The Management of Nongastric MALT Lymphomas


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The Peculiar Biology of MALT Lymphomas

The group of marginal zone B-cell lymphomas (MZL) comprises three different entities, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (currently called MALT lymphoma), nodal marginal zone B-cell lymphoma (previously known as monocytoid lymphoma), and splenic marginal zone B-cell lymphoma (with or without circulating villous lymphocytes).[1-3] Primary splenic and nodal MZLs are rare, each comprising approximately less than 2% of lymphomas, while the extranodal MZL of MALT type is not uncommon, representing approximately 7% to 8% of the total number of non-Hodgkin lymphoma cases.[4]

MALT lymphoma B cells have somatically mutated IGHV genes in all cases, with a pattern of somatic hypermutation and intraclonal variations suggesting that the tumor cells have undergone antigen selection and that their expansion may remain antigen-driven.[5,6] Indeed, MALT lymphoma usually arises in mucosal sites where lymphocytes are not normally present and where MALT is acquired in response either to autoimmune processes, such as Hashimoto thyroiditis or Sjögren syndrome, or to chronic infectious conditions. It is believed that, in the context of a persistent antigenic stimulation, successive genetic abnormalities can progressively hit a B-cell clone among the reactive B cells of the chronic inflammatory tissue and give rise to a MALT lymphoma.

The stomach is the most common site of localization, accounting for about one-third of cases, and the remission of most gastric MALT lymphomas after eradication of *Helicobacter pylori* strongly indicates a pathogenetic link between tumor cell proliferation and chronic *H pylori*-induced inflammation. Several studies have confirmed the high efficacy of *H pylori* eradication in gastric MALT lymphomas; many of these report long-lasting remissions, with no need for more aggressive therapies in most patients.[5]

Other microbial agents have been implicated in the pathogenesis of MALT lymphomas arising in other extranodal sites, such as the skin (*Borrelia burgdorferi*), the ocular adnexa (*Chlamydophila psittaci*), and the small intestine (*Campylobacter jejuni*).[5] The prevalence of hepatitis C virus (HCV) has been reported to be higher in patients with MZLs, including MALT lymphomas, than in controls, suggesting a possible causative role for the viral agent.[7]

At least four recurrent chromosomal aberrations—the apparently mutually exclusive translocations t(11;18)(q21;q21), t(1;14)(p22;q32), and t(14;18)(q32;q21), and the 6q23.3 deletion—have been reported in MALT lymphomas; these affect the same signaling pathway, resulting in the activation of nuclear factor kappa B, a transcription factor with a central role in immunity, inflammation, and apoptosis.[8-14] The occurrence of the translocations varies according to the anatomic site. Moreover, there are suggestions that the incidence and distribution of these translocations varies with geography, possibly reflecting different genetic backgrounds of the patients or of infectious agents.[15]

Besides playing a role in lymphomagenesis, these site-specific biologic differences may influence outcome and therapeutic approaches. Indeed, while antibiotic therapy is nowadays well established as the standard of care in patients with *H pylori*-associated gastric MALT lymphoma, much less is known about the value of antibiotic therapy in nongastric MALT lymphomas, and their standard treatment is less well defined.

Diagnosis of MALT Lymphoma

The diagnosis of MALT lymphoma should be made in accordance with the current World Health
Organization (WHO) classification, and it is recommended that the diagnosis be confirmed by an expert hematopathologist. Differentiation from other indolent lymphomas that can present at extranodal sites is not always clear-cut and should be confirmed; hence, a minimum immunohistochemistry panel should include CD20, CD10, CD5, and cyclin D1. The presence of lymphoepithelial lesions is not essential for the diagnosis, and their presence is not pathognomonic, as these can be seen both in some reactive conditions and in other extranodal lymphomas. Since scattered large cells are usually present, ruling out a potential associated large B-cell lymphoma is crucial.[1] While the presence of the chromosomal translocation t(11;18)(q21;q21) may give an indication of the likelihood of response of a gastric lymphoma to *H pylori* eradication alone, no consistent prognostic markers have been identified that could affect the initial clinical management in nongastric MALT lymphoma.

