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Pathogenesis of ocular adnexal lymphoma

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The relationship between non-Hodgkin lymphoma (NHL) and bacterial infections is a relative recent issue, since the first description of *Helicobacter pylori* (Hp) infection occurrence in patients with gastric extranodal marginal zone B-cell lymphomas of MALT-type (MALT-NHL). This link is so far the best available documented example, and a causative role for Hp infection in gastric MALT development has been definitively proven. Since then, other bacteria with different lines of evidence have been proposed as potential candidates, in particular, *Borrelia burgdorferi* in cutaneous MALT-NHL and *Campylobacter jejuni* in IPSID. More recently, our group described the association between Ocular Adnexal Lymphomas (OAL) and Chlamydophila psittaci (Cp) infection. Several lines of evidence link these bacteria to OAL. In fact, Cp DNA has been detected within lymphomatous lesions through at least two independent PCR, confirmed by direct sequencing. Chlamydia has been visualized within the cytoplasm of monocytes/macrophages present within OAL (mostly MALT-NHL) through immunohistochemistry, single and double immunofluorescence, and electron microscopy; most importantly, the specific presence of Cp has been confirmed by direct sequencing of PCR products obtained from laser-capture assisted selection of immunohistochemically-selected monocytes/macrophages; this approach also confirmed the specific localization of Cp in these cells, as opposed to other microenviromental non-neoplastic cells as well as lymphomatous elements. In addition, we provided evidence that Cp is viable, infectious and circulating in patients with OAL. An extremely important implication on therapeutic level is the observed clinical response, often represented by complete clinical remission, in patients with Cp-positive OAL MALT NHL. Current lines of investigation regard the evaluation of specific immunological response to Cp inpatients with Cp-associated OAL MALT NHL and the plan for the development of an animal model for Cp infection in these lymphomas; these improvements would allow fulfilling Koch's postulates in order to ultimately define a causal role for Cp in OAL.

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Marginal zone B-cell lymphomas

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Marginal zone B-cell lymphomas comprise three separate clinicopathologic entities with variable clinical presentations, namely, the extranodal marginal zone lymphomas also known as mucosa-associated lymphatic tissue (MALT) lymphoma, the nodal marginal zone lymphoma, and the splenic marginal zone lymphoma. The extranodal type is the most common, accounting for approximately 8 percent of all cases of non-Hodgkin lymphoma.

The marginal zone B cells usually have small- to medium-size, irregular nuclei with dispersed chromatin, and inconspicuous nucleoli, resembling centrocytes and express surface immunoglobulins, pan-B antigens (CD19, CD20, and CD79a) and marginal zone-associated antigens (CD35 and CD21), but lack CD5, CD10, CD23, and cyclin D1 expression.

Recurrent karyotype abnormalities have been described. All marginal zone lymphoma types present gains of chromosomes 3 and 18 at a higher frequency in comparison with other B-cell lymphomas. Rearrangements and deletions affecting chromosome 7q are most common in primary splenic lymphoma. In extranodal marginal zone lymphoma, three disparate translocations [t(11;18)(q21;q21), t(1;14)(p22;q32), and t(14;18)(q32;q21)], despite involving different genes, appear to affect the same signalling pathway, resulting in the activation of nuclear factor-kappa B (NF-κB), a transcription factor with a central role in immunity, inflammation, and apoptosis.

These translocations are not present in splenic and nodal marginal zone lymphomas. Deletions or mutations of the tumor necrosis factor-α-induced protein 3 gene (TNFAIP3, A20, a negative regulator of the NF-κB pathway) on chromosome 6q was described in all subtypes of marginal zone lymphoma and appear to represent another pathogenetic mechanism that can lead to NF-κB activation.

