review

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Ocular adnexal MALT lymphoma: an intriguing model for antigen-driven lymphomagenesis and microbial-targeted therapy

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Non-Hodgkin's lymphomas constitute one half of malignancies arising in the orbit and the ocular adnexae. Mucosa-associated lymphoid tissue (MALT)-type lymphoma is the most common histological category in this anatomic region. The incidence of ocular adnexal lymphoma of mucosa-associated lymphoid tissue-type (OAML) is increasing and recent studies offered new relevant insights in molecular, pathogenetic and therapeutic issues on these neoplasms. A pathogenetic model of antigen-driven lymphoproliferation similar to that reported for *Helicobacter pylori*-related gastric MALT lymphomas has been hypothesized for OAML. This notion is supported by the association between OAML and *Chlamydophila psittaci* infection, an association that is of likely pathogenetic relevance and may influence both the biological behavior and the therapeutic management of these neoplasms. However, this association displays evident geographical variability indicating that other etiopathogenic agents could be involved. These recent acquisitions coupled with the occurrence of chromosomal translocations and other genetic alterations, as well as additional risk factors like autoimmune disorders have contributed to render OAML an exciting challenge for a broad group of physicians and scientists. OAML is an indolent and rarely lethal malignancy that, in selected patients, can be managed with observation alone. Lymphomatous lesions are frequently responsible for symptoms affecting patient's quality of life, requiring, therefore, immediate treatment. Several therapeutic strategies are available, often associated with relevant side-effects. However, the therapeutic choice in OAML is not supported by consolidated evidence due to the lack of prospective trials. In this review, we analyze the most relevant biological, molecular, pathological and clinical features of OAML and propose some therapeutic guidelines for patients affected by this malignancy.
Key words: chlamydia, extranodal lymphomas, interferon, MALT, ocular adnexae, rituximab

introduction

Non-Hodgkin's lymphomas constitute one half of all orbital malignancies [1]. Five to fifteen per cent of all extranodal lymphomas arise in the ocular adnexae, such as the conjunctiva, the lachrymal gland, the orbital fat, the eyelid and the lachrymal sac [2]. Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)-type (OAML, ocular adnexal lymphoma of MALT-type) is the most common lymphoma category arising in these anatomical structures, varying from 50–78% of all ocular adnexal lymphomas in Western countries to 80–90% in Japan and Korea [3]. The incidence of OAML is rapidly increasing, with annual rates >6%, and no evidence of peaking [4]. These epidemiologic features are not correlated to changes in classification schemes considering that a comparable increase has not been observed at other extranodal organs displaying similar overall percentages of MALT lymphomas [4].

The distinctive epidemiologic patterns of OAML call for further studies to identify environmental and genetic risk factors and pathogenetic mechanisms, including the potential role of infectious agents [4]. The recently reported association between chlamydial infection and OAML [5] offered new pathogenetic insights that have led to the development of innovative antimicrobial therapies. However, the optimal treatment of OAML is closely related to several clinical and biological variables, and the characterization of genetic

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alterations may be potentially useful to predict therapeutic response and identify the best candidates for the different treatments.

In this review, we summarize current knowledge on pathogenesis, molecular, pathological, radiological and clinical features as well as available therapeutic strategies for OAML. Moreover, we discuss new therapeutic strategies that, by exploiting targets and mechanisms different from those of conventional radiotherapy and chemotherapy, may avoid the undesirable side-effects frequently associated with these approaches.

pathological features

The orbital region lacks both resident lymphoid tissue and lymphatic drainage, and it is controversial whether MALT is present in normal conjunctiva. OAML may derive from the MALT tissue acquired following chronic inflammatory or autoimmune disorders [6]. Many ocular adnexal neoplasms previously classified as 'pseudolymphomas' or 'benign lymphoid hyperplasia' may actually contain clonal B-cell expansions [7] and are, presumably, B-cell lymphomas. In different studies, a variable number of cases were diagnosed as 'lymphoma, not further specified', mostly because of the scarcity of diagnostic tissue; the majority of the entities hereby described, however, fall into the 'low-grade lymphoma' category.

OAML displays the well-known classical histopathology and immunophenotype profile of most MALT lymphomas. Classically, the histopathology of MALT lymphomas encompasses either neoplastic or non-neoplastic cells. Lymphomatous cells may be heterogeneous in appearance, since centrocytic-like cells, monocytoid cells or small-sized lymphocytes may coexist in the same tissue, albeit with different proportions varying from case to case. In some cases, a striking plasma cell differentiation is present. In those sites provided by epithelium, i.e. conjunctiva and lachrymal gland, tumor cells may infiltrate either glandular or superficial epithelium determining the formation of the so-called 'lymphoepithelial lesions'. Sometimes, neoplastic lymphocytes may selectively grow within germinal centers (follicular colonization), and a few scattered large cells (blasts) are usually encountered throughout the section. Tumor population is accompanied by non-neoplastic cells, including reactive germinal centers, a moderate to high amount of reactive T cells and histiocytes.

The classical immunophenotype of MALT lymphoma comprises CD20+, CD79a+, usually IgM+ with light-chain restriction, PAX5+, bcl-2+, TCL1+, CD11c+/−, CD43+/−, CD21+/−, CD35+/−, and IgD−, CD3−, CD5−, CD10−, CD23−, cyclin D1−, bcl-6−, MUM1− cells. OAML displays some histopathologic and immunophenotypic peculiarities with respect to other MALT lymphomas, mostly regarding marked plasmacellular differentiation and altered expression of molecules regulating the cell cycle and apoptosis (Table 1). The main histopathological differential diagnoses of OAML are mantle cell lymphoma (CD5+, CD23−, cyclin D1+), small lymphocytic B-cell lymphoma/chronic lymphocytic leukemia (CD5+, CD23+) and follicular lymphoma (CD10+, bcl-6+).