**Clinical Features**

MALT lymphomas only seldom form prominent tumor masses and are often difficult to distinguish from the inflammatory lesion that underlies the acquisition of MALT from which the lymphoma arises. The presenting symptoms are largely related to the primary location. Only a small minority of patients present with elevated lactate dehydrogenase (LDH) or β2-microglobulin levels, and constitutional B symptoms are extremely rare.[16-20]

MALT lymphoma usually remains localized for a prolonged period within the tissue of origin, but spreading to multiple sites is not uncommon, and presentation with disseminated disease is reported in up to one-fourth of cases and seems more common in nongastric MALT cases.[18,21-23] Bone marrow involvement is reported in up to 20% of cases.[20,24] In a retrospective survey from the International Extranodal Lymphoma Study Group (IELSG), the nongastric MALT lymphoma patients with disease classed as stage IV because of bone marrow or lymph node involvement had an inferior overall survival rate compared with those with multiple mucosal localizations only.[18] The finding that dissemination to multiple mucosal sites does not change the outcome has also been shown in other series, and most patients have a favorable outcome, with overall survival usually higher than 80% at 5 years.[21,25]

The most common nongastric MALT lymphoma sites are the salivary glands, skin, orbits and conjunctiva, lung, thyroid, upper airways, breast, other GI sites, and liver.[18,19,21,23] The anatomic site may have prognostic relevance because of organ-specific clinical problems, but because different genetic lesions may be associated with different localizations,[15] it is possible that the different sites have a distinct natural history. In a study from Princess Margaret Hospital in Toronto evaluating the long-term outcome of 167 patients with localized (stage IE and IIE) MALT lymphoma treated with involved-field radiotherapy, gastric and thyroid lymphomas had a significantly better outcome, and distant failures were more common for other sites.[26] In general, despite frequent relapses, MALT lymphomas most often maintain an indolent course.[18] In the above-mentioned study, the 10-year recurrence-free rate was 76%, the overall survival rate was 87%, and the cause-specific survival rate was 98%.[26] Histologic transformation to large-cell lymphoma is reported in 4% to 20% of cases, most often as a late event and independent of dissemination.[21,25-27]

**Recommended Procedures for Initial Staging and Follow-Up of Patients With Nongastric MALT Lymphoma**

Because of the risk of occult disseminated disease, extensive work-up procedures are recommended in all MALT lymphomas, irrespective of their presentation site,[28] and should comprise a history and physical examination (including lymph node regions, eye and ear, nose and throat, liver and spleen clinical evaluations); complete blood cell counts and basic biochemical studies, including evaluation of renal and liver function; LDH and β2-microglobulin levels; serum protein immunofixation; human immunodeficiency virus (HIV), HCV, and hepatitis B virus (HBV) serologies; CT scan of the chest, abdomen, and pelvis; and bone marrow aspirate and biopsy. We also consider gastrodudodenal endoscopy with multiple biopsies to exclude a concomitant gastric involvement, particularly when localized radiotherapy is planned. The value of a positron emission tomography (PET) scan is still controversial, with uncertain clinical consequences; although it is not recommended, there is mounting evidence that most nongastric sites are usually PET-positive (Table 1).[29-43] Additional, site-specific procedures are summarized in Table 2.

**Treatment of *H pylori*-Independent Gastric MALT Lymphoma and**
Nongastric MALT Lymphoma

There is no clear consensus for the treatment of patients with gastric MALT lymphoma who require further therapy beyond \textit{H pylori} eradication or who have extensive disease. No definite guidelines exist for the management of nongastric lymphoma (nor for \textit{H pylori}-negative cases). Several retrospective series showed no significant survival difference between patients who received different initial treatments (including chemotherapy alone, surgery alone, surgery with additional chemotherapy, and radiation therapy).

Radiation therapy

A modest dose of involved-field radiotherapy (25–35 Gy) gives excellent disease control.\cite{26,44} The emerging literature on localized MALT lymphomas confirms a high rate of local control, with a high proportion of patients likely to be cured of the disease. Indeed, radiotherapy has become a standard treatment, at least in North America, for patients with stage I/II MALT lymphoma of the stomach without evidence of \textit{H pylori} infection or with persistent lymphoma after antibiotics, as well as for most nongastric localized presentations.\cite{45-54} The use of radiotherapy in this setting has been recommended by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.\cite{55} Modern radiotherapy planning techniques, such as three-dimensional conformal radiotherapy and intensity-modulated radiotherapy, facilitate the determination of the clinical target volume, reducing the toxicity that is related to the irradiation of nontarget organs.\cite{56,57} In general, the moderate doses of radiation required for cure are associated with mild and reversible side effects and a low risk of long-term toxicity, although special considerations are needed for particular localizations, such as the eye or the lung.\cite{26,56,58,59}

