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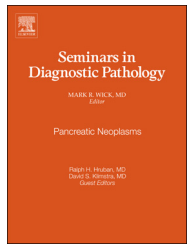

An update on ocular adnexal lymphoma

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ABSTRACT

Ocular adnexal lymphoma (OAL) is a relatively common lesion in the practice of ophthalmic oncology. Although OALs are usually primary tumors, secondary involvement of the ocular adnexae by systemic lymphoma is also possible. The clinical and radiological features of OAL are non-specific. Thorough morphological evaluation, aided by immunostaining, cytogenetic studies and molecular testing, are necessary for accurate diagnosis.

Lymphoma is a malignant neoplasm that is derived from a monoclonal proliferation of T- or B-lymphocytes, or, rarely, natural-killer (NK) cells. Ophthalmic lymphomas can be intraocular or adnexal in location. Accessory visual structures such as the eyebrows, eyelashes, eyelids, conjunctiva, lacrimal apparatus, and orbital soft tissue constitute the ocular appendages, and they are rarely involved by malignant hematopoietic proliferations. Although any type of lymphoma can involve the orbit, ocular adnexal lymphomas (OALs) are virtually all of the non-Hodgkin (NHL) type. Hodgkin lymphoma is extremely uncommon in ophthalmic practice, and will not be discussed here.

Non-specific clinical symptoms and signs of OAL overlap with those of many other orbital diseases, and can result in delayed diagnosis. Although mortality is limited in patients with OALs, untreated cases may result in blindness. We will herein review the available literature on OAL and discuss its salient features.

Definitions and classification

The classification systems for lymphoma—including ophthalmic lymphoma—have been changed several times. Broadly speaking, OALs may be classified as 'primary' or 'secondary.' Primary lesions are isolated, and the ocular structures are the only extranodal site of involvement. In secondary OALs, involvement of the ocular adnexae is seen in patients who also have lymphoma elsewhere in the body. The Revised European American Lymphoma scheme and the World Health Organization (WHO) classification are the most recent and most often used clinically.[1,2]

Epidemiology

Lymphoma is the most common primary orbital malignancy in adults, representing 11% of all masses in that location and 34% of all orbital malignancies.[3] OAL is rare, accounting for 1% of all NHL cases and 5–15% of all extranodal lymphomas.[4,5] However, since the first report of OAL in 1952, its incidence has increased. In a study of malignant orbital tumors, Margo and Mulla[6] found that lymphomas accounted for 55% of all orbital malignancies, and secondary orbital involvement is present in 5.3% of systemic lymphomas.[7]

OAL is a disease of adults who are usually in the 6th to 8th decades of life.[8] Overall, no definite gender predilection is observed, as opposed to cases of non-ophthalmic extranodal NHL which show a slight male preponderance.[9] Nonetheless, high-grade OALs are more common in men.[10]

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Risk factors

Debate exists in the literature on the potential etiologic factors for OAL; autoimmunity, genetic susceptibility, and several infectious agents have all been implicated.

Infectious agents

The role of *Chlamydia*, *Helicobacter pylori*, human T-cell lymphoma virus (HTLV), Epstein–Barr virus (EBV), and hepatitis C virus (HCV) has been investigated by researchers, relative to the etiology of OAL.[11] Ophthalmic involvement by *Chlamydia trachomatis* causes conjunctivitis in babies who are born to infected mothers. A recent study in China demonstrated a higher prevalence of *Chlamydia pneumoniae* in non-mucosa-associated lymphoid tissues (nMALTs) as compared with MALTs.[12] Since the first suggestion of an association between *Chlamydia psittaci* and OAL by Ferreri et al.,[13] other studies have investigated that possibility. Results of those studies are mixed; some authors conclude that an association does exist between *Chlamydia* and the development of OAL, whereas others disagree.[14–20] Such variability of results may be attributable to differing geographic distributions of the organisms in question.[21] A positive response of OAL to treatment with doxycycline further bolsters a possible association between *C. psittaci* and that disease.[22] The linkage of *H. pylori* and gastric-MALT lymphoma is well established,[23] and there is a resemblance of OAL to the gastric tumor. Both pursue an indolent course, with a prevalence of marginal zone B-cell lymphoma.[24–26]