Table 1. Peculiar histopathological and immunophenotypic features of ocular adnexal lymphoma of mucosa-associated lymphoid tissue (MALT)-type (OAML) with respect to other MALT lymphomas

	Reference
Morphology	
Frequent absence of epithelium in surgical specimens	[8]
Frequent presence of Dutcher bodies (22% of cases)	
Rarity of follicular colonization	[9]
More pronounced degree of plasmacellular differentiation (40% of cases)[a]	[10]
Immunophenotype	
3–10% of OAML are CD5+	[8]
CD43+ is less common (12%) with respect to other MALT lymphomas	[11]
Cases with plasmacellular differentiated tumor cells exhibit aberrant immune profile for plasma cell-related antigens[b]	[10]
Altered expression of cell-cycle-related molecules: p16+, p21−, pRB−, p53−	[12]
Apoptotic machinery deregulation (i.e. diminished active caspase 3 and increased expression of the NFκB-related molecule p-IκBα)	[13]
bcl-10+ (nucleus and cytoplasm) in two-thirds of cases[c]	[14]

[a]Cases represented mainly by small lymphoplasmacytoid cells arising in ocular adnexae, thus generating differential diagnostic problems with lymphoplasmacytoid lymphomas, should be considered consistent with MALT lymphomas.

[b]This aberrancy may be useful in the differential diagnosis with reactive process.

[c]These bcl-10-positive cases may be associated with unknown gene alterations [14].

A few cases of OAML display CD5 immunoreactivity (Tables 1 and 2), increasing differential diagnostic difficulties; in this setting, morphology coupled to cyclin D1 assessment as well as FISH analysis (i.e. absence of chromosome abnormalities frequently observed either in chronic lymphocytic leukemia or in mantle cell lymphoma) can be helpful for a correct diagnosis. Some histopathological and immunophenotypic parameters useful as predictors of outcome have been reported, although mostly in small series (Table 2).

molecular features and cytogenetics

Similarly to other MALT lymphomas, PCR analysis of immunoglobulin heavy-chain gene rearrangement showed a clonal B-cell population in 55% of OAML [3] and somatic hypermutations in two-thirds of these cases [16]. In particular, the V_H3 family is expressed in nearly half of the cases, followed by V_H4 in 23% of cases, showing thus a biased usage in comparison to adult peripheral blood B lymphocytes [16]. The most frequently involved germline genes (DP-8, DP-10, DP-53, DP-63, DP-49, DP-54, DP-47) [3, 16] are those commonly implicated in the assembly of autoantibodies. Ongoing mutations have been described in OAML; their frequency is

lower than that reported in gastrointestinal MALT lymphomas, but it is higher in cases with follicular dendritic cell networks, supporting a potential role of microenvironmental stimuli [9]. Taken together, these features support the view that OAML represent a clonal expansion of post-germinal-center memory B cells, where, in two-thirds of the cases, antigen selection may have occurred [16].

Some chromosomal translocations, including t(11;18)(q21;q21)/API2-MALT1, t(1;14)(p22;q32)/IGH-BCL10, t(14;18)(q32;q21)/IGH-MALT1 and t(3;14)(p14;q32)/IGH-FOXP1, are associated with MALT lymphomas, but their frequency markedly varies among different mucosal sites (Table 3). t(11;18), t(1;14) and t(14;18)/IGH-MALT1 are nearly exclusively found in MALT lymphoma and their oncogenic products share the ability to enhance the activation of NFκB, a master transcriptional factor for a number of genes relevant for lymphocyte activation, proliferation and survival [26]. The t(3;14) has been detected both in MALT and in other B-cell lymphomas [22, 25], although the molecular mechanism of FOXP1-mediated lymphomagenesis remains to be investigated. The overall frequency of MALT-associated chromosomal translocations in OAML is reported in Table 3; their clinical significance in these malignancies remains to be defined.

There are only limited cytogenetic data in OAML (Table 3). Both conventional karyotyping and interphase FISH-based cytogenetic analyses demonstrated that aneuploidy, particularly trisomy 3 and 18, occurs frequently in t(11;18)-negative OAML [17–19, 23]. Trisomy 3 and 18 and t(14;18)(q32;q21) deserve to be further investigated as possible predictors of multifocal disease [27]. OAML with trisomy 18 seems to have distinct clinical features: it involves the conjunctiva, occurs in young females and shows a high recurrence rate [19]. On the other hand, trisomy 3 is significantly less common in conjunctival MALT lymphomas with respect to orbit lymphomas (12% versus 81%) [11]. Comparison of European [18] and American [11] series seems to indicate the existence of geographic variability in the incidence of recurring cytogenetic abnormalities in OAML. Variables influencing these features should be further investigated.

Comparative genomic hybridization (CGH) carried out in 10 OAML cases showed recurrent chromosomal gains at 6p21 and 9q33-qter, in addition to trisomy 3, 12 and 18 [28]. It will be noteworthy to survey the genomic gains and losses of OAML using array CGH to explore whether these MALT lymphomas are also characterized by a conserved pattern of chromosomal gains, as reported for other MALT lymphomas [29], and how these genomic alterations correlate with chlamydial infection and treatment response.

Table 2. Histopathological parameters with proposed prognostic value

Parameters	Observation	Reference
MIB-1 rate >20%	Advanced stage and poor outcome	[8, 12]
Higher proliferation rate, overexpression of cyclin A, cyclin E, survivin and bcl-XL	High-grade transformation	[13]
Increased blast cells, immunoreactivity for p53, bcl-6, pRB, MUM1 and MIB1	Poor prognosis	[12]
Increased bcl-6+ blast cells	High risk of local recurrence and disseminated disease	[12]
Plasmacytic differentiation	Advanced disease	[11]
CD5 immunoreactivity	Stage >I	[8]
CD43 expression	Adverse prognosis	[15]
bcl-10 nuclear expression	Conflicting results	[13, 14]

pathogenesis

OAML shares several clinicopathologic features with other MALT lymphomas. In fact, OAML arises in tissues normally devoid of innate immune system [6], often develops on a background of preexisting chronic inflammation (i.e. conjunctivitis) [9] and usually shows an indolent clinical course. The presence of a preexisting inflammatory background seems to be of pathogenetic relevance for MALT lymphomas, underlying the possible role of exogenous triggers (infections) and autoimmune reactions. Somatic immunoglobulin ongoing mutations detected in OAML (see above) are consistent with a process driven by chronic antigenic stimulation. Moreover, the biased usage of V_H genes, frequently rearranged in autoantibodies production [30] and often overrepresented in B-cell malignancies [31], further supports

