Ocular adnexal non-Hodgkin’s lymphoma: a review of epidemiology and risk factors


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Ocular adnexal non-Hodgkin’s lymphoma (NHL), the most common form of ophthalmic NHL, has a unique incidence pattern showing a steady and rapid increase in the past few decades, nearly equal rates among both genders, and predominance among Asians/Pacific Islanders. No major cause for ocular adnexal NHL has been identified, although infectious agents, immune disorders and genetic/epigenetic factors have all been implicated in its etiology. Identifying putative risk factors and biologic mechanisms leading to carcinogenesis in ocular adnexal NHL may enable implementation of effective preventive and/or therapeutic approaches for this malignancy. This article summarizes current knowledge on epidemiology of ocular adnexal NHL and the role of various potential risk factors in its etiology.

Keywords: epigenetic changes and NHL • extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue • genetic factors and NHL • immune factors and NHL • infectious agents and NHL • ocular adnexal non-Hodgkin’s lymphoma

Non-Hodgkin’s lymphoma (NHL) is the sixth most common malignancy among both genders in the USA, with an estimated 65,540 new cases and 20,210 deaths projected in 2010 [1]. NHL is comprised of a group of heterogeneous neoplasms deriving from clonal proliferations of either B or T lymphocytes. NHL can arise in lymphatic nodal or extranodal (outside of lymph nodes, spleen, thymus and Waldeyer’s ring) sites [2]. Primary ophthalmic lymphoma represents 1–2% of all NHLs and 5–15% of all extranodal NHLs [3,4]. The great majority of ophthalmic NHL is of B-cell origin and involves ocular adnexal regions, which include orbit, conjunctiva, lacrimal gland or eyelid [5].

In Florida, NHL is reported to represent 55% of all orbital tumors [6]. Intraocular NHL, the other main category of ophthalmic NHL, can arise in the cornea, retina, choroid or ciliary body [7] and can be considered a subset of CNS lymphomas [7,8]. Although rare, coexistence of both types of ophthalmic NHL in the same individual has been reported [9]. Secondary ocular adnexal involvement has been found in up to 5.3% of generalized systemic lymphoma cases [10].

The staging and classification systems for ophthalmic and other forms of lymphomas have changed multiple times in the past 40 years. The most widely used staging systems for both nodal and extranodal NHL are the Ann Arbor [11] and modified Ann Arbor [12] systems. Recently, a tumor-, node-, metastases-based staging system based on anatomic documentation of disease extent and possibility of biomarker incorporation has been proposed for ocular adnexal lymphomas [13]. Revised European–American Lymphoma (REAL) [14], WHO [15] and the revised WHO [16] are the most recent and comprehensive lymphoma classification systems in use. According to these classification systems, extranodal, marginal zone, B-cell lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) type, is the most common histologic type of primary ophthalmic NHL [17], accounting for 38–100% of ocular adnexal NHL [18–27]. MALT is considered the third most common form of NHL [28], accounting for 6–7% of all nonophthalmic extranodal NHL [14,15,29,30]. MALT can occur in a number of extranodal sites possessing a natural submucosal reservoir, such as the salivary gland and thyroid, as well as in sites that are naturally devoid of organized lymphoid tissue, such as the orbit, skin and stomach. At nonnodal sites, lymphoma may arise from MALT acquired in the context of chronic inflammation and/or inflammatory disorders with infectious or autoimmune etiology.
These observations have given rise to the theory of infection-associated lymphomas occurring as a result of antigen-driven lymphoproliferation [31].

Recent debate regarding a potential infectious etiology for primary ocular adnexal NHL in certain populations prompted us to study its descriptive patterns and conduct a review of its epidemiology and suggested risk factors.

**Methods**

A literature search was conducted using Pubmed and Medscape interfaces on the Medline database. The search strategy included retrieval of references on several keywords, phrases and abbreviations related to epidemiology and risk factors for lymphoma, NHL, ocular adnexal lymphoma, ophthalmic NHL, EMZL and MALT lymphoma. Articles published during 1988–2010 were selected for review; these included all cohort studies, case–control studies, case series and case reports. Relevant articles in French were included; articles in other foreign languages were only included if their abstracts were in either English or French. Book chapters were scanned for relevant references and original papers were obtained and reviewed for inclusion.

**Descriptive epidemiology of ocular adnexal NHL**

Different histologic subtypes of NHL have different incidence and mortality patterns [32]; NHL rates, in general, have increased worldwide in the past few decades [32–34]. The AIDS epidemic is believed to account for a portion of the increase in NHL rates in most countries [35–37]; a USA study in 1992 put the estimate of the then current AIDS-related NHL cases at approximately 10% [38].

Descriptive data on rates and trends of ophthalmic and ocular adnexal NHL are sparse in the literature. The most recent report based on the analysis of incidence data from 13 Surveillance, Epidemiology, and End Results (SEER) areas in the USA spanning 1992–2007 revealed nearly equal male and female rates among 1604 cases of ophthalmic NHL and 1565 cases of ocular adnexal NHL, with higher rates of the disease among Asians/Pacific Islanders [34]. Analysis of rates in New York state during 1998–2007 also revealed nearly equal rates among both genders for 574 cases of ophthalmic and 553 cases of ocular adnexal NHL as well as predominance among Asians/Pacific Islanders [34]. A previous report had investigated descriptive patterns of ophthalmic NHL based on 858 cases reported in 12 SEER areas during 1992–2001 and found equal rates of ophthalmic NHL among both genders as well as predominance among Asians/Pacific Islanders [39]. The unique gender and ethnic distributions of ophthalmic NHL noted in both analyses of SEER data as well as in New York state were in contrast to other extranodal NHLs, which showed predominance among males and white individuals throughout all age groups. Ophthalmic NHL rates among all races showed steady increase with advancing age similar to other forms of extranodal NHL [39].

