Ocular adnexal lymphoma: an updated review of pathogenesis, diagnosis, and treatment

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Lymphoma is the most common primary tumor of the orbit, accounting for 55% of all orbital malignancies. When divided into histopathological subtypes, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) comprises the largest proportion. Clinical manifestations are unspecific, but in patients with slow-growing painless orbital mass, or red conjunctival lesion suggestive of ‘salmon patch’, ocular adnexal lymphoma (OAL) should be suspected. Although the pathogenetic mechanism of ocular adnexal MALT lymphoma (OAML) is not yet fully understood, the relationship between OAML and *Chlamydia psittaci* has been hypothesized recently, similar to that between gastric MALT lymphoma and *Helicobacter pylori*. This suggests a new treatment option for OAML; bacterial eradication therapy with systemic antibiotics. Several other treatment methods for OAML have been introduced, but no treatment guidelines have been established yet. In this article, we summarize the current knowledge on the clinical features, pathogenesis, diagnostic methods, therapeutic strategies, and prognosis of OAML.

Keywords: Etiology; *Chlamydia psittaci*; Marginal zone B-cell lymphoma; Ocular adnexal lymphoma; Orbital neoplasms

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**Introduction**

Lymphoma is a type of blood malignancy that begins in lymphocytes which include B-lymphocytes, T-lymphocytes, and natural killer (NK) cells. There are two main categories of lymphoma: those presenting with a specific type of cellular abnormality dubbed a Reed-Sternberg cell, called classic Hodgkin lymphomas (HLs), and the others called non-Hodgkin lymphomas (NHLs) [1]. HL accounts for approximately 10% of all lymphomas, while the remaining 90% are NHL [2]. NHL is also divided into B-cell and T-cell lymphomas. B-cell lymphoma accounts for more than 85% of all lymphoid neoplasms [1]. Although orbital lymphoma is rare, accounting for only 1% of all NHL cases, it is the most common primary orbital cancer in adults, accounting for 55% of all malignancies in the orbit [3-5]. The majority of NHL of the orbit and ocular adnexa are extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [6]. This review article summarizes the previously published literature on ocular adnexal MALT lymphoma (OAML), with an overview of its clinical features, treatment options, and prognostic outcome.

**Clinical features**

Ocular adnexal lymphoma (OAL), which mainly involves the conjunctiva, lacrimal gland, orbital fat, lacrimal sac, and eyelid, has various clinical presentations depending on the lesion. In addition, it cannot be easily differentiated from other orbital diseases because it has no pathognomonic signs or symptoms.

Conjunctival involvement is observed in 26% of OALs, which shows a characteristic red, swollen, painless lesion called 'salmon
patch,’ making it easier to detect the disease [7]. However, a high index of suspicion is required because it may mimic chronic conjunctivitis in rare cases [8].

Intraorbital lymphoma usually presents with a variety of symptoms, including proptosis, palpable mass, swelling, ptosis, limited eye motility, displacement of the eye, and diplopia [7,9-12]. In particular, computed tomography (CT) or magnetic resonance imaging (MRI) should be considered in patients with proptosis, especially unilateral proptosis, since it is the most common symptom of orbital B-cell lymphoma [11,13].

Pathogenesis

The histopathological features of OAML are similar to those of other MALT lymphomas. Under physiological conditions, the connective tissues of the orbit are devoid of lymphoid tissue and lymphatic drainage [14]. Hence, for lymphoma to develop in the orbit, organized lymphoid tissue must be acquired first, as observed in gastric MALT lymphoma [15]. Several conditions, including chronic inflammation and autoimmune disorders, are associated with the pathogenesis of OAML.