Table 3. Molecular cytogenetics in ocular adnexal lymphoma of mucosa-associated lymphoid tissue (MALT)-type (OAML)

Features	Genes involved	Organs	Frequency in OAML	Reference
t(11;18)(q21;q21)	API2, MALT1	Lung (40%), stomach (25%)	0–10%	[17–21]
t(1;14)(p22;q32)	IgH, BCL10	Lung (9%), stomach (4%)	0%	[18, 21]
t(14;18)(q32;q21)	IgH, MALT1	Skin (14%), salivary gland (5%)	7–11%[a]	[19, 21]
t(3;14)(p14;q32)	IgH, FOXP1	Thyroid (50%), skin (10%)	0%[b]	[22]
Trisomy 3	–		38–62%	[17–19, 23]
Trisomy 18	–		14–47%	[17–19, 23]

IgH = immunoglobulin heavy chain.

[a]t(14;18) was found in three out of eight analyzed cases of OAML in the original study [24].

[b]t(3;14) was originally reported in four out of 20 cases of OAML [25], whereas more recent studies showed that this translocation is absent in OAML [22].

the occurrence of an antigen selection process during OAML development. As paradigmatic example, *Helicobacter pylori* (*Hp*) infection triggers a chronic antigenic stimulus that would drive the development of overt gastric MALT lymphoma along a continuum pathway (Figure 1). A similar pathogenetic model of antigen-driven lymphoproliferation may be hypothesized for OAML. In fact, the DNA of *Chlamydophila psittaci* (*Cp*), an obligate intracellular pathogen, has been detected in 80% of OAML patients and immunohistochemical data identified cells of the monocyte/macrophage system as likely carriers of the infection [5]. Chlamydiae are responsible for a wide spectrum of human diseases [32]; these bacteria have a tendency to cause persistent infections, inhibit apoptosis of infected cells and have complex immunomodulatory effects that may play a role in tumorigenesis [32–34]. *Cp* is the etiologic agent of psittacosis, a human infection caused by exposure to infected birds, cats and other household animals [32]. Notably, half of OAML patients reported close contacts with household animals [5]. Moreover, Chlamydiae are also etiologically linked to chronic infections of the conjunctiva, which may display features of follicular or 'inclusion' conjunctivitis [35]. In OAML patients, *Cp* establishes a systemic infection, as demonstrated by the detection of the DNA of the bacterium in peripheral blood mononuclear cells of 40% of these patients [5]. Such a systemic infection persists over time in a high proportion of cases, even >5 years, further supporting the possible involvement of *Cp* in sustaining lymphoma cell growth [5]. Microbial persistence may be favored by molecular mimicry, a phenomenon by which antigens derived from microorganisms are able to induce immune reactions cross-reacting with host self-antigens [36]. In fact, the expression of antigenic motifs shared with the host allows the long-lasting persistence of microbial pathogens since the immune system is usually tolerant towards autoantigens. It remains to be defined whether, similarly to *Hp* [37], Chlamydiae may also provide antigens, like heat-shock proteins [38], which may act as 'molecular mimickers'. For instance, heat-shock proteins produced by Chlamydiae may trigger both humoral- and cell-mediated immune responses that at least partially cross-react against the human protein counterpart and other related self-antigens [39]. This phenomenon may contribute to break local tolerance, leading to a chronic stimulation by antigens that cannot be successfully eliminated by the host and that may ultimately favor the onset of OAML [40].

The prevalence of *Cp* infection in OAML patients varies among the different reported studies (Table 4), and a geographical variability in this association has been indicated [44]. However, these variations could also be explained by methodological pitfalls as well as by the effect of some confounding factors like the use of wide-spectrum antibiotics and the involvement of other microbial agents. Most studies used a 'multiplex' touchdown enzyme time release-PCR [5], while, sometimes, these primers were used in 'monoplex' PCR, and direct sequencing to confirm the specificity of the amplified DNA was not always carried out. This is a relevant issue considering that taxonomic classification of chlamydiaceae is evolving and that the target DNA fragment may contain sequences largely overlapping although belonging to unrelated chlamydiaceae. Heterogeneity in tissue specimens, experimental conditions, DNA extraction protocol, PCR sensitivity and amount of DNA template could have contributed to results