The unique gender distribution of ophthalmic NHL has also been observed internationally, and a recent study in Denmark reported both genders being equally afflicted with ophthalmic NHL, although high-grade tumors were found to be more common among males [40]. International incidence data pertaining to ethnic and racial variations in rates of ophthalmic and ocular adnexal NHL are lacking. Nonetheless, lymphoma has been reported as the most common primary malignant orbital tumor in Asian countries [23,41,42]. Accurate population-based estimates of ophthalmic NHL rates from other countries are needed for comparison with the USA.

Population-based analyses of ophthalmic NHL incidence among white individuals in the USA (SEER 9) reported a rapid increase in incidence among both genders from 1975 to 2001 [39]. International data on temporal trends of ophthalmic NHL were available from Denmark, where the rates were found to be highly dependent on the patient’s age, with an annual average increase of 3.4% during the period 1980–2005 for all ages [40].

Morbidity and mortality associated with ophthalmic NHL is relatively low. Ophthalmic NHL can lead to blindness and/or death in cases of untreated and/or histologically aggressive disease (such as large-cell and/or immunoblastic types); death may also occur in cases of prior or systemic disease [43]. The 5-year (observed and relative) survival rates for ophthalmic (75.5 and 88.4%, respectively) and ocular adnexal NHL (76.6 and 89.7%, respectively), estimated based on cases diagnosed from 1999 to 2006 in 13 SEER areas and followed through 2007, were reported to be higher than those of other extranodal and nodal NHL [34]. Better survival for ophthalmic NHL may be related to its etiology and/or to its more accessible location or histological characteristics.

Comprehensive assessment of 114,548 lymphoid neoplasms diagnosed during 1992–2001 in 12 SEER registries revealed striking differences in incidence patterns by histologic subtypes classified according to the WHO, suggesting etiologic heterogeneity [44]. Socioeconomic status, urbanization, increase in the aging population, higher prevalence of immunosuppressive conditions, improvements in diagnostic technologies and the change in the lymphoma classification system have each been implicated in the etiology of NHL at different anatomic sites [45]. An infectious etiology has also been suggested for some forms of extranodal NHL based on increased risks among individuals affected with HIV [46,47]. Although ocular adnexal NHL, the most common form of ophthalmic NHL, is relatively rare, its unique incidence patterns, as outlined in this section, compared with other extranodal NHLs, warrants an investigation of potential risk factors involved in its etiology.

**Risk factors for ocular adnexal NHL**

There is much debate in the literature with respect to the etiologic factor(s) for ocular adnexal NHL; several pathogens, various autoimmune disorders and genetic susceptibility have all been implicated in the etiology of this disease. It is plausible that a combination of these factors could account for susceptibility to this malignancy. Later, we discuss what is known about the role of each putative factor in ocular adnexal NHL development.

**Infectious agents & ocular adnexal NHL**

Several studies have investigated the role of *Chlamydia, Helicobacter pylori*, human herpesviruses (HHV), Epstein–Barr virus (EBV), human T-cell lymphotropic virus type 1 (HTLV-I)
and hepatitis C virus (HCV), as well as other infectious agents, in the etiology of ocular adnexal lymphoma. The results of the individual studies have ranged from strong associations to limited or no associations. Besides differences in the distribution of these infectious agents in different geographic regions accounting for variable associations, differences in terminology and classification systems as well as improvements in laboratory techniques, which allow for a more accurate detection of viral or bacterial DNA in lymphoid tissue, could contribute to the variability of results from different studies.

The mechanisms of B-cell transformation and/or lymphoproliferation leading to ocular adnexal lymphomas brought about by these bacteria, viruses and parasites remain to be elucidated. Several hypotheses attempt to describe the etiologic role of infectious agents in NHL; one hypothesis of particular relevance to ocular adnexal NHL is chronic antigenic stimulation. Below, we will give a brief description of studies investigating the role of each infectious factor in ocular adnexal NHL causation followed by a section describing the potential mechanism(s) leading to lymphoproliferation and lymphoma.

Chlamydial infections

Chlamydia are obligate intracellular bacteria with a tendency to cause persistent infections that may play a role in oncogenesis. There are three known species of Chlamydia, namely, Chlamydia trachomatis, Chlamydothila psittaci and Chlamydothila pneumoniae. C. trachomatis is a sexually transmitted disease and is typically linked to ophthalmic involvement in the form of conjunctivitis in babies born to infected mothers. C. pneumoniae is the more commonly occurring pathogen that causes pneumonia. C. psittaci is the agent responsible for psittacosis, an atypical pneumonia, resulting from exposure to excretions of infected birds, cats and some other household pets. Previously C. psittaci and C. pneumoniae could not be distinguished from each other, but now newer technology has made this differentiation possible. C. pneumoniae was initially detected in a case of ocular adnexal lymphoma in Hong Kong. Other studies have not found a significant association between C. pneumoniae and ocular adnexal lymphoma. A collaborative study examining the presence of Helicobacter pylori and C. pneumoniae showed a high prevalence of the latter organism in primary ocular adnexal lymphoma cases in China, but overall the prevalence of C. pneumoniae was higher in non-MALT samples compared with MALT samples.

