Pathogenesis and treatment of extranodal lymphomas: the fascinating model of mucosa-associated lymphoid tissue lymphoma

Extranodal lymphomas of the mucosa-associated lymphoid tissue (MALT) account for approximately 8% of all non-Hodgkin's lymphomas and comprises up to 50% of primary gastric lymphomas, however they can arise in virtually any extranodal site.[1-3] Their histologic features are similar regardless of the site of origin.[4]

MALT lymphoma usually arises in mucosal sites where lymphocytes are not normally present and where a MALT is acquired in response to either chronic infectious conditions or autoimmune processes (such as *Helicobacter pylori* gastritis, Hashimoto's thyroiditis, Sjögren's syndrome). Certain histological features suggest that the cells of MALT lymphoma may be participating in an immune response. These include the presence of scattered transformed blasts, the plasma cell differentiation, the presence of reactive T-cells, and the follicular colonization.[1-3]

In the stomach the onset of MALT lymphoma is preceded by the acquisition of MALT as a result of *H. pylori* infection and there is a compelling evidence for a pathogenetic role of this infection in gastric lymphoma supported by epidemiological, molecular and clinical findings.[5-8] The association of *H. pylori* with gastric MALT lymphoma has led to the hypothesis that the microorganism may provide the antigenic stimulus for sustaining the growth of the lymphoma in the stomach.[1-3] However, the tumor-derived immunoglobulin usually does not recognise *H. pylori* but recognises various autoantigens.[9] Sequence analysis of the immunoglobulin genes expressed by the gastric MALT lymphoma B cells shows a pattern of somatic hypermutation that suggests that the tumor cell has undergone antigen selection in germinal centers. In addition, ongoing mutations (intraclonal variation) of the immunoglobulin genes have been found in many cases.[10-12] This finding suggests that clonal expansion of tumor cells continues to be at least partially driven by a long-term antigen stimulation, which gives the B-cell clones with increased affinity a growth advantage over those that cannot respond or that respond less efficiently to the antigen.[10] Because of the persistent antigenic stimulation, the clone may become more susceptible to genetic alterations that can result in neoplastic transformation and tumor progression.

The most common nonrandom structural chromosomal aberration is the t(11;18)(q21;q21), which results in a fusion of the apoptosis inhibitor gene API2 on chromosome 11q21 with the MALT1, a *paracaspase* gene on chromosome 18q21.[13-16] The t(11;18) is present in at least one third of cases and has been found in several anatomic localizations of MALT lymphomas (lung, stomach, orbit), but not in nodal marginal zone lymphoma, splenic marginal zone lymphoma or mucosal diffuse large cell lymphoma. It is often the sole cytogenetic alteration. This latter finding suggests a major pathogenetic role for this translocation.[2] A second nonrandom translocation, much more rarely detected, the t(1;14)(p22;q32), has been shown to deregulate the expression of a survival-related gene, BCL10,[17-18] which is highly expressed in the nucleus of the neoplastic B cells of MALT lymphomas carrying this translocation. Nuclear expression of Bcl10 is also present in the MALT lymphomas carrying the t(11;18)(q21;q21). It appears that nuclear localization of Bcl10 can occur as the result of two apparently independent cytogenetic events, while Bcl10 is expressed only in the cytoplasm in MALT lymphomas without these translocations as well as in non-neoplastic germinal center and marginal zone B cells.[3,19-20]

Indeed these two seemingly disparate translocations that target BCL10 and MALT1 appear to affect the same signaling pathway, the result of which is the activation of NFkB. NfkB is a transcription factor with a central role in the activation of genes involved in immunity, inflammation and apoptosis. Under physiological conditions, Bcl10 and MALT1 form a tight bond and synergize to increase activation of NFkB. Unlike wild type MALT1, which is dependent upon an interaction with Bcl10 as a mechanism for oligomerization and auto-activation, the API2-MALT1 fusion protein may possess a mechanism for self-oligomerization resulting in constitutive activation of the NFkB pathway independent of BCL10.[21-25] Thus, in MALT lymphoma, the t(1;14) or t(11;18) translocations lead to a dramatic increase in NFkB activity. This constitutive activation of the NFkB pathway is likely critical to lymphoma antigen-independent growth and lymphoma progression.[2-3] This may not only be important for the pathogenesis of MALT lymphomas but may also have a prognostic relevance. Indeed, the frequency of both t(11;18)(q21;q21) and nuclear BCL10 expression are significantly higher in tumors that have disseminated beyond the stomach.[3] Moreover, the t(11;18)(q21;q21) seems also strong-

ly associated with failure to respond to eradication of *H. pylori*.[26]