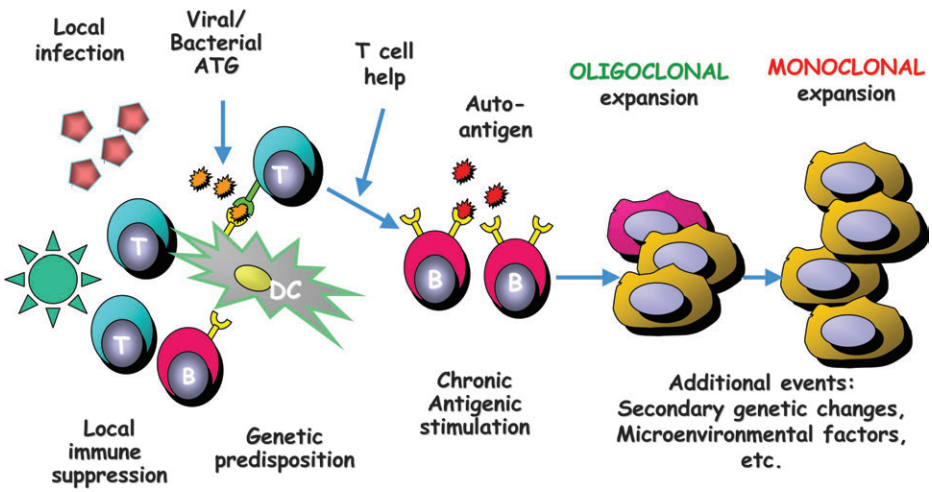

Figure 1. Mucosa-associated lymphoid tissue (MALT) lymphomagenesis associated with chronic infections: *Helicobacter pylori* (*Hp*) infection may trigger a chronic antigenic stimulus that would drive the development of overt gastric MALT lymphoma along a continuum pathway, starting from the development of acquired MALT, through low-grade lymphoma and ultimately leading to high-grade tumors. Both low- and high-grade lymphomas can acquire autonomous growth potential through the progressive accumulation of genetic changes. Neoplastic B cells from gastric MALT lymphomas were shown to proliferate strongly when cultured *in vitro* with heat-killed whole *Hp* cell preparations. These proliferative responses were strictly dependent on the contact with infiltrating CD4+ helper T cells (T), indicating that intratumoral T lymphocytes recognize *Hp*-derived antigens. Strikingly, immunoglobulins produced by gastric MALT lymphoma cells do not specifically recognize *Hp*-derived antigens but rather autoantigens. These autoreactive B lymphocytes may receive cognate help from *Hp*-specific T cells showing cross-reactivity with still poorly defined gastric autoantigens. This model indicates that antigens provided by infectious agents could trigger autoimmune reactivity and emphasizes the likely relevant role of autoimmune mechanisms in the pathogenesis of MALT lymphomas.

variability. From a clinical point of view, most patients with conjunctival or orbital lesions are firstly considered as affected by inflammatory or infectious processes instead of lymphomas, and are usually treated with topic or systemic wide-spectrum antibiotics, a common practice in OAML patients that could further reduce the local chlamydial population, resulting in PCR false negatives. Finally, the potential involvement of other microbial agents in the development and maintaining of OAML should be taken into account. This is indicated by the intriguingly tumor regression observed in one-third of *Chlamydia*-negative OAML after doxycycline treatment [46] (see '*Treatment*'). Available evidence seems to rule out the possible involvement of other infectious agents commonly associated with chronic eye diseases, such as *Chlamydia trachomatis*, herpes simplex virus 1 and 2 and adenovirus 8 and 19 [5, 55], whereas *Chlamydia pneumoniae* DNA was detected sporadically in a few cases of OAML [56, 57] (R. Dolcetti, unpublished data). Like for other B-cell lymphomas, hepatitis C virus (HCV) could play a role in the development of OAML. HCV seropositivity has been detected in 13% of OAML patients, and seems to be associated with more disseminated and aggressive lymphomas [58].

The study of putative mechanisms regulating lymphocytes homing to the ocular adnexa constitutes an interesting issue in the genesis and development of these neoplasms. Available data are preliminary and limited to the reported absence of expression of the α4β7 integrin, a crucial regulator of lymphocyte trafficking, and its ligand MAdCAM-1 [59], and to the expression of the chemoattractant cytokine CXCL13 on neoplastic lymphocytes [55].

Table 4. Prevalence of *Chlamydia psittaci* (*Cp*) infection in ocular adnexal lymphoma of mucosa-associated lymphoid tissue-type (OAML)

Geographical area	No.	*Cp*+	% *Cp*+ (95% CI)[a]	Reference
Austria	2	2	100 (16–100)[a]	[41]
Cuba	19	2	10 (1–33)	[42]
France	6	0	0 (0–46)[a]	[43]
Germany	19	9	47 (24–71)	[44]
Germany	23	0	0 (0–12)[a]	[45]
Hungary	2	1	50 (22–61)	[46]
Italy	24	21	87 (68–97)	[5]
Italy	15	2	13 (2–40)	[44]
Japan	18	0	0 (0–19)[a]	[47]
Japan	12	0	0 (0–26)[a]	[48]
South Korea	30	23	77 (58–90)	[49]
Southern China	37	4	11 (3–25)	[44]
The Netherlands	19	0	0 (0–18)[a]	[50]
The Netherlands	21	6	29 (11–52)	[44]
United Kingdom	33	4	12 (3–28)	[44]
USA, East Coast	17	6	35 (14–62)	[44]
USA, Florida	46	0	0 (0–8)[a]	[51]
USA, North-East	7	0	0 (0–41)[a]	[52]
USA, North-East	31	0	0 (0–10)[a]	[11]
USA, North-East	28	0	0 (0–11)[a]	[53]

Updated from Zucca and Bertoni [54]. No. = Number of analyzed patients; *Cp* + = number of *C. psittaci*-positive cases; % *Cp* + = percentage of *C. psittaci*-positive cases.

[a]Binomial exact 95% confidence intervals (95% CIs) were calculated; the one-sided, 97.5% CI is given when the percent of positive cases is either 0 or 100.

clinical features

clinical presentation

Lymphomas can infiltrate any orbital and ocular adnexal tissue. The clinical picture of OAML depends greatly on the structures compromised. Twenty-five percent of OAML displays conjunctival involvement, while intraorbital masses are present in 75% of cases and bilateral involvement is observed in 10–15% of cases, mostly in conjunctival forms [51,60–63]. It is difficult to differentiate clinically OAML from other orbital diseases due to the lack of pathognomonic signs or symptoms. Every lymphoma histotype can arise in the ocular adnexae, although with similar presenting symptoms and requiring surgical biopsy for histopathological diagnosis considering that treatment and prognosis remarkably vary among different lymphoma categories.

OAML usually arises after the fourth decade of age (median 65 years), with a higher prevalence among females [51,60–63]. The interval period between clinical onset and diagnosis is variable (median 6–7 months; range 1–135 months). Clinical presentation of conjunctival lymphoma consists of a classic 'salmon red patch' appearance with swollen conjunctiva (Figure 2). Patients with intraorbital lymphoma variably present with exophthalmos (27% of cases), palpable mass

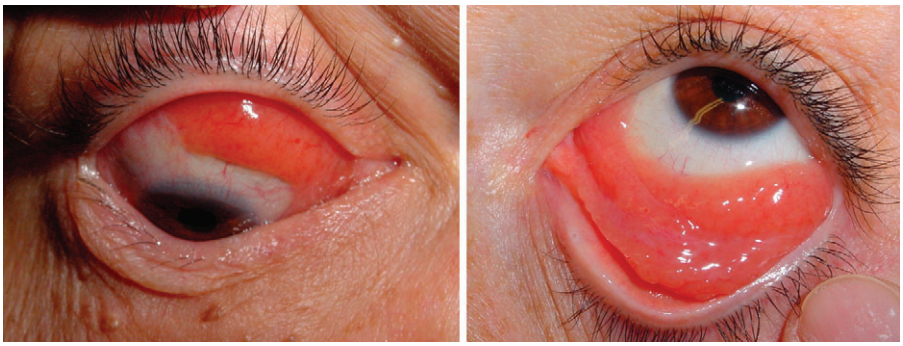

Figure 2. Two examples of classical presentation of conjunctival lymphoma, with 'salmon red patch' appearance and swollen conjunctiva. Histological diagnosis was marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)-type in both cases.