Several studies have examined the relationship between C. psittaci and ocular adnexal NHL. To date, results have been mixed: some studies have found associations, while several others have failed to demonstrate evidence of any link. Geographic variation of C. psittaci infection or other host and/or environmental factors may explain the contradictory results. A positive association between C. psittaci and ocular adnexal lymphoma was first suggested in 2004 by Ferreri et al. in an unmatched case-control study conducted among patients evaluated in Milan, Italy. The patients’ samples were also tested for the presence of DNA from C. trachomatis and C. pneumoniae. The results showed the presence of C. psittaci DNA in 80% (32 out of 40) of lymphoma lesions and in 11.5% (three out of 26) of reactive lymphadenopathy samples, but not in any of the 20 non-neoplastic samples. C. trachomatis and C. pneumoniae were not detected in any of the lymphoma samples in this study. A total of 43% (nine out of 21) of patients with C. psittaci-positive lymphomas also had C. psittaci DNA in their peripheral blood mononuclear cells (PBMCs) while none of the healthy individuals had any detectable C. psittaci DNA in their blood cells. These findings were further supported by regression of the lymphoma lesions in seven patients treated with doxycycline. In this and a subsequent intervention study, patients showed complete or partial remission after chlamydial eradication with doxycycline and the C. psittaci DNA was no longer detectable in the previously C. psittaci-positive patients.

Subsequent studies by the same group, investigating the viability and infectivity of this pathogen, confirmed the previous findings as C. psittaci DNA was detected in conjunctival swabs of ten out of 20 ocular adnexal lymphoma patients and in the PBMCs of one out of 42 control individuals. Cell cultures established from the swabs and PBMC samples of cases but not controls showed positive growth. Researchers in Korea provided further evidence of a causative role for C. psittaci in the development of ocular adnexal lymphoma. A case-control study involving 33 patients with ocular adnexal MALT lymphomas reported the presence of C. psittaci DNA in 79% (26 out of 33) of cases versus 24% (five out of 21) of controls, who had non-neoplastic ocular adnexal disease.

By contrast, studies among other populations were unable to replicate these findings. A case-control study in the USA failed to detect C. psittaci DNA in the lesions or the PBMCs of seven MALT and four non-MALT ocular adnexal NHLs, as well as in six benign conditions, including one case of Langerhans histiocytosis and five reactive lymphoproliferations. While the authors did not specifically test for other infectious agents, they proposed that the discrepant results may be an indication that the etiology of ocular adnexal NHL differs geographically. Chamut et al. conducted a large collaborative case-control study that specifically addressed this question of geographic variability. Cases and controls were selected from six different geographical regions (Southern China, Germany, Italy, The Netherlands, UK and the East coast of the USA), and evaluated for seven different infectious agents commonly involved in chronic eye diseases in order to assess their role in the development of ocular adnexal NHL. Overall, 22% (31 out of 142) of cases showed evidence of C. psittaci infection and this was statistically significantly higher than the prevalence of this pathogen among the controls. The prevalence of C. psittaci infection in MALT lymphoma cases, however, showed marked variation among the six regions: the frequency of infection was 47% in Germany, 35% in the East coast of the USA, 29% in The Netherlands, 13% in Italy, 12% in the UK and 11% in Southern China. No significant differences in the frequency of C. pneumoniae and C. trachomatis or any of the viral agents (herpes simplex virus, HSV1, HSV2 and adenosviruses 8 and 19) were found between lymphomas and controls.
A retrospective cohort study consisting of 62 ocular adnexal lymphoma cases followed over a 14-year period in the state of Florida (USA) evaluated 57 tumor specimens: C. psittaci DNA was not detected in any of these samples. The authors concluded that C. psittaci was not implicated in the etiology of ocular lymphoma in South Florida [18]. Similarly, a cohort study of 67 ocular NHL cases from The Netherlands, diagnosed between 1982 and 2003, failed to detect C. psittaci DNA in the tumors of any of the 67 patients with ocular MALT lymphoma [65].

A case series in Japan conducted a serological analysis to evaluate the presence of EBV, Chlamydia and HCV in 23 ocular adnexal lymphoma patients. Antibodies associated with autoimmune and antibodies against C. trachomatis were found in four patients, however there was no evidence of C. psittaci, HCV or EBV infection. The authors concluded that C. psittaci was not linked to the development of ocular adnexal lymphoma cases in Southern Japan [62]. A study conducted in Cuba on 26 ocular adnexal lymphoma cases, 20 non-ocular lymphoma cases and 20 cases of benign ocular lesions diagnosed and treated between 1993 and 2003 reported the presence of infection among ocular adnexal lymphoma cases, although the prevalence of C. psittaci DNA was low: 11% overall in the lymphoma cases (two out of 26 ocular adnexal lymphomas and three out of 20 non-ocular lymphomas) and zero in the benign ocular lesions [64]. Carugi et al. compared the prevalence of C. psittaci DNA in ocular adnexal MALTs in patients from Italy and Kenya; while the association with C. psittaci was confirmed in Italian cases, none of the Kenyan patients tested positive for the infection [68].