Chemotherapy and immunotherapy with anti-CD20 monoclonal antibodies

When systemic treatment is needed, enrollment in controlled clinical trials is advisable since, although chemotherapy (and/or immunotherapy with anti-CD20 monoclonal antibodies) is an obvious choice, there only a few compounds and regimens tested specifically in the setting of MALT lymphoma. Oral alkylating agents (either cyclophosphamide or chlorambucil) can result in a high rate of disease control. The purine analogs fludarabine\cite{60} and cladribine have demonstrated some antitumor activity in phase II studies, but they may be associated with an increased risk of secondary myelodysplastic syndrome.\cite{61} The activity of the anti-CD20 monoclonal antibody rituximab has also been demonstrated in a phase II study (with a response rate of about 70%), and this may represent an additional option for the treatment of systemic disease. The efficacy of the combination of rituximab and chlorambucil has been explored in the IELSG-19 randomized study in gastric MALT lymphomas in which antibiotics have failed, and in nongastric MALT lymphomas.\cite{62,63} Compared with chlorambucil alone, and with rituximab alone, the combination of chlorambucil plus rituximab resulted in increased complete remission and event-free survival rates, but the 5-year overall survival was nearly identical in all treatment arms.\cite{63,64} This combination is the only one thus far tested in a large randomized study. A polychemotherapy regimen comprising chlorambucil/mitoxantrone/prednisone has been reported to be effective and well tolerated in MALT lymphoma, irrespective of localization.\cite{65} Excellent activity with acceptable toxicity has also been reported for short-term front-line treatment with bendamustine plus rituximab in a phase II trial.\cite{66} More aggressive anthracycline-containing chemotherapy should be reserved for patients with high tumor burden (bulky masses, unfavorable International Prognostic Index). Finally, radiotherapy can be an effective therapy that provides local disease control for some patients with stage III or IV disease.\cite{67}

\textit{H pylori} eradication in nongastric MALT lymphomas

Although \textit{H pylori} eradication using antibiotic regimens combined with proton-pump inhibitors is nowadays the standard front-line therapy for patients with \textit{H pylori}-associated gastric MALT lymphoma, the role of antibiotic therapy in patients with nongastric MALT lymphoma is much less well defined. Anecdotal reports linking \textit{H pylori} to the growth of nongastric MALT lymphoma and describing regressions of nongastric MALT lymphomas in \textit{H pylori}-infected patients after \textit{H pylori} eradication have been published,\cite{68-70} but a larger series from Austria of 77 patients with extragastric MALT lymphoma
Lymphomas showed that this approach is not effective in the majority of patients with nongastric localization, in whom the incidence of *H pylori* infection was similar to the infection rate in the healthy Austrian population (and significantly lower than the incidence observed in gastric lymphomas).[71]

**Antibiotic treatment of MALT lymphomas of the ocular adnexa**

After *H pylori*, *C psittaci* is the most thoroughly studied of the other bacteria reported to have a potential pathogenetic role in MALT lymphoma. Evidence supporting a pathogenetic association between this bacterial agent and the development of MALT lymphoma of the ocular adnexa includes the identification of chlamydial antigens in tumor tissue by immunohistochemistry, detection of bacterial DNA in tumor biopsy specimens, visualization of the bacteria within tumor-infiltrating macrophages by electron microscopy, and the isolation of the bacteria from conjunctival swabs and the peripheral blood of patients.[72-77] Moreover, development of metachronous *C psittaci*-related lymphomas in the same patient after prolonged exposure to an infected animal has been described.[73] The finding that *C psittaci* has been detected in up to ~80% of Italian patients with ocular adnexa MALT lymphoma provided the rationale for the antibiotic treatment of localized lesions.[74,75] In addition, eradication of *C psittaci* infection using doxycycline as targeted therapy for patients with ocular adnexa MALT lymphoma resulted in lymphoma regression in approximately 50% of patients, including those with multiple treatment failures, previously irradiated lesions, or regional lymph node involvement.[76,77]

