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Major review

Malignant lymphoma of the conjunctiva

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ABSTRACT

Conjunctival lymphomas constitute 25% of all ocular adnexal lymphomas. The majority are B-cell non-Hodgkin lymphomas (NHLs) (98%), whereas conjunctival T-cell NHLs are rare (2%). The most frequent subtype of conjunctival B-cell lymphoma is extranodal marginal zone lymphoma (EMZL; 81%), followed by follicular lymphoma (8%), diffuse large B-cell lymphoma (3%), and mantle cell lymphoma (3%). Extranodal marginal zone lymphoma occurs slightly more often in women and, along with follicular lymphoma, presents late in the seventh decade of life, whereas diffuse large B-cell lymphoma and especially mantle cell lymphoma have a predilection for the male gender and typically present in the eighth decade. Extranodal marginal zone lymphoma and follicular lymphoma present most frequently in the forniceal and bulbar conjunctiva. Conjunctival diffuse large B-cell lymphoma, mantle cell lymphoma and T-cell NHLs are characterized by a short duration of symptoms before the first ophthalmologic consultation. External beam radiotherapy is the treatment of choice for extranodal marginal zone lymphoma and follicular lymphoma, whereas diffuse large B-cell lymphoma, mantle cell lymphoma, and T-cell NHLs are mainly treated with chemotherapy. Conjunctival T-cell NHLs are associated with a particularly poor prognosis, with 50% of patients having progression or recurrence during a 1-year follow-up period.

1. Introduction

1.1. *The conjunctiva*

The conjunctiva is the mucous membrane that lines the inner surface of the eyelids and curves onto the anterior surface of the eye, where it extends to the corneoscleral limbus.[113] Although it is a continual structure, the conjunctiva can be divided into 6 different topographic zones with a distinct morphology: marginal, palpebral or tarsal, orbital, forniceal, bulbar, and limbal areas.[73] The conjunctiva functions as a major support tissue for the preservation of the optical function of the cornea. It is equipped with a natural, submucosal reservoir of lymphoid tissue within its substantia propria,

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which belongs to the mucosal immune system of the body and is thereby able to provide immune protection for the ocular surface, including the cornea.[73]

1.2. *Lymphoma*

Lymphoma, a malignant neoplasm derived from a monoclonal proliferation of B- or T-lymphocytes, and less frequently natural killer cells (NK-cells), may be divided into 2 major groups: Hodgkin lymphoma and non-Hodgkin lymphomas (NHLs).[127]

The NHLs, a large heterogeneous group of neoplasms, can be further subdivided into those originating from B-lymphocytes or their precursors (80%), T cells (14%), and NK cells (6%).[127] All three lymphoma subgroups may occur in the conjunctiva and can be further classified into a number of subtypes.

2. Frequency and demographics

2.1. *Frequency*

A total of 1,014 conjunctival lymphoid neoplasms are described, 98% of which are of B-cell lineage (Tables 1 and 2). The most common subtypes of B-cell lymphoma in the conjunctiva are the low-grade extranodal marginal zone lymphoma (EMZL), with 818 identified cases (81%) and follicular lymphoma (FL), with 77 cases (8%). These are followed by the high-grade mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma (DLBCL), with 29 cases (3%) of each.[32,45,119] The frequency of DLBCL in the conjunctiva is markedly lower than in the remaining ocular adnexal region (13%).[117] Of the less common B-cell lymphoma subtypes, there are 12 lymphoplasmacytic lymphomas, 10 small lymphocytic lymphomas, and 10 plasmacytomas, which are low-grade malignancies, and 2 cases of lymphomatoid granulomatosis and 1 of Burkitt lymphoma, which are high-grade malignancies.[45,88,121,144,152] Furthermore, there is also a case of multiple myeloma, which can be an aggressive or an indolent disease depending on the variant.[11]

The remaining 2% of reported lymphomas include 18 cases of T-cell lymphoma, 1 NK-cell lymphoma, and 6 lymphomas that could not be classified (Tables 3 and 4).[4,39,66] The most frequent subtypes of T-cell lymphoma in the conjunctiva appear to be the adult T-cell lymphoma and anaplastic large-cell lymphoma, with 3 cases of each reported.[17,27] Moreover, there are 2 cases of mycosis fungoides and 1 case each of angioimmunoblastic T-cell lymphoma, diffuse large T-cell lymphoma, acute lymphoblastic lymphoma of T-cell type, and NK/T-cell lymphoma.[29,47,54,98,145]

2.2. *Age at presentation*

Conjunctival lymphoma is primarily a disease of the elderly, but has been described in patients from 33 months up to 92 years of age. There is a significant difference in age distribution among the different types of conjunctival lymphomas (Tables 1 and 3). Thus, the low-grade subtypes of conjunctival B-cell lymphoma generally present earlier than the high-grade subtypes. EMZL and FL commonly present in patients in their late 60s, whereas DLBCL and MCL usually occur in patients in their 70s.[6,19,130] Conjunctival T-cell lymphomas typically present in middle-aged and elderly individuals.[31,71]

2.3. *Gender*

Conjunctival lymphoma in general does not appear to have a gender predilection; however, several of its subtypes do occur more often in a particular gender (Tables 1 and 3). For example, conjunctival EMZL occurs somewhat more frequently in women than in men, whereas the high-grade DLBCL and especially MCL have a predilection for male gender, with MCL occurring 5 times more frequently in men.[67,69,130] Conjunctival T-cell NHLs, on the other hand, are evenly distributed between males and females.[31,115]

3. Pathogenesis

3.1. *Chronic antigenic stimulation*

Much attention has been focused on determining whether ocular adnexal lymphomas, especially EMZLs, are caused by chronic antigenic stimulation. The organisms suggested as contributing to the pathogenesis of conjunctival EMZL are *Helicobacter pylori*, *Chlamydia psittaci*, and hepatitis C.[42,44,120]

One of the hallmark characteristics of EMZL is that the neoplasia is preceded by a benign, chronic inflammation.[58] Thus, EMZL appears to develop as a result of prolonged antigen stimulation that leads to loss of regulation of B-lymphocyte proliferation and differentiation.[37] Several characteristics of conjunctival EMZL give rise to the suspicion that this mechanism also triggers EMZL development in the conjunctiva: 1) conjunctival EMZL is often bilateral and may show spontaneous remission, which could be the result of bilateral conjunctival infection and clearance of an antigen, respectively[84,85]; 2) the t(11;18)(q21;q21) translocation, which is related to oxidative damage induced by genotoxic factors such as *H pylori* or *C psittaci* infection, is present in 19% of conjunctival EMZLs[148]; 3) in some cases, patients with conjunctival EMZL have a history of preceding infectious conjunctivitis.[42]

A number of studies have investigated the association between the infectious agents and conjunctival lymphoma. A Korean study detected *H pylori* DNA in all 15 analyzed cases of conjunctival EMZL.[78] *H pylori* DNA was likewise detected in tumor cells from 4 of 5 cases of conjunctival EMZL from China.[21] The prevalence of *C psittaci* positivity in conjunctival lymphoma appears to be about 16%, summing up the results of 3 studies from Europe, 1 from China, and 1 from the USA.[24] These data suggest that *H pylori* and *C psittaci* may play a role in conjunctival lymphoma.

On the other hand, a Danish study of 13 cases of conjunctival EMZL demonstrated no association between *H pylori* and EMZL of the conjunctiva, with all investigated cases being *H pylori* negative.[120] Likewise, in another study from China, all 16 specimens of conjunctival EMZL were both *H pylori* and *C psittaci* negative, indicating that there is possibly no association between conjunctival EMZL and the 2 microorganisms.