Comparing epidemiology of C. psittaci infection to that of ocular adnexal NHL may help shed more light on this potential association. The prevalence of C. psittaci infection in the general population is difficult to estimate because of its tendency to be asymptomatic or present in an atypical manner [69]. Symptomatic C. psittaci infection, namely, psittacosis, is a reportable disease. In addition to pet birds and cats, human C. psittaci infections have been reported to result from interaction with infected turkeys [70], ducks [71], sheep and new-born lambs [72]. In the USA, the annual incidence of psittacosis has fluctuated over time in parallel with reported outbreaks of C. psittaci infections in domestic animals or among pet shop or factory employees; however, the overall trend seems to have stayed the same [70]. In the UK, the number of cases of respiratory chlamydial infections reported to the Communicable Disease Surveillance Center (CDSC) has increased since the 1970s to over 300 per year. Most cases in the UK in previous years were diagnosed by serological methods that did not differentiate between C. psittaci and C. pneumoniae [73]. A study using updated methods attributed 76% of cases of human respiratory infections in the UK between 1986 and 1988 to C. psittaci and 24% to C. pneumoniae [74]. Despite the availability of psittacosis rates from the USA and the UK, it would be difficult to superimpose the rates of psittacosis and ocular adnexal NHL due to uncertainties about estimated under-reporting as well as cancer risk and lag-time associated with infection.

**Helicobacter pylori**

*Helicobacter pylori* are Gram-negative bacteria that are highly prevalent in developing countries. *H. pylori* have been identified as causative agents in gastric ulcers and gastric adenocarcinoma; furthermore, the pathogenic association between *H. pylori* and gastric MALT lymphoma is well established [75,76]. Based upon the observation that ocular adnexal MALT lymphomas share clinicopathological features with gastric MALT lymphomas, researchers have explored the possible association between *H. pylori* and ocular lymphoma. A study of cases from France and the USA found *H. pylori* DNA within the lesion in four out of five cases of conjunctival MALT lymphoma, while no evidence of *H. pylori* was detected in the surrounding normal tissue [77]. A similar study on ocular adnexal lymphoma cases from Italy also found the presence of *H. pylori* DNA within lesions in ten out of 31 patients [78]; coinfection with *C. psittaci* was reported for three out of ten patients [54,55]. In subsequent studies on Italian cases, antibiotic therapy targeting *H. pylori* alone was found to have no effect, while inclusion of doxycycline led to regression of lymphoma lesions [56]. More recent studies from Korea [79] and Austria [80] reported significant association between *H. pylori* in 100% (15 out of 15) and 38% (13 out of 45) of ocular adnexal MALT lymphomas, respectively. However, similar studies on ocular adnexal MALT lymphoma cases from Germany and Denmark found no evidence of *H. pylori* involvement [66,81].

**Human herpes virus**

The role of lymphotropic herpesviruses in the etiology of primary ocular adnexal lymphoma has also been investigated. A study in Japan assessing the presence of HHV-6, HHV-7 and HHV-8 in primary ophthalmic MALT lymphomas detected the presence of HHV-6 within the lesions [82]. Another study reported the presence of HHV-8 in primary intraocular lymphoma cases but not in normal or inflammatory lymphoma cells [83].

**Epstein–Barr virus**

Epstein–Barr virus is the most common virus in the human population persisting in 90% of adults [84]. *In vitro*, EBV transforms B lymphocytes and is associated with several lymphoproliferative diseases [7]. This pathogen has also been reported in association with AIDS-related lymphomas [85]. EBV DNA has been reported to coexist along with HHV-6 DNA in primary ophthalmic MALT lymphomas [82] and with HHV-8 DNA in primary intraocular lymphomas [83]. A recent study found the presence of HHV-8 and EBV DNA in the lesions of ten HIV-negative primary intraocular lymphoma cases [86]. These findings warrant further investigation as to the significance of coinfection and the roles of herpesviruses and EBV in the pathogenesis of ocular adnexal lymphoma.

**T-cell lymphotropic virus type 1**

T-cell lymphotrophic virus type 1 is an RNA retrovirus transmitted via sexual contact, blood transfusion and breast feeding. Several reports have described ophthalmic manifestations of HTLV-1 in patients with adult T-cell leukemia/lymphoma as including primary ocular adnexal lymphomas [87–91].
Hepatitis C virus
Hepatitis C virus is a linear, single-stranded RNA virus often reported to be associated with autoimmune disorders [92]. HCV has also been reported in association with non-Hodgkin’s B-cell lymphomas [93–95]. A few studies have looked specifically at the relationship of HCV with ocular adnexal lymphomas. In a study by Ferreri et al., of 55 patients with MALT-type ocular adnexal lymphoma, 13% were seropositive for HCV; seropositive patients were significantly more likely to have disseminated disease and more aggressive tumor behavior [96]. Subsequent studies among French and Austrian patients with primary ocular adnexal lymphoma found even lower levels of HCV seropositivity: 2% (one out of 54) and 4% (two out of 45), respectively [80,97]. However, none of these studies utilized a control group with benign conditions to directly assess for an association between HCV and ocular adnexal lymphoma.