(19%), eyelid ptosis (6%), diplopia (2%), eyelid nodule, orbital edema, epiphora and a variable degree of impaired ocular motility [51,60–63]. Extraocular muscle imbalance and limitation of the excursion of the eye are usually indicators of expansive effect of the lesion rather than of muscle damage. Clinical manifestations usually consist of a slowly growing, painless mass that displaces the normal structures, but sometimes are acute, with inflammatory-like signs and symptoms. Only in rare cases of rapidly growing tumors, visual acuity and field defects or choroidal folds are observed, and a few cases of OAML infiltrating the eye with devastating consequences have been reported [64].

staging procedures

More than 75% of OAML presents with a single lesion (stage I_E). With conventional lymphoma staging procedures, regional lymphadenopathies are detected in <5% of cases (stage II_E), and extraorbital disease, mostly in extranodal organs, is observed in 10–15% of cases (stage IV_E), rarely in patients with conjunctival lymphoma [5, 51,61–63]. Conversely, the use of more extensive and invasive staging showed that 38% of OAML patients have at least one concomitant, extraorbital site of disease at diagnosis [27]. The usefulness of extended staging in OAML remains a matter of debate. On one hand, the definition of stage I disease is important because these patients are usually treated with radiotherapy alone. On the other hand, even if patients with stage I disease have significantly better relapse-free survival in comparison to those with advanced disease, no difference in cause-specific survival between these subgroups has been reported [63]. Comprehensively, OAML patients should be assessed with conventional lymphoma staging procedures, whereas an extensive gastrointestinal workup in the absence of clinical symptoms suggestive of lymphoma does not seem necessary [27].

Some OAML patients have a history of autoimmune disorders, mostly thyrotoxicosis (5% of cases) or Sjögren syndrome [65], the concomitance of which should be assessed at diagnosis since their negative impact on therapeutic outcome in extraorbital MALT lymphomas [66].

neuroimaging

Neuroimaging techniques are fundamental for distinguishing OAML from other orbital masses and for accurate staging and therapeutic response definition since they allow precise volumetric measurements. At neuroimaging examination, OAML usually present as well-defined lesions, mostly placed in the superior-lateral quadrant of the orbit, often surrounding and displacing extraocular muscles, without signs of ocular infiltration. On basal computed tomography images, OAML appears homogeneously iso- or slightly hyperdense compared with extraocular muscles. OAML contrast enhancement is homogeneous and its intensity is comparable to that of lachrymal glands and extraocular muscles. Magnetic resonance imaging (MRI) shows a great potential in differentiating OAML from other orbital expansive lesions. Location, margins and the distinctive T2 and diffusion-weighted imaging (DWI) signal intensities allow OAML identification and characterization (Figure 3). Similarly to what was observed in lymphomas of other districts, OAML presents high DWI signal and low apparent diffusion coefficient (ADC) values due to the high cellularity and high nucleus-to-cytoplasm ratio. Preliminary data indicate that ADC of OAML is lower than that of all orbital normal structures and expansive lesions, being thus useful for differential diagnosis. Furthermore, DWI is helpful in establishing involvement or persistence of disease in the lachrymal gland, where both signal intensity and contrast enhancement do not allow unambiguous differentiation between normal and pathologic tissue. A- and B-scan orbital ultrasonography provides additional information to MRI for distinguishing OAML from other orbital masses (Figure 4).

clinical behavior and prognosis

OAML shows a better prognosis in comparison to other lymphoma categories arising in the ocular adnexae [63]. Most OAML patients display good prognostic indicators like limited disease, good performance status and absence of systemic symptoms, and, if adequately treated, these patients exhibit a favorable outcome [51, 67]. Some anecdotal cases of spontaneous tumor remission in OAML patients have been reported, mostly in Japanese patients with conjunctival MALT lymphoma [68]. However, the real rate of this phenomenon warrants further investigation since some of these patients have been treated with topical steroids or antibiotics, which could have affected results interpretation. Presenting symptoms are sometimes severe, requiring a proper and timely treatment. Local control rates vary according to the used therapy, with a 5-year relapse-free survival of ~65%. Some patients experience multiple relapses, which usually involve the contralateral orbit and distant extranodal organs, particularly in patients treated with radiotherapy. Systemic dissemination occurs in 5–10% of cases, being rare in patients with conjunctival lymphoma. Less than 5% of OAML patients die of lymphoma, with a 5-year cause-specific and overall survival of 100% and >90%, respectively [62, 63]. Reliable prognostic factors remain to be defined. A few studies conducting multivariate analysis indicated that nodal involvement (<5% of cases), systemic symptoms (1%), increased lactate dehydrogenase serum levels (1%) and non-conjunctival sites are negative predictors of outcome [51, 61, 62]. Some of these aggressiveness parameters predict high-grade transformation, which has been reported in 1–3% of cases [67, 69].

treatment

Current therapeutic knowledge in OAML results from a limited number of small, and variably treated, retrospective series, which included different lymphoma categories, diagnosed before the World Health Organization classification era and a single prospective trial [46]. Thus, universally accepted therapeutic guidelines for OAML do not exist. Therapeutic decision is usually driven from appraisal of several variables related to the patient (age, performance status, co-morbidity—i.e. autoimmune disorders—concomitant infections useful as therapeutic targets), to the lymphoma (stage, site of disease—i.e. surgical accessibility—symptoms due to infiltration, histological

and molecular indicators of aggressiveness and response) and to the risk of severe treatment-related toxicity and sequelae. Efficacy and kinetic of response are two important parameters for therapeutic choice, mostly in 'less-indolent' lymphomas that could determine a fast impairment of ocular function.

surgical resection

Surgical resection is a necessary diagnostic step and, in selected cases, a part of therapeutic approach to OAML (Figure 5). Complete excision can be carried out in many conjunctival and lachrymal gland MALT lymphomas, especially in pseudoencapsulated lesions. However, additional efforts to completely resect lymphomatous lesions should be avoided in OAML patients since an aggressive approach could be associated with a high risk of complications, especially in the area of the lachrymal gland and in the deeper orbit, and considering that the extent of surgical resection does not influence survival [67]. 'Wait and watch' strategy after surgical resection or biopsy in patients with stage I disease produces similar results, in terms of time to progression, systemic dissemination, high-grade transformation and lymphoma-related deceases, to those reported with immediate radiotherapy, with a 10-year overall survival of 94% [67]. This strategy could be safely proposed to selected OAML patients, like elderly patients or patients with severe co-morbidity, completely resected lesions and/or indolent and asymptomatic disease.