A study in Japan has demonstrated the presence of human *Herpesvirus*-6 (HHV-6) in the lesional tissue of patients with ophthalmic MALT lymphoma.[27] EBV has been associated with conjunctival NK/T-cell lymphomas, orbital Burkitt lymphoma, and plasmablastic lymphoma of the orbit,[28–30] and serum antibodies to HTLV-1 likewise have been demonstrated in patients with orbital lymphoma.[31] Ferreri et al.[32] showed 13% seropositivity for HCV in patients with OAL-MALT lymphomas, and they further associated the HCV with dissemination of lymphoma and aggressive behavior. Similar findings have also been documented by other researchers.[33,34]

Infection with human immunodeficiency virus (HIV) is associated with a greater risk of developing OAL.[35] Possible mechanisms for lymphomagenesis in that setting include activation or genomic insertion of oncogenes from the pathogen, as well as chronic antigenic stimulation.[11,24]

Autoimmunity and other immune disorders

Several autoimmune disorders, such as Graves' disease, Sjogren syndrome, rheumatoid arthritis, and systemic lupus erythematosus, carry an increased risk for development of NHL.[30,36–39] The exact pathogenetic mechanisms for that observation have yet to be elucidated. Acquired immunodeficiency syndrome (AIDS) is also associated with the same risk.[11] Possible mechanisms include coinfection by oncogeneic viruses (e.g., EBV and human *Herpesvirus*-8) or immune modulation by the HIV.[11]

Genetic and epigenetic factors

Not many studies exist on the role of heredity in the causation of OAL. The Swedish Family Cancer Database documented an increased risk of NHL in the offspring of patients who had been diagnosed with NHL previously.[40] Some analyses have evaluated cases of OAL for cytogenetic abnormalities, with inconsistent results.[41–43] Studies on a Danish population showed chromosomal aberrations in only 5% of MALT cases, whereas a similar evaluation in Chinese patients detected such alterations in 61% of patients with ocular adnexal MALT lymphoma.[41,42] The latter authors suggested that trisomy 18 was the commonest abnormality in primary OAL.[42] The most frequent translocation, *t*(11;18)(q21;q21) seen in 15–40% patients of MALT lymphoma, results in the juxtapositioning of the apoptosis inhibitor 2 (API2) gene on 11q21 and the MALT lymphoma translocation gene 1 *MALT1* on 18q21.[43] Another 10% of MALT lymphomas show fusion of the *MALT1* gene and the IgH promoter gene on 14q32.[44] Other aberrations in OALs include chromosomal loss at 6q23.3, 7q36.3, 13q34 and gain at 3, 15q15, 18q, and 6p.[45] All of these cytogenetic abnormalities may affect the NFκB complex, leading to induction of transcriptional genes that are felt to be operative in lymphomagenesis.[43] The role of epigenetic alterations in this context is unknown, but it possibly could include the silencing of host genes, gene methylation, histone remodeling, and RNA-mediated inhibition of gene expression.[11]

The *t*(14;18)(q32;q21) chromosomal translocation is the hallmark of follicular lymphoma (FL) and seen in 80–90% cases ocular adnexal FL.[46,47] It results in juxtapositioning of the B-cell lymphoma/leukemia 2 (*Bcl2*) protooncogene on 18q21 with the immunoglobulin heavy chain gene (*IGH*) promoter region on 14q32 with resultant overexpression of Bcl-2 protein in the neoplastic follicles. This causes accumulation of inappropriately rescued B-cells having a prolonged life span and are prepared for additional hits required for the development of FL.

The primary oncogenic mechanism in the development of mantle-cell lymphoma (MCL) is *t*(11;14)(q13;q32) resulting in juxtapositioning of the *IGH* promoter gene on 14q32 with *CCND1* at 11q13. This causes constitutive overexpression of cyclin D1 and dysregulation of the cell cycle at G1/S transition. Recent studies have shown other mechanisms such as DNA damage response alterations and cell cycle pathway activation too drive MCL oncogenesis.[48] Hypermutations of the IGH variable region (IGHV) have been demonstrated in 15–40% cases of MCL.[49]

Based on the cell of origin, diffuse large B-cell lymphomas (DLBCL) are sub-divided into 3 types: (a) germinal center B-cell like (GCB) DLBCL derived from germinal center centroblasts, (b) activated B-cell like (ABC) DLBCL derived from BCR-activated B-cell or plasmablastic B-cell, and (c) primary mediastinal large B-cell lymphoma (PMBCL) from the thymic post-germinal center B-cells. Translocations involving Bcl-2, gains of EZH2 and mutations involving *MLL2*, *CREBBP*, *EP300*, and *MLL3* have been reported in the GCB-subtype.[50] Activation of nuclear factor kappa-light-chain enhancer of activated B-cells (NFKB) is seen in the ABC-subtype.[51]