While not specifically assessing ocular adnexal lymphoma, Morgensztern et al. compared the prevalence of HCV infections among patients with NHL with a control group with nonlymphoid solid tumors in South Florida and detected infections in only 2.2% (two out of 90) of patients with lymphoma versus 4.1% (four out of 96) of controls [98].

Other infectious agents
Patients with HIV/AIDS have an increased risk of developing NHL and the lymphoma is mostly of high-grade B-cell type [46,47]. The type of ophthalmic disease among AIDS patients depends on the level of immune function and the extent of disease as well as opportunistic infections with EBV, HHV or Toxoplasma gondii. Intraocular lymphomas among AIDS patients have been described in a few case reports [99–101]. The most common presentation is a primary CNS lymphoma with ocular involvement characterized by vitreitis and subretinal (choroidal) infiltrates; diffuse large B-cell subtypes appear to predominate where described [99–102]. The role of HIV in ocular adnexal etiology needs further investigation.

Toxoplasma gondii is an intracellular parasitic protozoan that causes acute and chronic systemic infection in humans. The infection is asymptomatic in the majority of immunocompetent people. Immunocompromised patients are at greatest risk for acute toxoplasmosis. Infection may involve the eye, producing acute necrotizing retinitis and chorioretinitis; chronic complications may follow [103]. In a study involving ten HIV-negative patients with primary intraocular B-cell lymphoma, Shen et al. postulated that T. gondii might be responsible for a subset of primary intraocular lymphomas after finding T. gondii DNA in the lymphoma cells of two patients [86]. Based on this association, a role for T. gondii in ocular adnexal NHL has also been proposed, although direct evidence of an association is, thus far, lacking.

**Potential pathogenic mechanisms leading to ocular adnexal NHL**
A variety of processes have been proposed as possible pathogenic mechanisms for the development of NHL. [104]. Those related to ocular adnexal NHL involve the immune function and genetic–epigenetic mechanisms. Chronic antigenic stimulation, as may occur with persistent infections, is a mechanism that is related to both immunologic and genetic processes; this mechanism has been studied with respect to ocular adnexal NHL and is discussed in the following section. Another mechanism of relevance to ocular adnexal NHL is the role of viral oncogenes in tumor development. EBV and HTLV-1 are known human oncogenic viruses that are associated with lymphoma and adult T-cell leukemia, respectively. These viruses encode oncogenes that alter cellular pathways leading to molecular signaling dysregulation, cellular proliferation and immortalization [105]. There are no reports on investigations into the role of virally encoded oncogenes or other pathogen-related processes such as insertion mutagenesis in ocular adnexal NHL development.

**Chronic antigenic stimulation**
A potential mechanism for pathogen–ocular adnexal NHL associated risk is through a state of chronic antigenic stimulation. The chronic antigenic stimulation hypothesis suggests that specific bacterial and viral infectious agents may create antigenic stimuli, which, over the lifetime of an individual, could lead to clonal expansion and proliferation of B cells [31]. This clonal expansion could allow for accumulation of genetic alterations including point mutations and chromosomal translocations, as well as epigenetic changes causing activation of oncogenes and inactivation of tumor-suppressor genes, leading to malignancy via dysregulation of key cellular pathways such as cell growth and differentiation, DNA repair, apoptosis and cell cycle regulation.

**Helicobacter pylori**-associated gastritis and subsequent gastric MALT NHL is the best-studied example of this model [106]. H. pylori produces a chronic gastritis, which, through ongoing stimulation of host antigen-presenting T cells, leads to reactive lymphoid infiltrate and subsequent clonal expansion of B cells, forming MALT lymphoma in a small percentage of patients [76,107]. Similarities between gastric MALT lymphomas and ocular adnexal MALT NHLs has led some to suggest a role for chronic antigenic stimulation in the etiology of this ophthalmic disease [108]. This hypothesis has gained strength from a recent report by Ferreri et al. indicating that 85% of cases infected with C. psittaci versus 38% of controls in their studies resided in rural areas and reported a history of chronic conjunctivitis and prolonged contact with household animals [57]. The authors suggested that prolonged exposure to this pathogen and potential chronic infection causing conjunctivitis may lead to lymphoma [84]. Interestingly, conjunctivitis was noted as a feature of psittacosis during a pandemic in the UK during the period 1922–1930 and C. psittaci has been reported as the cause of conjunctivitis in both humans and guinea pigs [109]. There have also been reports of individuals with mammalian strains of C. psittaci who owned cats suffering from conjunctivitis [70].

The observations that MALT lymphomas arise at sites of chronic antigenic stimulation caused not only due to infection (such as H. pylori and gastric MALT lymphomas [107]) but also due to autoimmune disorders (such as Hashimoto thyroiditis [110]) also lend support to the chronic antigenic stimulation hypothesis.
Immune disorders & ocular NHL

Autoimmune & other chronic inflammatory disorders

An increased risk of NHL has been reported with several autoimmune disorders such as Hashimoto thyroiditis [110], Sjögren’s syndrome [111–113], Graves’ disease [114], rheumatoid arthritis [115,116], Celiac disease [127,118] and systemic lupus erythematosus [119]. In an investigation involving NHL patients from a population-based lymphoma registry, 7.8% of patients were found to have an autoimmune disorder including rheumatoid arthritis (2.7%), Graves disease (1.4%) and Sjögren’s syndrome (1.0%) [120]. Two European studies reporting associations between primary Sjögren’s syndrome and NHL indicated that extranodal MALT lymphomas were the predominant histologic subtypes in patients with this autoimmune condition (15 out of 16 patients in one study [111] and 33 out of 33 patients in the second study [113]). Interestingly, salivary glands, particularly parotid glands, were the most commonly involved extranodal sites in both studies; neither study reported association with ocular adnexal lymphomas [111,113].