1. Chronic antigenic stimulation

Over the last few years, the relationship between lymphoma and chronic antigenic stimulation has garnered increasing attention. As a paradigmatic example, *Helicobacter pylori* infection triggers chronic antigenic stimulation and plays a key role in the development of gastric MALT lymphoma [15]. Likewise, the detection of *Chlamydia psittaci* DNA in 80% of patients with OAML suggests that *C. psittaci* infection is related to the development of OAML [16]. *C. psittaci* is the known causative bacterium of psittacosis, which is caused by contact with infected animals, and half of the OAL patients have reported close contact with household animals [16,17]. Potential pathogenesis of OAML related to chlamydial infection is similar to that of gastric MALT lymphoma caused by *H. pylori*. This pathogenesis model is also observed in cutaneous B-cell lymphoma caused by *Borrelia burgdorferi* and small intestinal MALT lymphoma caused by *Campylobacter jejuni*. The chronic inflammation induced by *C. psittaci* facilitates the development of MALT in the orbit. Then, clonal expansion and proliferation of B-cell in the marginal zone of lymphoid follicles could occur in a state of persistent chlamydial infection. These clonal B-cells (antigen-dependent lymphoma clones) invade the germinal center of lymphoid follicles, causing chromosomal aberrations, resulting in an environment in which clonal expansion can continue without antigenic stimulation (antigen-independent lymphoma clones) [18]. Several studies have confirmed an association between *C. psittaci* and OAL, while others did not, which indicates the possibility of geographical variation [7,13,19-26]. Interestingly, tumor regression was observed in 38% of *C. psittaci* DNA-negative OAL after bacterial eradication therapy with doxycycline, suggesting that other microbial agents, such as doxycycline-sensitive bacteria, may be involved in the development of OAL [27]. Epstein-Barr virus (EBV), human T-cell leukemia virus type 1 (HTLV-1), hepatitis C virus (HCV), and human herpes simplex virus-8 are known to be associated with malignant lymphoma, and one study reported HCV seropositivity in 13% of OAL patients [28,29].

2. Immune disorders

Lymphoma is the most common cancer and the most common cause of cancer-deaths in human immunodeficiency virus (HIV)-infected patients [30,31]. Although the mechanism of lymphoma development in HIV patients is not clearly known, one study found that virologic suppression with highly active antiretroviral therapy reduces the risk of lymphoma [31]. Hence, advanced immunosuppression, higher levels of circulating viremia, and a high prevalence of oncogenic viruses (especially EBV) may be associated with an increased risk of lymphoma in HIV patients [31-34].

In addition, it has been reported that there is an increased risk of NHL in patients with autoimmune disorders such as Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto thyroiditis, immune thrombocytopenic purpura, and autoimmune hemolytic anemia [35,36].

3. Genetic abnormality

Similar to other malignancies, several chromosomal abnormalities are observed in the OAL. In the case of MALT lymphoma, different chromosomal alterations are detected depending on the site of origin [20]. In particular, trisomy 3 and 18, 5q (ODZ2) and 9p (JMJD2C), t(11;18)(q21;q21), t(14;18)(q32;q21), t(3;14) (p14.1;q32), and A20 inactivation (6q23 deletion) are associated with OAML [20,37]. One study reported a higher incidence of trisomy 3 in orbital MALT lymphoma than in conjunctival MALT lymphoma, while another reported that trisomy 18 was more common in young women with conjunctival involvement, which shows a high recurrence rate [38,39]. However, there is not much data yet on the genetic aspect of OAL, so further investigation is needed to fully understand it.

Diagnosis

The definitive diagnostic method of OAL is histopathologic verification. However, neuroimaging techniques, including CT or MRI, are also necessary to measure the size of the lesion or to differenti-
ate it from other orbital diseases. In a two-phase contrast enhancement CT scan, orbital lymphoma shows a decrease in density in the delayed phase, which is in contrast to the orbital inflammatory pseudotumor showing increased density on delayed imaging [40]. An MRI scan shows a mass with isointensity on the T1 image and an iso-hyperintense signal on T2. Furthermore, quantified tumor blood flow (TBF) values measured by arterial spin labeling and apparent diffusion coefficient (ADC) on diffusion-weighted imaging could be helpful in differentiating lymphoma from other expansive orbital diseases. In particular, lymphoma represents high TBF and low ADC values compared to idiopathic orbital inflammatory pseudotumors, which may be difficult to differentiate clinically [41,42]. After determining the size and location of the lesion, a histopathologic examination should be performed through an open biopsy [1]. Histopathologic examination of OAML may not always be conclusive since it mainly consists of small lymphoma cells that lack cellular atypia, and have a similar appearance to small lymphocytes [43,44]. Thus, it is often challenging to differentiate lymphoma from reactive lymphoid hyperplasia [44]. In this case, determining the clonal B-cell population by polymerase chain reaction (PCR) analysis of immunoglobulin heavy chain gene rearrangement can help in the differential diagnosis [45]. Further immunohistochemical examination shows CD20+, CD79a+, IgM+ with light-chain restriction, PAX5+, bcl-2+, TCL1+, CD11c+, CD43+, CD21+, CD35+, IgD–, CD3–, CD5–, CD10–, cyclin D1+, bcl–6–, and MUM1– cells as classical immunophenotype [38,46-51]. In addition, systemic evaluation, such as full-body positron emission tomography-CT and bone marrow biopsy should also be performed [52,53].

