Best Practice & Research Clinical Haematology xxx (2016) 1–13

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

# Ocular adnexal marginal zone lymphoma: Clinical presentation, pathogenesis, diagnosis, prognosis, and treatment

Marianna Sassone [a], Maurilio Ponzoni [a, b, c], Andrés J.M. Ferreri [a, *]

[a] Unit of Lymphoid Malignancies, Department of Onco-Hematology, IRCCS San Raffaele Scientific Institute, Milano, Italy
[b] Pathology Unit, IRCCS San Raffaele Scientific Institute, Milano, Italy
[c] Università Vita e Salute, IRCCS San Raffaele Scientific Institute, Milano, Italy

*Keywords:*
MALT lymphoma
Conjunctival lymphoma
Ocular adnexa
*Chlamydia psittaci*
Lymphomagenesis
Doxycycline

A B S T R A C T

Ocular adnexal marginal zone lymphoma (OAML) represents 1–2% of all non Hodgkin lymphomas. In the last few years many advances in understanding the pathogenesis and the molecular basis involved in its development have been done. Many potential risk factors have been proposed; a dysregulation of immune response in association with a chronic antigenic stimulation, have been hypothesized as possible pathogenic mechanism. In particular, *Chlamydia psittaci* infection has been related to OAML arising, and eradicating antibiotic therapy has been addressed as a safe and cost-effective approach. Management of OAML is still heterogeneous and matter of debate. There is no consensus about the best upfront treatment and therapeutic decision should take into account several patient-, lymphoma- and treatment-related factors. Novel agents and chemotherapy-free strategies are being investigated to reduce side effects and improve tumor control. This review is focused in recent knowledge improvements in this lymphoma.



## Introduction

Ocular adnexal lymphoma (OAL) represents 1–2% of all non-Hodgkin Lymphoma (NHLs) and 5–15% of all extranodal NHLs [1,2]; with an incidence of approximately 0.28 per 100,000 subjects [3]. Most OALs are B-cell NHL, belonging approximately for 80% to extra-nodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT), while only a small subgroup are classified as follicular, diffuse large B-cell, mantle cell, or lymphoplasmacytic lymphoma [4–8]. According to the analysis of population based incidence data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER), OAL incidence rates increased rapidly and steadily from 1975 to 2001, at 6.2% and 6.5% per year among males and females, respectively, with no evidence of peak [9]. Environment, occupational exposure, autoimmune disorders, and infectious agents have been variously investigated as potential risk factors to justify increasing incidence of OAL. Several studies have reported an increased incidence among individuals exposed to livestock, mainly cattle and pigs [10,11], or working with meat [12]. An Italian case control study has suggested that the risk of OAML compared with nodal NHLs is markedly increased after prolonged contact with animals, particularly by occupational exposure as slaughter and breeding [13].

* Corresponding author. Unit of Lymphoid Malignancies, Department of Onco-Hematology, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milano, Italy. Fax: +39 02 26437603.
*E-mail address:* ferreri.andres@hsr.it (A.J.M. Ferreri).

http://dx.doi.org/10.1016/j.beha.2016.11.002
1521-6926/

## Clinical presentation

In the Western countries, OAML usually affects elderly patients (median age, 65 years), with a higher prevalence among females. The interval between developing of symptoms and diagnosis is variable, with a median of 6–7 months (range 1–135 months). The clinical presentation of OAML depends on involved structures with 25% showing conjunctival lesions, intraorbital masses in 75% of cases, and bilateral (mostly conjunctival) involvement reported in 10%–15% of cases [14]. Conjunctival OAML usually appears as the typical "salmon red patch" (Fig. 1), while intraorbital lymphoma may cause exophthalmos (27% of cases), palpable masses (19%), ptosis (6%), diplopia (2%), orbital edema or nodules, epiphora, and potentially impaired ocular motility [14]. At physical examination, MALT lymphoma may be undistinguishable from other orbital diseases, since different lymphomas affect the ocular adnexa; histologic diagnosis is mandatory for correct treatment.