Two case-series have reported on the prevalence of autoimmune disorders in patients with ocular adnexal lymphomas; autoimmune disorders were found in nearly 22% (ten out of 45) of a group of patients in Austria [80] compared with only 3% (two out of 62) of patients with ocular MALT lymphomas in a study conducted in Japan [121]. Interestingly, in the latter study, the prevalence of autoimmune disease was 47% among 15 patients with benign ocular adnexal lymphoid hyperplasia.

Richter syndrome, a fast-growing large B-cell lymphoma, is also associated with an increased risk of NHL [112]. Associations with NHL have also been reported among patients with chronic inflammatory conditions including psoriasis, ulcerative colitis and Crohn’s disease [104]. The role of autoimmune and other chronic inflammatory disorders in the etiology of ocular adnexal NHL needs further investigation.

Immunosuppression

Acquired immunodeficiency syndromes, such as AIDS, are also associated with significantly increased risks of NHL at all sites. Incidence rates of NHL approach 50% among those who have survived 3 months of antiretroviral treatment with azidothymidine [46,47]. Possible mechanisms of lymphomagenesis that have been proposed include coinfection with oncogenic viruses (e.g., EBV and HHV-8) and genetic or immune dysfunction induced directly by HIV [112]. The majority of AIDS-related ophthalmic lymphomas reported have been intraocular, as described in several case reports [99–101].

Induced immunosuppression, as in the case with transplant recipients, is also associated with an elevated risk of NHL at all sites, particularly at extranodal sites. The vast majority of post-transplant NHL has been associated with EBV and may occur as early as 6 months to a year after transplant [124]; EBV-negative NHL cases are much less common and tend to occur later following two or more years of immunosuppression [125]. Similar to acquired immunodeficiency, the majority of ophthalmic NHL reported in association with induced immunosuppression have been primary intraocular B-cell lymphomas following transplants and immunosuppressive treatments [126–128]. A link between induced immunosuppression and ocular adnexal NHL has not yet been established. Furthermore, tissue analyses were not performed in any of the aforementioned cases to assess for possible etiologic associations with genetic alterations or microbial agents. Therefore, the role of immunosuppression in the etiology of ocular adnexal NHL is not clear.

Another mechanism that has been implicated in the immunosuppression-associated NHL risk is the dysregulation or suppression of T-cell function leading to EBV-driven B-cell proliferation and transformation [104]. There are no reports specifically investigating the role of immunosuppression-associated T-cell dysregulation in the etiology of ocular adnexal NHL.

Genetic & epigenetic factors & ocular adnexal NHL

Inherited susceptibility

Familial clustering of NHL has been described, including a report of 38 families with multiple cases of NHL [129]. A large case–control study (the Scandinavian Lymphoma Etiology [SCALE] study) undertaken in Denmark and Sweden found a history of hematopoietic disorders among any first-degree relatives to be a significant risk factor for all NHLs (odds ratio: 1.8; 95% CI: 1.2–2.5) [130]. However, despite evidence of familial aggregation, it is unlikely that segregation of genes with high penetrance account for a significant proportion of NHL (including ocular adnexal NHL) cases or explain the geographic or temporal incidence patterns of this malignancy. On the other hand, segregation of genetic polymorphisms and/or mutations with low penetrance along with their interactions with environmental factors leading to ocular adnexal NHL development cannot be ruled out.

Although studies of familial and hereditary NHL risks have not focused on ocular adnexal NHL specifically, Altieri et al., using the nationwide Swedish Family Cancer database, found the strongest association for an increased NHL risk to be with B-cell lymphomas among the offspring of individuals diagnosed with NHL (standardized incidence ratio: 11.8; 95% CI: 2.2–34.8) [131]. Since the majority of ocular adnexal NHLs consist of MALT and other types of B-cell lymphomas, the results of this study suggest that inherited genetic factors may play some role in the etiology of these tumors.

While epidemiologic studies have reported associations between several genetic polymorphisms with NHL risk, there are no reports of genome-wide association studies of ocular adnexal NHL specifically. A European, Canadian and USA consortium case–control study of NHL reported an increased risk of the disease, particularly that of diffuse large B-cell lymphoma, associated with single nucleotide polymorphisms in TNF and IL-10 genes, which code for components of inflammatory response and immune balance pathways [132]. Similarly, another group studying 66 cases of gastric MALT lymphomas in England found associations between this condition and genetic variants of IL-1 and glutathione S-transferase Theta-1 (GSTT1) [133]; IL-1 is a mediator of inflammation [134] and GSTT1 is believed to play a role in cellular protection against oxidative stress [135]. Before
an accurate interpretation can be offered, these results need to be confirmed by other groups and among other NHL cases. Understanding the role of genetic susceptibility in the etiology of ocular adnexal NHL awaits results from family-based and population-based genetic–epidemiologic studies incorporating gene–gene and gene–environment interactions.