**Staging**

The Ann Arbor staging system, commonly used in the staging of NHL, is a system for the staging of HL [54-56]. This staging system divides the disease into four stages: (I) single localized disease, (II) two or more lesions on one side of the diaphragm, or (III) both sides of the diaphragm, and (IV) metastatic disease. The involvement of the localized extranodal site is recognized by the subscript E (i.e., stage IE) [57]. However, the Ann Arbor system is not suitable for the staging of OAML because it does not consider anatomic location, multicentricity, bilaterality, or extent of primary tumor infiltration; thus, two-thirds of OAML cases are classified as stage I [56,58,59]. To overcome this limitation of the Ann Arbor system, the American Joint Committee on Cancer proposed a new staging system for OAL [60]. This TNM staging system determines the stage of OAL based on the size and extent of the primary tumor (T), involvement of local lymph nodes (N), and the presence or absence of tumor metastasis (M) [56,59]. Although several studies have demonstrated the usefulness of TNM staging for OAL, new treatment protocols based on this staging system remain to be investigated [58,59].

**Treatment**

Although many treatment options for OAL have been reported, no definite guidelines have yet been universally accepted. When a therapeutic decision for OAL is made, the location and extension of the tumor, the presence or absence of metastasis, prognostic factors of the patients, and treatment-related toxicity or adverse effects should be considered.

1. **Surgical resection**

Surgical resection is listed first, not only because it is the most conventional treatment option for tumors but also because it is necessary for the diagnosis of OAL. Some MALT lymphomas of the conjunctiva or lacrimal glands can be completely resected; however, excessive efforts to completely resect lymphoma are not recommended, as they could be associated with a high risk of complications. Furthermore, a study reported that complete resection of OAML did not affect overall survival rates [61]. Surgery can be used in combination with other treatment options, such as chemotherapy and radiation therapy, to reduce the tumor size. For localized low-grade MALT lymphoma in older patients who do not want invasive treatment, the watch-and-wait strategy could be an option after surgical resection or biopsy [61,62].

2. **Radiation therapy**

Radiation therapy is frequently used in the treatment of OAL and has been the mainstay of treatment for many years. It may be used to eradicate tumors and is also used to reduce the size of the tumor before surgery or as a combination therapy with chemotherapy or immunotherapy. Although there is no gold standard for the dose of radiation, 28–36 Gy is commonly prescribed for low-grade lymphomas such as MALT lymphoma or follicular lymphoma, and 30–40 Gy for high-grade lymphomas such as diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma (MCL) [62]. In low-grade lymphoma, the 5-year local control rate was 86% for < 30 Gy and 100% for ≥ 30 Gy. In the case of MALT lymphoma alone, the overall local control rate was 96% at 5 years and 86% at 10 years (range, 23.1–45 Gy; median D1.8, 31.8 Gy) [63]. As noted in many studies, radiation therapy shows a good local control rate, but it can cause some adverse effects, including cutaneous reactions, cataracts, dry eyes, macular degeneration, retinopathy, and corneal ulceration, particularly at doses of 30 Gy or higher [64-67].

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Therefore, some authors prefer ultra-low-dose radiation therapy, which uses only 4–8 Gy in total, and the minimal incidence of adverse effects has been reported [68,69]. However, this remains controversial, as some authors reported a high recurrence rate in low-dose treatment, especially below 30 Gy [12,24,63]. Likewise, a lens shielding technique using a lead contact lens or cylindrical shield to prevent the development of cataract is worth considering, although there are some reports of high recurrence rates [11,12,50,64,65].

3. Chemotherapy
Chemotherapy is often used in OAL with systemic involvement or high-grade lymphomas such as DLBCL. The combination regimen of cyclophosphamide, doxorubicin (hydroxydaunorubicin/adriamycin), vincristine (Oncovin; Eli Lilly and Company, Indianapolis, IN, USA), and prednisone (CHOP) is the most commonly used. Other common combination regimens include hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine) and CVP (cyclophosphamide, vincristine, and prednisone). As a monotherapy, chlorambucil is frequently used for treating indolent lymphomas, showing a 79% complete response and 21% partial response (PR) rate with good tolerability in orbital MALT lymphoma [70]. Oxaliplatin and purine analogs, including fludarabine and cladribine, have also been used recently [50,71-73].