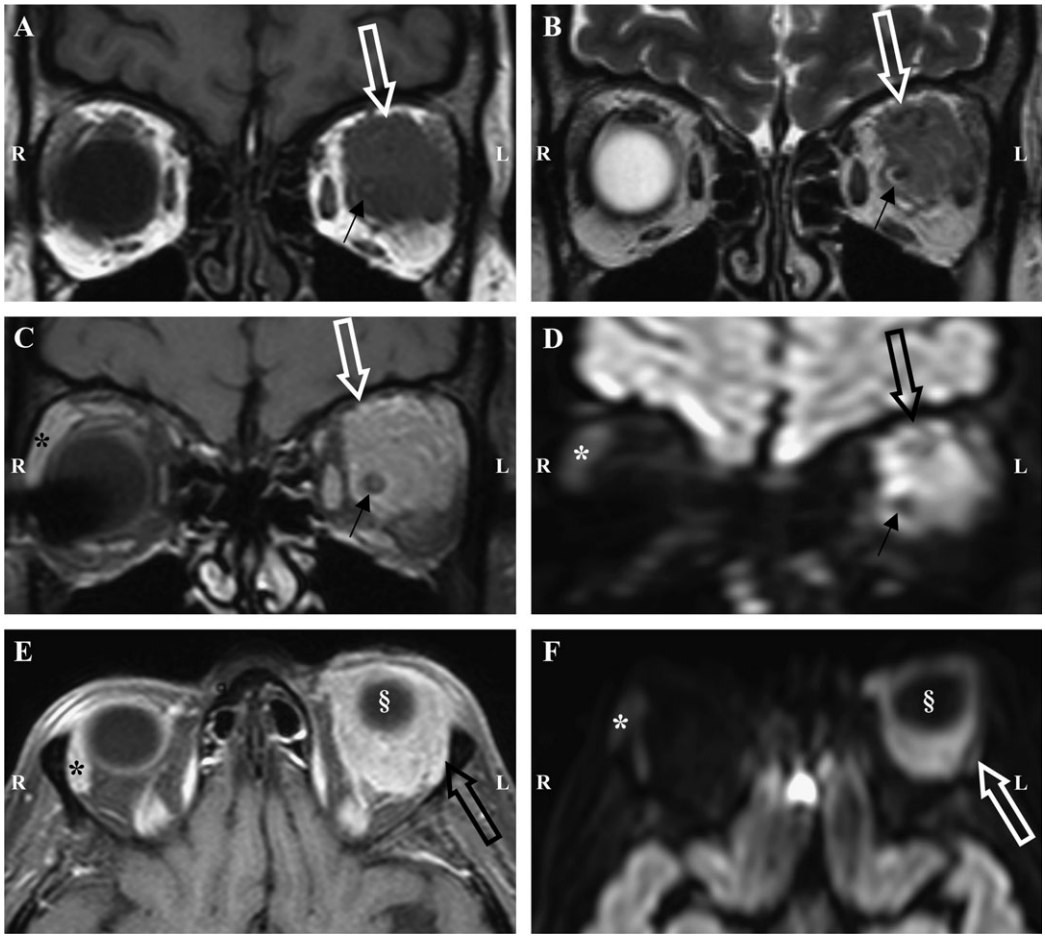

Figure 3. Magnetic resonance imaging (MRI) of ocular adnexal lymphoma of mucosa-associated lymphoid tissue-type (OAML). Coronal basal T1-weighted (w) (**A**), coronal T2-w (**B**), coronal and axial post-gadolinium T1-w (**C**, **E**), coronal and axial diffusion-weighted imaging (DWI) (**D**, **F**) image, obtained with a *b* value of 700 mm^2/s. The OAML (large arrow) is located in superior-lateral quadrant of the left orbit and involves both intra- and extraconal structures. It surrounds the optic nerve (small arrow) and the superior pole of the left ocular globe (§), the lateral rectus and the superior extraocular muscles (EOM). The left lachrymal gland is infiltrated. On T1-w image (**A**), the OAML signal is comparable to that of EOM. On the T2-w image (**B**), OAML presents the same signal intensity of cerebral gray matter and is slightly hyperintense to EOM. Usually, T1 and T2 signal intensities within the lesion are homogeneous. OAML contrast enhancement is uniform and its conspicuity is comparable to that observed in lachrymal glands and EOM. Using parallel imaging technique is now possible to obtain DWI images of the orbit with reasonable scan times and without occurrence of significant susceptibility artifacts (**D**, **F**). DWI is an MRI-based technique that evaluates the rate of microscopic water diffusion in tissues and represents a useful technique for characterizing lymphomas of the central nervous system, the neck and the orbits. On DWI images, OAML appears hyperintense compared with all other orbital structures. DWI is also helpful in establishing involvement of the lachrymal gland, where both signal intensity and contrast enhancement do not allow unambiguous differentiation between normal and pathologic tissue. Please compare the contrast enhancement and DWI signal intensity of affected left lachrymal gland and normal right one (*).