**Somatic genomic aberrations**

Mucosa-associated lymphoid tissue lymphomas can affect many organs besides the eye and its adnexa, including the stomach, lung, salivary glands, thyroid, skin and intestine [136]. MALT tumors at many anatomic sites have been associated with somatic alterations, including genomic translocations such as t(11:18)(q21;q21) [137, 138], t(1:14)(p22;q32) [139] and t(14:18)(q32;q21) [140], as well as numeric genetic abnormalities such as trisomy 3 and trisomy 18 [141]. More recent studies assessing immunologic and cytogenetic characteristics of extranodal MALT lymphomas have found t(11:18)(q21;q21) and t(1:14)(p22;q32) in approximately 50% of cytogenetically abnormal low-grade MALT lymphomas. A study investigating the occurrence of common chromosomal aberrations such as trisomies and translocations within MALTs found a high frequency of trisomy 3 (68%) and 18 (56.6%), but no translocations and/or gene rearrangements. The authors also reported occurrence of concurrent or subsequent lymphomas in those with aberrations [142].

All of the aforementioned genetic aberrations are believed to occur during the process of transformation of lymphoid tissue to lymphoma [143]. The MALT1 gene on 18q21, which is believed to code for a component of the NF-κB activation pathway is often the gene involved in t(11:18)(q21;q21) and t(14:18)(q32;q21) translocations and immunoglobulin heavy chain (IGH) gene on 14q32 is often the gene involved in t(14:18)(q32;q21) and t(1:14)(p22;q32) translocations. These translocations are believed to also lead to overexpression of apoptosis inhibitor 2 (API2) on 11q21, which codes for an inhibitor of apoptosis, and truncation of B-cell leukemia/lymphoma 10 (BCL10), an apoptosis signaling gene on 1p22, respectively. These translocations are believed to cause malignancy owing to the inability of cells harboring them to induce apoptosis [144–149].

A few studies have also evaluated ocular adnexal lymphomas with regard to their cytogenetic characteristics [142, 150–153]. A recent study in Denmark examined immunologic and cytogenetic characteristics of ocular adnexal MALT lymphoma lesions in 116 patients diagnosed during the period 1980–2005 and found translocations in only 5% (two out of 42) of specimens reclassified and confirmed as being MALT; the authors concluded that translocations are rare events in ocular adnexal MALT lymphomas [150]. By contrast, a study in China investigating genetic and clinicopathologic characteristics of 32 primary ocular adnexal lymphoma and five reactive lymphoid hyperplasia cases found chromosomal aberrations in 61% of ocular adnexal MALT lesions. Of particular interest was the presence of trisomy 18 in all ocular adnexal MALT lesions with genetic abnormalities, leading to the presence of three copies of the MALT1 gene on 18q21. The authors concluded that trisomy 18 is a common aberration in primary ocular adnexal lymphomas [151].

A study in South Korea investigating genomic aberrations in primary ophthalmic, pulmonary and nodal MALT lymphomas found chromosome loss at 6q23.3 in 38% (nine out of 24), loss at 7q36.3 in 8% (two out of of 24), loss at 13q34 in 8% (two out of 24), gain at 3 in 38% (nine out of 24), gain at 15q15 in 16% (four out of 24), gain at 18q in 16% (four out of 24) and gain at 6p in 8% (2 out of 24) in these tumors. Translocations were not detected in any of the ocular adnexal MALT lesions in this study despite their presence in approximately 63% (five out of eight) of pulmonary MALT lymphomas tested. None of the genomic alterations found in ocular adnexal and pulmonary lesions were detected among nodal MALT lesions in this study [152]. The authors concluded that the genomic abnormalities detected were distinct for each of the three MALT lymphoma sites. Their conclusion is consistent with the findings of an investigation into the clonal relationship of extranodal MALT lymphomas at different sites reporting that MALT lymphomas involving multiple sites are unrelated and arise independently [154].

A comprehensive study analyzing the frequencies of MALT lymphoma-associated genetic aberrations at several different extranodal sites reported the presence of at least one translocation and/or copy number abnormality in 62.2% (23 out of 37) of ocular adnexal MALTs. The observed aberrations included t(11:18)(q21;q21) in 2.7% (one out of 37), t(14:18)(q32;q21) in 24.3% (nine out of 37), trisomy 3 in 37.8% (14 out of 37) and trisomy 18 in 13.5% (five out of 37) of ocular adnexal MALT lesions in this study [148].

A recent paper attempting to correlate *C. psittaci* infection with genetic aberrations in ocular adnexal MALT lymphomas reported the presence of t(11:18)(q21;q21) in a small portion of *C. psittaci*-negative cases [68]. The significance of this finding is that cytogenetic abnormalities may represent alternative pathogenic pathways to malignancy; this has been suggested to be the case in gastric MALT lymphomas where specific cytogenetic abnormalities are normally only present in *H. pylori*-unrelated cases [155, 156]. Other recent studies have reported deletions and mutations of TNF-α-induced protein 3 (TNFAIP3), a negative regulator of the NF-κB pathway, in ocular adnexal MALT lymphomas [157, 158]. Based on limited data so far, one group has postulated that two alternative pathways, both converging on NF-κB activation, could lead to ocular adnexal MALT lymphoma: one pathway would be triggered by infections, not so far associated with genetic aberrations, while the other pathway, characterized by genetic alterations, would be triggered by factors not yet identified [159].