## Histopathological and molecular features

In the orbital region there is no evidence of both lymphoid tissue and lymphatic drainage, and it is uncertain whether MALT is present in normal conjunctiva; however, chronic antigenic stimulation, determined by chronic infections and/or autoimmune disorders may induce the accumulation of MALT, which represents the ideal environment for the development of MALT-type lymphoma [14,15].

OAML shows the classical morphology and immunophenotype profile of most MALT lymphomas. At the microscope, OAML is characterized by an expansion of a varied cell population as centrocytic-like cells, monocytoid cells or small-sized lymphocytes that can coexist in different proportions from case to case. OAML cells, which may show immunoglobulin light-chain restriction, are CD20+, CD79a+, IgM+/−, PAX5+, bcl-2+, TCL1+, IRTA1+/−, CD11c+/−, CD43+/−,CD21+/−, CD35+/−, and IgD−, CD3−, CD5−, CD10−, CD23−, cyclin D1−, bcl-6−, MUM1−. A remarkable plasmacellular differentiation may occur [16]. The differential diagnoses must be made with mantle cell lymphoma, small lymphocytic B-cell lymphoma/chronic lymphocytic leukemia and follicular lymphoma. Non-neoplastic elements including reactive T cells, reactive germinal centers epithelial cells are part of the morphological spectrum of this disease.

PCR analysis to detect Ig heavy chain rearrangement reveal a monoclonal B cell population in 55% of OAML [17] and somatic hypermutations in almost 60% of cases [18]. The VH3 family is represented in 54% of OAML, followed by VH4 in the 23%: interestingly, the involved germline genes are associated with autoantibodies production (DP-8, DP-10, DP-53, DP-63 and DP-49). These findings support the OAML derivation by a clonal expansion of post germinal center B cells [18].

Several chromosomal translocations have been associated with MALT lymphomas [19], including t(11;18)(q21;q21)/API2-MALT1, t(1;14)(p22;q32)/IGHBCL10 and t(14;18)(q32;q21)/IGH-MALT1. The oncogenic activity of these alterations is directed toward a constitutive activation of NF-κB pathway, which is involved in lymphocyte activation, proliferation and survival [20]. The t(14;18)(q32;q21) brings the MALT1 gene under the control of the enhancer region of the Ig-heavy-chain gene and causes its overexpression [21]. This alteration is more frequent in non-gastrointestinal MALT lymphomas, particularly those of the liver, lung and ocular adnexa [21], but its clinical role is still uncertain. The detection of the t(11;18)(q21;q21) is more common in gastric MALT lymphoma (24%), while its frequency in OAML is lower than 3% [19,22].

Limited cytogenetic data are available. FISH analyses have demonstrated the presence of aneuploidy, trisomy 3 and/or 18 in particular. Trisomy of chromosome 18 is associated with some clinical features such as: usually young age, female gender, conjunctiva involvement and a higher recurrence rate [23].

The variability of genomic profiles across anatomical sites of primary involvement has also been investigated in a series of 130 MALT lymphomas [24].

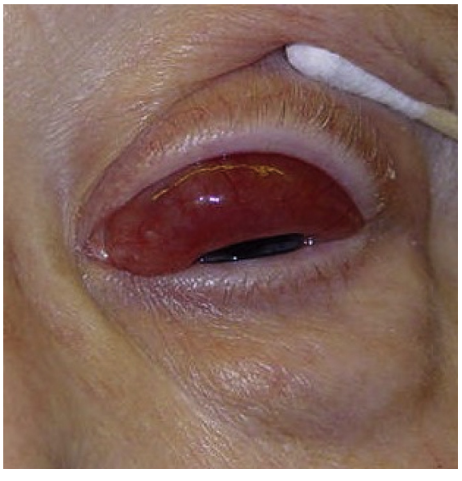

**Fig. 1.** Conjunctival localization of OAML, with typical "red salmon patch" aspect.

Please cite this article in press as: Sassone M, et al., Ocular adnexal marginal zone lymphoma: Clinical presentation, pathogenesis, diagnosis, prognosis, and treatment, Best Practice & Research Clinical Haematology (2016), http://dx.doi.org/10.1016/j.beha.2016.11.002