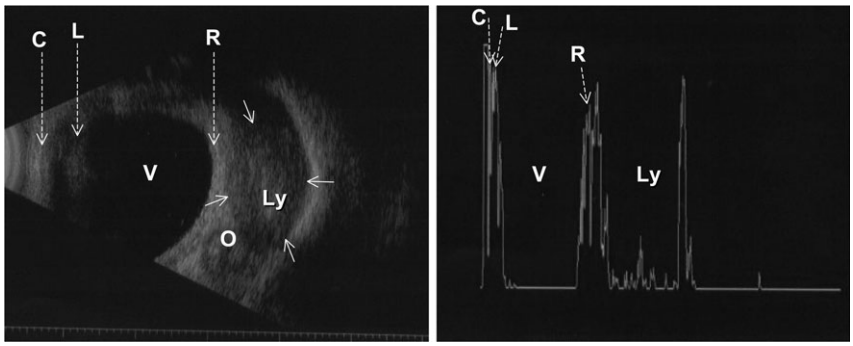

Figure 4. A- and B-scan orbital ultrasonography plays an important role in differential diagnosis of orbital masses. B- (left side) and A-scan (right side) orbital ultrasonography of the eye and the orbit in a patient with a retrobulbar ocular adnexal lymphoma of mucosa-associated lymphoid tissue-type (OAML). C, cornea; L, lens; V, vitreous humor; R, retina. B-scan orbital ultrasonography (left side) shows a well-delimited, hyporeflective retroocular solid mass (Ly; surrounded by arrows). A-scan orbital ultrasonography (right side) confirms the presence of a retroocular, homogeneously hyporeflective lesion (Ly) delimited by two peaks. Histological diagnosis was OAML. Orbital ultrasonography provides useful information on the site, morphology and structure of the lesion (B-scan) and on the acoustic structure, internal reflectivity, vascularization and margins of the lesion (A-scan). Low reflectivity is characteristic in OAML and other lymphomas of the orbit, which is due to the high cellular density distinctive for these disorders. Kindly provided by Dr Luisa Pierro, Ophthalmology Unit, San Raffaele Scientific Institute, Milan, Italy.

radiotherapy

Radiotherapy is the most extensively studied treatment in OAML patients. However, only a few series have been focused on OAML treated exclusively with radiotherapy [62, 63, 70, 71]. An universally accepted radiation schedule for OAML patients does not exist. Recent studies indicate a radiation field including a gross tumor volume with 0.5- to 1-cm margin for a planning target volume and a dose of 25–30 Gy in 10–15 fractions (minimal target dose >25 Gy) [62, 70, 71]. Electron beams (4–12 MeV) and 4–9 MV photon beams are advisable in conjunctival and intraorbital lymphomas, respectively. A single anterior field or a wedge pair of anterior fields has been used in most series. In conjunctival lymphomas, the entire conjunctiva and eyelid should be irradiated, while preliminary data seem to indicate that the entire orbit should be irradiated in patients with intraorbital lymphoma [62]. Brachytherapy can provide local control in conjunctival lymphomas, but the risk of complications and marginal relapses is unacceptably high [72].

Most irradiated patients with stage I OAML achieve an objective response, which is slow and gradual [62, 70]. In-field relapses are rare and seem to be related to low-radiation doses [71] or to the use of lens shielding [62]. Relapse rate at 4 years is 20–25%; most relapses involve the contralateral orbit (half of relapses) and distant extranodal organs [63, 70, 71].

With the above-indicated schedule, radiotherapy is usually well tolerated [62, 70]. The most common toxic effects of grade ≥2 are cataract (38% of cases), retinal disorders (17%), xerophthalmia (17%) and glaucoma (2%) [70]. Toxicity is more common with doses >36 Gy [70]. Presently, the role of upfront radiotherapy is being reviewed due to its related toxicity, the development of new therapeutic strategies and the recent insights into the biology of OAML.

chemotherapy

Prospective trials assessing chemotherapy efficacy in OAML do not exist; in most retrospective OAML series, only a small proportion of patients has been treated with chemotherapy alone. The largest experience regards chlorambucil, an alkylating agent largely used in indolent lymphomas. This drug is an active and well-tolerated therapy for stage I OAML, with a 100% overall response rate, a 79% complete remission rate and a 5-year relapse-free survival of 60% [69]. Relapses after chlorambucil mostly involve extraorbital tissues, with rare cases (3%) of high-grade transformation [69]. Chlorambucil could be proposed especially to OAML patients who experience relapse in previously irradiated areas or with disseminated or bilateral disease and in the case of radiotherapy inaccessibility (Figure 5). The use of other drugs, like fludarabine [73], cladribine [74] and oxaliplatin [75], deserves more caution. Tolerability of these drugs is sometimes unsatisfactory [74], and evidence of their efficacy is limited to a few prospective trials on unselected MALT lymphomas including a small number of OAML patients. The use of upfront anthracycline-based chemotherapy did not show any clinical advantage in comparison with chlorambucil alone [2].

bacteria-eradicating therapy

In gastric MALT lymphoma, antibiotic therapy, aimed to eradicate the *Hp* infection, is followed by lymphoma regression in 60–70% of stage I_E cases [26]. Although a role for *Hp* in sustaining the growth also of non-gastric MALT lymphomas was hypothesized, reported evidence shows that gastric *Hp* infection in OAML patients does not influence clinical presentation and course and that *Hp*-eradicating antibiotic therapy is not active against OAML [76]. Conversely, the eradication of *Cp* infection with doxycycline, a tetracycline derivative largely used in the treatment of psittacosis, has been proposed as a valid alternative for OAML patients. In a multicenter phase II trial [46], 11 patients with *Cp*-positive OAML and 16 with *Cp*-negative OAML have been treated with doxycycline, obtaining, after a median follow-up of 14 months, an overall response rate of 48%. Lymphoma regression was usually slow and gradual and has been observed in both *Cp*-positive and -negative patients (overall response rate = 64%