The role of epigenetic abnormalities in ocular adnexal NHL initiation and/or progression is not known. Potential epigenetic mechanisms that may be triggered by viral or bacterial infections and lead to malignancy through silencing of essential host genes include abnormal methylation, histone remodeling and RNA-mediated inhibition of gene expression. Aberrant methylation of several CpG islands in *H. pylori*-infected gastric mucosa were reported in one study [160]. Recent findings that some animal viruses encode miRNAs that target host genes [161–164] may suggest a similar mechanism involving human viruses whereby these pathogens may be able to use these small regulatory RNAs to
inhibit gene expression, leading to silencing of genes involved in the host defense system. The epigenetic abnormalities that may be present in viral or bacterial-related ocular NHL tumors and the potential biologic pathways leading to the occurrence of such abnormalities remain to be illustrated.

Expert commentary
A major etiologic risk factor for ocular adnexal NHL has not yet been identified although several infectious, genetic and immunologic factors have been suggested to play roles in its causation. So far, there is equivocal evidence for the involvement of infectious agents in the etiology of ocular adnexal NHL. Geographic variability of infectious agents may account for discrepant results from studies involving different countries and populations. The disparate results may also be partly due to the differences in the design, methodology and quality of studies performed so far to elucidate the role of infectious agents in ocular adnexal NHL development. While some studies have taken a multifaceted approach consisting of traditional as well as molecular and genetic epidemiologic methods, most studies have focused on one or a limited number of risk factors. Ocular adnexal NHL is most likely a multifactorial condition with a multitude of extrinsic (environmental, including infectious) and intrinsic (genetic, epigenetic and immunologic) factors playing synergistic roles in its etiology. The possibility of multiple risk factors acting in synergy to cause ocular adnexal NHL through alternative pathways and mechanisms, such as chronic antigenic stimulation and/or oncogenic transformations, necessitates the design of comprehensive, descriptive and molecular epidemiologic investigations. Such comprehensive studies would involve investigations into the role of a multitude of factors in the etiology of ocular adnexal NHL, in the context of other types of extranodal NHL, in order to delineate interactions among risk factors as well as gain clues from common elements between NHL at different sites.

Five-year view
Multicenter comprehensive studies of ocular adnexal NHL, in the context of other extranodal NHL, investigating a multitude of environmental (including infectious agents, chemicals and toxins) and intrinsic (inherited, somatic genetic, epigenetic alterations and polymorphisms as well as molecular markers of infection and immune function) factors will be the next step. These collaborative, multidisciplinary investigations may include both observational and intervention studies and should ideally incorporate such aspects as descriptive epidemiology of the disease and the pathogens, demographic and family-history characteristics of subjects, information on environmental and occupational exposures obtained through validated epidemiologic questionnaires and biological samples for appropriate molecular studies.

Elucidating the mechanisms by which infectious agents alone or in association with other factors contribute to ocular adnexal NHL may enable the management, treatment and prevention of this condition to one day parallel what is already in place for other cancers, such as gastric MALTs, for which the main causative agent(s) have been identified. Antibiotic treatment and vaccines against infectious agents may become possible for individuals at an increased risk due to genetic, environmental and/or occupational susceptibility. Understanding the role of germline and somatic genetic abnormalities associated with an increase in risk of ocular adnexal NHL may empower implementation of person-alized genomics-based medicine measures in order to prevent and/or successfully manage/treat this and similar malignancies.

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Key issues
- Ocular adnexal non-Hodgkin’s lymphoma (NHL) has a unique incidence pattern.
- Studies of the role of infectious agents in the etiology of ocular adnexal NHL have produced equivocal results.
- Geographic variations in the prevalence of infectious agents, variations in mechanisms leading to malignancy among different populations, chance associations and differences in classification systems between different studies could have all contributed to disparate findings.
- Immune disorders and recurrent chromosomal abnormalities have been reported in association with ocular adnexal NHL; the significance and nature of these associations need further investigations.
- Chronic antigenic stimulation, triggered by autoimmune processes and/or infections, may be a relevant mechanism for ocular adnexal NHL development.
- The role of pathogen-induced oncogenic transformations as a potential mechanism in ocular adnexal NHL development needs further exploration.
- Ocular adnexal NHL is most likely a multifactorial condition with a multitude of genetic, epigenetic, immunologic and environmental factors playing synergistic roles in its etiology.
- Comprehensive epidemiologic investigations incorporating descriptive epidemiology of ocular adnexal NHL and the putative pathogens, as well as information on molecular markers of infection and immune function, familial risk factors for ocular adnexal NHL, and presence of inherited and/or somatic genetic and epigenetic abnormalities, are essential in elucidating the causative mechanism(s) of this complex disorder.
**References**

Papers of special note have been highlighted as:

- of interest
- of considerable interest


•• Description of mucosa-associated lymphoid tissue lymphomas and the role of chronic antigenic stimulation in their etiology.


•• The only descriptive study of ocular adnexal non-Hodgkin’s lymphoma (NHL) and the most recent descriptive study of ophthalmic NHL in the USA.


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Review


The most recent paper by the group who reported the initial associations between ocular adnexal NHL and Chlamydia psittaci.


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Ocular adnexal non-Hodgkin’s lymphoma: a review of epidemiology & risk factors

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Summary of positive associations between ocular adnexal NHL and C. psittaci infection with speculations as to the pathogenic pathways involved.