Following the first demonstration that doxycycline treatment may cause tumor regression in patients with *C psittaci*-associated lesions, subsequent reports on the efficacy of antibiotics in ocular adnexa lymphoma showed conflicting data and apparent geographic variations.[75,78] Indeed, the prevalence of *C psittaci* infection in ocular adnexal lymphoma varies among countries and among different regions within the same country. It is higher in Italy, Austria, Korea, and Germany; and it is virtually absent in Japan, France, and China.[75,79]

A prospective international phase II study was then conducted by the IELSG, in which 34 untreated patients with stage 1 ocular adnexal MALT lymphoma had doxycycline treatment (100 mg orally twice daily for 3 weeks) and were assessed for chlamydial eradication and lymphoma response.[72] In this study, *C psittaci* DNA was detected in nearly 90% of the lymphoma biopsy specimens, while no other Chlamydiaceae were detected. Twenty-nine patients had *C psittaci* DNA in baseline swabs or blood samples and were evaluable for chlamydial eradication, which was achieved in 48%.

Lymphoma regression was complete in 6 patients and partial in 16, with an overall response rate of 65%. At a median follow-up of 37 months, the 5-year progression-free survival was 55%. *C psittaci* eradication was associated with improved response rate and progression-free survival. Indeed, 86% of patients who achieved successful eradication of the bacteria attained a major and durable lymphoma regression. These findings confirmed the critical role played by *C psittaci* in sustaining the lymphoma growth. In this study, a consistent concordance between *C psittaci* detected in tumor tissue and *C psittaci* on conjunctival swabs indicated that conjunctival swabs may be a simple, noninvasive tool for monitoring the infection.

Overall, doxycycline treatment has been studied in about 120 patients with ocular adnexa MALT lymphoma (Table 3), with responses seen in about half of these.[80] The best responses are usually achieved within 6 months. However, analogous to *H pylori* eradication in gastric MALT lymphoma, in some patients, responses are slow and gradual and may require up to 36 months.[77] How long a patient can be safely observed after doxycycline treatment before starting a different treatment remains to be clarified.

Of interest, lymphoma regression after doxycycline treatment has been observed in some lymphomas where there is no evidence of *C psittaci*, as well as in cases where this treatment failed to eradicate the *C psittaci* infection.[72,77,81] This contrasts with results in the better-studied gastric MALT lymphoma (*where H pylori*-negative patients are generally unresponsive to antibiotic treatment) and might suggest that other doxycycline-sensitive microorganisms may be linked with the lymphoma. The optimal administration schedule for doxycycline also remains to be defined.[72,81] and further investigations are warranted to identify other potential infective agents and to improve antibiotic efficacy.[78] Moreover, mechanisms leading to lymphoma regression have yet to be elucidated, and direct anti-inflammatory or antiproliferative effects of doxycycline cannot be ruled out.

Some antineoplastic activity of macrolides has been shown in murine cancer models, providing the basis for an exploratory study of a 6-month oral clarithromycin regimen in 11 patients with ocular adnexa MALT lymphoma.[82] In this study, five patients who had been previously unsuccessfully...
treated with doxycycline responded to the clarithromycin therapy. Because lymphoma responses were seen in patients who had persistent disease several months after eradication of the chronic infection, the authors concluded that an antitumor or immunomodulatory effect, rather than the direct antimicrobial activity of clarithromycin, might be the cause of the observed lymphoma regressions.[82]

### Antimicrobial therapies in cutaneous marginal zone lymphoma and ‘other’ nongastric MALT lymphomas

*B. burgdorferi* chronic infection may induce a typical B-cell infiltration known as cutaneous “pseudolymphoma.” This spirochetal agent has also been reported to have a potential pathogenetic role in marginal zone lymphomas of the skin,[83] but its association with cutaneous lymphomas presents striking geographic variations.[80] A few case reports have documented that the eradication of *B. burgdorferi* following ceftriaxone therapy appeared to have resulted in regression of an associated cutaneous marginal zone lymphoma[80]; therefore, the demonstration of a *B. burgdorferi* infection may be sought in endemic areas where it may have some therapeutic implications. However, the evidence comes from such a limited number of patients (Table 3) that no sound recommendations can be made. Several other case reports and small series—recently reviewed by Kiesewetter and Raderer[80]—have described the potential association of various chronic infections with MALT lymphomas localized in the lungs, parotid and salivary glands, breast, thyroid, and bladder; however, the results of some of these studies were controversial. No conclusion can be drawn from the available information on antibiotic treatment in these lymphomas; the published data are scanty and possibly biased by the preferential publication of positive results.[80] Along with the above-mentioned bacterial infections, high rates of HCV infection have been reported in MALT lymphomas, particularly in patients with subcutaneous or salivary gland localization.[7,84,85] Although there are important geographical differences in HCV infection,[86] responses after antiviral therapy have been observed,[85] and anti-HCV treatment should be considered in patients with active chronic infection.