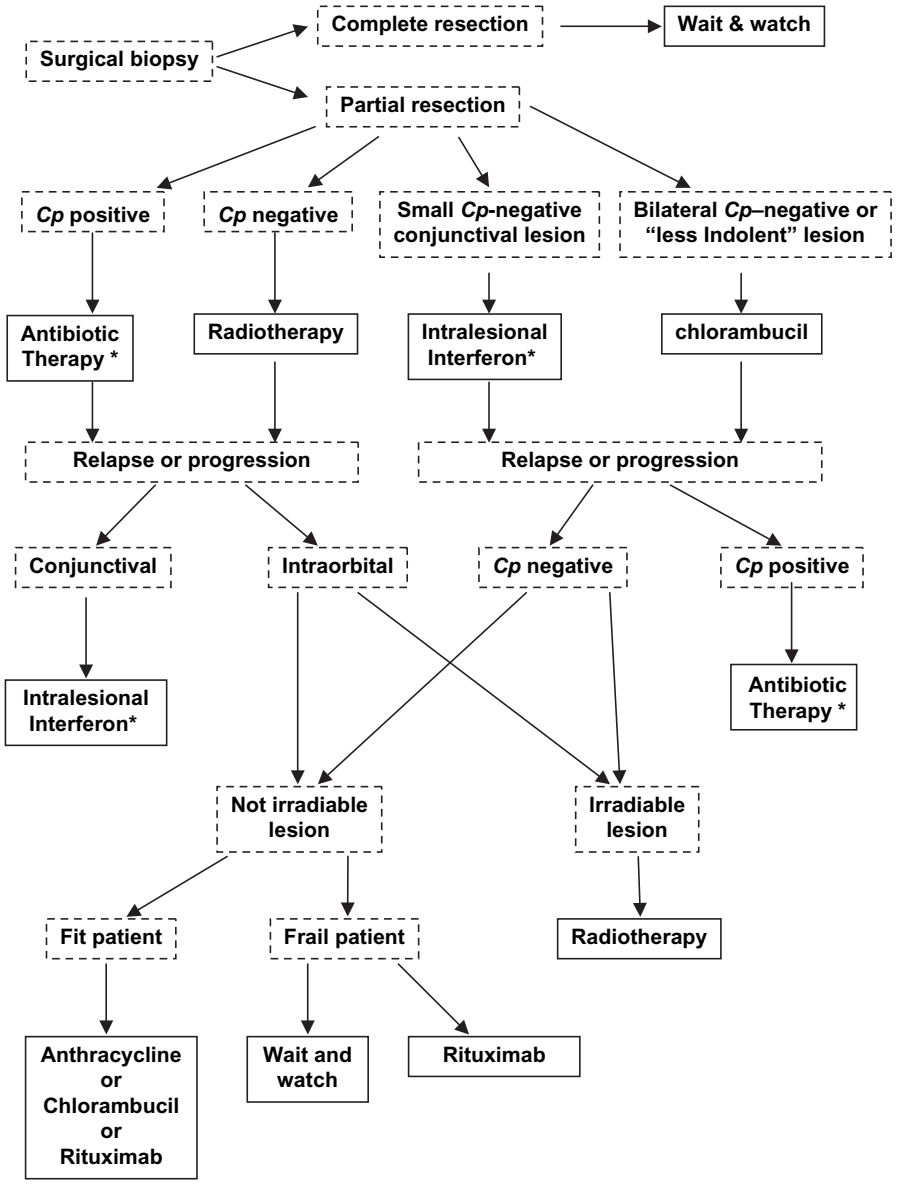

Figure 5. Flow chart of therapeutic recommendations for patients with limited disease ocular adnexal lymphoma of mucosa-associated lymphoid tissue-type. Dotted lines = clinical conditions; continuous lines = treatment. *Investigational approach.

versus 38%; $P = 0.25$), with a 2-year failure-free survival of 66%. This trial confirmed that doxycycline is a fast, cheap, safe and active therapy for *Cp*-positive OAML and that is a valid alternative even in patients with multiple failures, involving previously irradiated areas or regional lymphadenopathies [46]. This latter feature is distinctive from gastric MALT lymphomas, where the detection of perivisceral lymphadenopathies is rather considered as a negative response predictor [77].

One-third of patients with Chlamydia-negative OAML experienced tumor regression after doxycycline treatment [46], indicating that doxycycline could be used in most OAML patients, independently of the diagnosis of *Cp* infection. However, smaller studies where OAML patients received doxycycline without a previous molecular assessment for chlamydial infection led to conflicting results [78, 79]. Eradicating antibiotic therapy remains an experimental strategy that should be always preceded by chlamydial infection assessment, at least until ample, worldwide experience will be available (Figure 5).

immunotherapy

Rituximab, a chimeric mAb directed against the B-lymphocyte antigen CD20, has been largely used in the treatment of B-cell lymphomas. Even if active in MALT lymphomas [80], rituximab has been only anecdotally used in OAML patients [80–82]. Rituximab activity is high in patients with newly diagnosed OAML, but response duration is usually short and relapse rate is clearly higher than those reported for gastric MALT lymphoma [82]. Rituximab could be, however, used to obtain transient symptomatic benefit in OAML patients for whom other therapeutic strategies are contraindicated [81, 82].

Intralesional injection of interferon α is a relatively simple and quick procedure that has been successfully used for conjunctival lymphomas [83, 84] (Figure 5). Side-effects consist of local hemorrhage, chemosis and minor systemic effects [83, 84]. The efficacy of this approach remains, however, to be defined considering that follow-up of reported cases is short and that unsuccessfully treated patients may have not been reported.

future perspectives

Future studies will investigate whether *Cp* infection is responsible for the rapidly increasing incidence of OAML. The role of putative *Cp*-derived antigens in lymphomagenesis, the involvement of distinct *Cp* strains as well as the mechanisms of tolerance and antigenic chronic stimulation induced by this microorganism, that may ultimately favor the onset of OAML, should be addressed in well-designed studies. From a therapeutic point of view, and following the example of gastric MALT lymphoma [85], the analysis of pathologic and molecular predictors of response will play an important role in selecting the best candidates for *Cp*-eradicating antibiotic therapy. Well-designed prospective trials will lead to establish new therapeutic strategies that, exploiting novel mechanisms, could contribute to further improve the outcome of these patients. For instance, the efficacy of antiviral therapy with interferon and ribavirin [86] in HCV-positive patients or new antibiotic combinations should be investigated. In the years ahead, it is hoped that international, multidisciplinary efforts could address most of the fundamental, clinical and biological research questions for OAML.

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