodal non-Hodgkin's small B cell lymphomas, first largely characterized before current classification systems or diagnostic tools existed (2). The term "ocular adnexa" refers to the structures surrounding the eye itself including the orbital soft tissues, eyelids, conjunctiva, lacrimal production and drainage system and the extraocular muscles; each of these sites can be afflicted with disease. The typical low-grade lymphoma of this area presents as a painless mass that molds to the structures within this orbital space. In the orbit specifically, lymphoma is the most commonly encountered neoplasm. The mucosal associated lymphoid tissue of the conjunctiva lends specifically to the development of extranodal marginal zone lymphoma (EMZL) in many cases, often as the primary site of disease (3).

Over a decade ago, Ferry *et al.* expanded the understanding of OA lymphomas, characterizing nearly 400 cases clinically and histopathologically (4). This series confirmed that indeed, the vast majority of OA lymphomas are low grade B cell lymphomas arising in elderly patients, more than half of which are EMZL occurring primarily (i.e., stage IE). Approximately half involve the orbital soft tissues and the remainder involve other adnexal structures (conjunctiva, lacrimal gland, etc.). Follicular lymphoma, as in other studies, was the next most frequently encountered entity. EMZL and follicular lymphoma together accounted for three quarters of the cases in this series. Diffuse large B cell lymphoma (DLBCL) accounted for 8% of cases, a subset of which likely involved the orbit as part of a larger destructive facial process. Overall, the histopathologic characteristics and immunophenotypes of these well characterized lymphomas were similar to those seen in other sites of nodal or extranodal involvement.

In a recent multicenter retrospective analysis of material spanning nearly 40 years, Olsen *et al.* expanded on the clinical characterization of orbital lymphomas by specific subtype in the largest published cohort of these patients (5). Unlike prior large series, this study focused only on orbital disease, excluding other adnexal sites and thus resulting in slight variations in the reported frequencies of certain lymphoma subtypes. The findings validate much of what has been reported in the literature regarding the clinical presentation and outcomes of lymphomas in this unique anatomic site.

Patients were again elderly (median age 64 years) and presented with periorbital edema, an orbital mass and/or proptosis. As has been well described in prior reports, over half of patients were diagnosed with EMZL (58%). This cohort was largely treated with external beam radiation with excellent control of disease; in EMZL patients with orbital disease, chemotherapy was not beneficial. When restricting lymphomatous involvement to the orbit alone, DLBCL emerged as the second most prevalent disease, afflicting 15% of patients. Patients presented more rapidly, although still had symptoms for a median of 2 months at diagnosis. Secondary DLBCL had a worse prognosis than disease primarily involving the orbit, and patients with primary disease were also treated with local radiotherapy, combined with standard R-CHOP chemotherapy. Follicular lymphoma accounted for 11% of patients, a lower percentage than in other large cohorts (4,6) since the ocular adnexa outside the orbit was not included in this study.

These patients were also treated with chemo-radiotherapy and those with secondary involvement of the orbit fared worse than those with primary orbital disease. Low (grades I–II) versus high grade (III) follicular lymphoma was not distinguished. Mantle cell lymphoma accounted for 8% of the patients in the Olsen series, nearly all with stage IVE disease (and secondary involvement of the orbit) and these patients typically received only chemotherapy. Since T cell lymphomas tend to occur in the skin, included in the category of "ocular adnexa," but rarely involve the orbit, few cases were identified of T cell lymphomas.

As expected, patients with indolent, low-grade lymphoma subtypes had an excellent prognosis, as in other sites, especially with stage 1E (primary involvement) with an overall 10-year disease-free survival of 92% for EMZL and 71% for follicular lymphoma. These patients can be successfully treated with radiotherapy alone, as has been recommended by the American Academy of Ophthalmology (7). However, with a median follow-up of 35 months, it may be difficult to detect long term variation in outcomes based on treatment of these indolent lymphomas.

Interestingly, anatomic site has traditionally been cited in the ophthalmic literature as a highly predictive factor in OA lymphoma, with conjunctiva traditionally being quoted as having the best overall prognosis, followed by orbit and then eyelid (2). Since it is well established that low-grade lymphomas have a better prognosis, a more appropriate method of comparison is that of a given lymphoma subtype at each anatomic site. In this study, orbital EMZL had an excellent 5-year disease specific survival (DSS), nearly identical to that previously reported in the conjunctiva. The same was true for orbital versus conjunctival/eyelid follicular lymphoma (8). Mantle cell lymphoma of the orbit, however, with a 5-year DSS of 53% in the orbit, has a much better prognosis than what has been previously reported in the conjunctiva and DLBCL patients with disease in the orbit and a 5-year DSS of 54% fared markedly better than what has been reported in the eyelids (5).

In this largest study of lymphomas specifically within the orbit, Olsen *et al.* confirm much of what has been described regarding OA lymphomas in a more extensive cohort spanning a period before and after the standard use of rituximab and modern imaging techniques for staging. In the orbit specifically, four subtypes of lymphoma are primarily encountered: EMZL, DLBCL, follicular lymphoma and mantle cell lymphoma. The clinical presentations are similar. As would be predicted, outcomes are largely driven by histologic subtype. The study provides additional information regarding site specific (orbital) disease-free survival within lymphoma subgroups.

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Footnote

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