Very recently a third nonrandom translocation has been described in MALT lymphomas, a t(14;18)(q32;q21), which is cytogenetically identical to the translocation involving BCL2 in follicular lymphoma, but involves MALT1 (which is localised about 5Mb centromeric of BCL2).[27-28] MALT1 and the immunoglobulin heavy chain gene are rearranged in this t(14;18)(q32;q21), which was detected in approximately 20% of MALT lymphomas and appears to be more common at sites other than the gastrointestinal tract and lung. In contrast to t(11;18)(q21;21) — which is commonly found as a solitary genetic abnormality in MALT lymphomas of the stomach or the lung — tumors with t(14;18)(q32;q21) may also harbor additional genetic abnormalities.[27-28] These findings seem to suggest that site-specific pathogenetic pathways may sustain the growth of MALT lymphomas at different anatomical localizations. Deregulation of MALT1 due to genomic amplification was also found in some lymphoma cell lines, thus generating the hypothesis that MALT1 can be a dominant oncogene with a role in the pathogenesis of B-cell lymphomas.[27]

Understanding the role of *H. pylori* infection in the development of gastric MALT lymphoma has led to the successful use of antibiotic treatment in the cases localized to the stomach. Hopefully a better comprehension of the additional pathogenetic events may result in further treatment improvement also at other anatomic sites.

Indeed, definite evidence indicates that eradication of *H. pylori* with antibiotics can be effectively employed as the sole initial treatment of localized gastric MALT lymphoma. Following the initial report of Wotherspoon *et al*.[28] several independent groups have confirmed the clinical efficacy of antibiotics, which can induce high rates of histologic lymphoma regression.[29-37] The lymphoma may take up to a year or more to regress. Histologic and endoscopic remission does not necessarily mean a cure. A polymerase chain reaction assay for the detection of monoclonal B cells can remain positive, without progression, in about half of histological remissions, possibly related to small monoclonal aggregates of lymphocytes.[38-39] Histologic transformation into a diffuse large cell lymphoma has also been described in some cases. Therefore we recommend that strict follow-up is carried out (we perform a breath test 2 months after treatment to document *H. pylori* eradication and repeat post-treatment endoscopy with multiple biopsies every 6 months for 2 years, then yearly to monitor the histologic regression of the lymphoma).

In addition to the t(11;18) translocation,[26] other factors that predict a poor response to antibiotics are the presence of a bulky mass, the deep infiltration of the gastric wall, the involvement of perigastric lymph nodes and a negative *H. pylori* immunostaining.[1-2] Several trials demonstrated the prognostic utility of endoscopic ultrasonography to identify locally advanced disease that is unlikely to respond to the *H. pylori* eradication therapy.[31-34]

No definite guidelines exist for the management of patients after antibiotic failure and for the subset of cases in which no evidence of *H. pylori* can be found. A choice can be made between conventional oncological modalities but there are no published randomised studies to help the decision.

Surgery has been widely and successfully used in the past.[40] The use of local treatment is evidently associated with an excellent disease control, but the precise role for surgical resection must nowadays be redefined in view of the promising results of the conservative approach.[1-2] Very encouraging results have been reported with low- to moderate-dose local radiotherapy in patients with stage I-II MALT lymphoma of the stomach, without evidence of H. pylori infection or with persistent lymphoma after antibiotics, as well as in those with localized disease at nongastric sites.[41-45]

Chemotherapy has never been adequately evaluated in gastric MALT lymphomas because it was usually not administered, or given after surgery or radiotherapy. Only few compounds have been tested specifically in MALT lymphomas. A non-randomized study reported that oral alkylatyng agents (either cyclophosphamide or chlorambucil, with a median treatment duration of one year) can result in a high rate of disease control with projected 5-year event-free and overall survival of 50% and 75%, respectively.[46] A more recent phase II study demonstrated some anti-tumor activity of the purine analog cladribine (2-CDA) with a complete remission rate of 84%. However, in this study, additional anti-*Helicobacter* treatment might have contributed to the very high remission rate in patients with gastric lymphoma since only 43% of patients with extragastric presentation achieved a remission.[47]

In the presence of disseminated or advanced disease, chemotherapy is an obvious choice. The activity of the anti-CD20 monoclonal antibody rituximab has also been shown in a phase II study (with a response rate of about 70%), and may represent an additional option for the treatment of systemic disease, but the efficacy of its combination with chemotherapy still needs to be explored in this histological type.[48] Most of the available information on the management of MALT lymphoma has been obtained from studies of gastric lymphoma. Non-gastric MALT lymphomas have been difficult to characterize because these tumors, numerous when considered together, are distributed so widely throughout the body that it is difficult to assemble adequate series of any given site. Yet, few series

have recently addressed the characteristics of non-gastric MALT lymphomas.[2] The *International Extranodal Lymphoma Study Group* (IELSG) published a retrospective survey of a large series of patients who were diagnosed as nongastric MALT lymphoma. The IELSG study confirmed the indolent course of non-gastric MALT lymphomas despite the fact that one quarter of cases presented with stage IV disease and regardless of treatment type the 5-year survival was approximately 90%.[49]

The optimal management of non-gastric MALT lymphomas has not yet been clearly established. Retrospective series included patients treated with surgery, radiotherapy and chemotherapy, alone or in combination. Whether different sites have a different natural history remains an open question.[2,49] Location can be an important factor because of organ-specific problems, which result in particular management strategies. Since optimal management of MALT lymphomas has not yet been clearly defined the treatment choice should be *patient-tailored*, taking into account the site, the stage and the clinical characteristics of the individual patient.

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