### Immunoproliferative Small Intestinal Disease

Immunoproliferative small intestinal disease (IPSID), previously also known as alpha-heavy-chain disease or Mediterranean lymphoma, is a special subtype of MALT lymphoma.[1,87,88] The typical and peculiar feature of IPSID is the production of alpha heavy chain. The latter is secreted and, in up to 75% of cases, is detected in the serum, urine, saliva, and duodenal fluid; in the remaining cases, the alpha heavy chain is not secreted but it is still demonstrable by immunohistochemistry. IPSID typically affects young adults, predominantly males. Although it is endemic in the Middle East, especially in the Mediterranean area, IPSID can also be diagnosed in industrialized Western countries, usually in immigrants from the area where it is endemic.

IPSID has a prolonged natural history, often over many years, including a potentially reversible early phase; the disease is usually confined to the abdomen. If left untreated, the lymphoma can undergo a histologic transformation to a diffuse large B-cell lymphoma. Surgery has no therapeutic role, since the lymphoma usually presents with diffuse involvement of the intestine. In its early phases, IPSID can be treated with sustained antibiotic therapy (eg, tetracycline or metronidazole and ampicillin for at least 6 months), which can lead to a durable remission. These results suggest a role for an infectious agent, and *C. jejuni* is, so far, the best candidate.[89] Indeed, at an early stage, antibiotic treatment directed against *C. jejuni* may lead to lymphoma regression.[89] Anthracycline-containing regimens, combined with nutritional support plus antibiotics to control diarrhea and malabsorption, represent the best chance of cure in the advanced phases.[87]

### Conclusions

No definite guidelines exist for the management of nongastric MALT lymphoma. Retrospective series have included patients treated with different modalities, and excellent cause-specific and overall survival have been demonstrated, independent of the type of treatment adopted.[18,21,23,25] Involved-field radiotherapy encompassing the involved organ alone, with a dose of 24 Gy to 36 Gy,[26,44,56,58] has a well-established role in the treatment of localized lesions. However, there is no clear consensus as to whether radiation is more or less effective than systemic therapy in MALT lymphomas at different locations, and the experience of each center and the patient’s preferences in
terms of adverse effects are important parameters to include in the decision-making process.[78] Because no curative treatment exists, expectant observation is an adequate initial policy in most patients with advanced disease. In general, the treatment should be “patient-tailored,” taking into account the site and stage of the disease, and the clinical characteristics of the individual patient. When systemic treatment is needed, the use of chemotherapy together with rituximab seems obvious; however, the regimen of choice is controversial, and the combination of rituximab with chlorambucil is the only one that has been tested in a randomized study[64]; the treatment schedules used are described in the Figure.

In comparison with gastric MALT lymphoma, much less is known about the role of antibiotic therapies in nongastric tumors. At present, only the association of C psittaci with ocular adnexal MALT lymphoma has been adequately tested; even so, the promising results of doxycycline therapy still lack long-term follow-up data. Nevertheless, the activity reported by Ferreri et al in untreated patients[72] appears not inferior to that reported with chemotherapy and radiotherapy,[90,91] and the toxicity is negligible, suggesting that upfront doxycycline is a reasonable and effective treatment that can be proposed for patients with stage I C psittaci-positive MALT lymphoma of the ocular adnexa before consideration of more aggressive strategies. This may allow durable remission, avoid adverse effects, and delay more intensive treatments. In all other instances, antibiotic treatment of nongastric lymphomas should be regarded as investigational.

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Table 1: Sensitivity of 18-FDG PET/CT in MALT Lymphomas in Recent Reports

Table 2: Recommended Site-Specific Workup in Nongastric MALT Lymphomas

Table 3: Antibiotic-Induced Lymphoma Remission in Ocular Adnexa and Cu...

Figure: Regimens Used in the IELSG-19 Randomized Study

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