The most common site of MALT lymphoma is the stomach, although primary involvement may occur at many other sites, including small intestine, lung, salivary gland, thyroid, skin, and other tissues. Most MALT lymphomas arise at sites normally devoid of lymphoid tissue, often preceded by a chronic inflammatory condition (infections or autoimmune disorders), such as Sjögren syndrome, Hashimoto thyroiditis, or, in the case of gastric MALT lymphoma, infection with *Helicobacter pylori*. Other infectious agents may have a pathogenetic role (*Borrelia burgdorferi* in cutaneous localizations, *Chlamydophila psittaci* in the ocular adnexa, and *Campylobacter jejuni* in the small intestine). Hepatitis C virus is associated with a subset of nodal and splenic marginal zone lymphomas. Appropriate antibiotic therapy eradicating *H. pylori* infection can lead to the regression of gastric MALT lymphoma in more than 75 percent of cases. Patients who do not respond to antibiotic therapy may be considered for involved-field radiotherapy.

Chemotherapy and immunotherapy with rituximab can be effective in patients with disseminated disease. Patients with splenic or nodal marginal zone lymphoma and hepatitis C virus infection may achieve a lymphoma remission after treatment of this viral infection. Once hepatitis C virus infection is ruled out, most patients with nodal or splenic lymphoma can be managed initially with a wait-and-see policy. When treatment is needed, splenectomy has been considered until now the treatment of choice for the splenic lymphomas. However, Rituximab, is also very active and may also be used. Rituximab, alone or in combination with chemotherapy should always be considered for patient who have contraindication to splenectomy. Alkylating agents and purine analogues have been reported to be active and can be used as single agent or in combination. Rituximab and chemotherapy are generally accepted as standard treatment for nodal marginal zone lymphoma. There is no clear evidence in the published literature to recommend any specific drug or regimen for the chemotherapy treatment of marginal zone lymphoma; it should, however, be mentioned that tretment with purine analogs might be associated with an increased risk of secondary myelodisplasia. The efficacy of the combination of rituximab with chlorambucil in either non-gastric or gastric antibiotic-resistant MALT lymphoma is currently being explored in a randomised study of the International Extranodal Lymphoma Study Group (IELSG) [NCT00210353]. Another potentially active class of anti-cancer agents drugs are those targeted to the inhibition the NFkB pathway, the common target of the recurrent translocations in MALT lymphoma. Indeed, the proteasome

inhibitor bortezomib has shown some activity in a recently completed phase II study of the IELSG (NCT00210327).
Aggressive anthracycline-containing regimens are not usually necessary and should be reserved for the few patients with high tumor burden and for those with diffuse large cell infiltration. These latter, indeed, should be treated according to the recommendations for diffuse large cell lymphoma.

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Primary mediastinal lymphoma

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Primary mediastinal B-cell lymphoma is now recognised as a discrete clinico-pathologic entity. Molecular analysis reveals it to be different from other types of large B-cell lymphoma, particularly in the activation of the NF-kB pathway and expression of nuclear transcription factors. Retrospective analysis of large series suggests that it may respond better to multi-agent dose-dense chemotherapy regimens than to the more commonly-used CHOP, although this has not been examined prospectively. The addition of Rituximab may mitigate such differences, and may also diminish the role of consolidation radiotherapy, which is widely used to treat residual mediastinal masses. FDG-PET scanning is increasingly used in the management of lymphoma for the evaluation of residual masses after initial therapy, although there are important questions about specificity, particularly in large B-cell lymphoma following treatment with Rituximab, where the false positive rate appears to be relatively high. This is a particularly relevant issue for PMBL, and requires prospective examination, in the hope that this may allow the de-escalation of treatment if it can be shown to yield reliable prognostic information. The relative rarity of this type of lymphoma necessitates international collaboration in clinical trials, with the prospective clinico-pathologic study, IELSG 26 already underway.

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Molecular pathology of B cell lymphoma

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B-cell derived Non-Hodgkin Lymphoma (B-NHL) represent a heterogeneous group of malignancies among which diffuse large cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and Burkitt lymphoma (BL) represent common entities for which some understanding of their pathogenesis has been acquired. With the exception of MCL, all B-NHL arise by malignant transformation of B cells within the germinal center (GC), the structure where antigen-stimulated B cells undergo rapid proliferation and