4. Systemic antibiotics
More than 90% of gastric MALT lymphomas are related to H. pylori infection, and after this was proven, bacterial eradication therapy with systemic antibiotics became an important part of treatment [74-76]. A similar relationship between C. psittaci and OAL has been proposed. Several authors have reported high rates of C. psittaci infection in patients with OAML, 80% in Italy [16] and 78% in South Korea [77]. However, no such association has been found in Japan [21,78], the Netherlands [22], France [79], Cuba [80], and the United States [7,23,38,81], suggesting geographical variation. A multicenter prospective phase II trial conducted in four countries (Chile, Italy, Spain, and Switzerland) showed a good response rate to first-line eradication therapy with doxycycline for OAML; complete remission (CR) in 18%, PR in 47%, and overall response rate (ORR) of 65% [26]. In South Korea, a study on 90 patients with OAML found a 34% ORR with first-line doxycycline treatment. In addition, this study reported that the ORR of second-line treatment with radiotherapy for patients who progressed after doxycycline treatment was 100% [82]. Furthermore, considering that doxycycline treatment was effective even in 38% of C. psittaci DNA-negative patients according to one study, it seems that it could be used in most OAML patients [27]. On the other hand, one author reported that doxycycline treatment in patients who had not been tested for chlamydia infection showed no effect on OAML [83]. In summary, the effectiveness of bacterial eradication therapy with doxycycline for OAML remains controversial, but it is worth considering as it is a safe and cost-effective treatment option.

5. Immunotherapy
Rituximab is a chimeric human/mouse monoclonal antibody against CD20 and B-lymphocyte surface antigens [84]. The function of CD20 is not fully known, and it is thought to be involved in the activation and regulation of B-cells [85]. Although rituximab is a mainstay in the treatment of B-cell NHL, it is not commonly used as monotherapy in OAML patients, and only a few authors have reported the efficacy of this monoclonal antibody [86,87]. Except in the case of relapsed OAML, rituximab shows a good response, but its efficacy is lower than that reported in gastric MALT lymphomas due to its high recurrence rate [87]. Rituximab is also widely used as part of a combination regimen with chemotherapy. For example, the combination of rituximab and chlorambucil showed great success in OAL patients with EMZL and follicular lymphoma as first-line treatment (CR in 89%, PR in 11%, ORR in 100%) [88]. In addition, combination therapy with CHOP (R-CHOP) has improved treatment outcomes in patients with DLBCL and MCL [89,90]. Several authors have reported successful results from intralesional interferon-α injection in conjunctival MALT lymphoma with minimal side effects [91-93], although further research through large clinical trials is needed.

Prognosis
Based on the available scientific literature, the histological subtype may act as the most important predictor of mortality in OAL. One study found that the 5-year lymphoma-related mortality rate was as follows: 12% for EMZL, 19% for diffuse lymphoplasmacytic lymphoma, 22% for follicle center lymphoma, 48% for DLBCL, and 53% for other lymphoma variants (i.e., MCL, chronic lymphocytic lymphoma, etc.) [94]. Another study reported lymphoma-related mortality as 2% for EMZL, 33% for follicular lymphoma, 38% for DLBCL, 100% for MCL, and 100% for peripheral T-cell lymphoma and NK cell lymphoma [95]. Other prognostic factors include the stage at presentation, primary or secondary status, and whether the disease is unilateral or bilateral [95-97]. According to a study, the rates of extraorbital spread and lymphoma-related death are the lowest in conjunctival lymphoma, followed by deep orbital lymphoma and lacrimal gland lymphoma.

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and the highest in eyelid lymphoma [97].

**Conclusion**

As the most common cancer that occurs in the orbit, the characteristics of OAL should be noted. Furthermore, the incidence of OAL has been reported to increase steadily over the past few decades [5,25,98]. In South Korea, OAML accounts for a particularly higher proportion of OAL compared to that in Western countries [99,100]. The size and location of the tumor should be measured using radiology imaging techniques such as CT and MRI, and an open biopsy should be performed to make a histopathological diagnosis. OAL has different prognostic outcomes depending on its histological subtype, and MALT-type lymphoma has a good ORR if treated properly. Although the TNM staging of OAL is not yet widely used and no large-scale clinical trial has been conducted, further research should be conducted in the future to establish a first-line treatment protocol based on it.

**Notes**

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Author contributions**

Conceptualization, Formal analysis, Project administration, Supervision: JHS; Data curation: HUC; Writing-original draft: HUC; Writing-review & editing: JHS.

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