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Overview on the management of non-gastric MALT lymphomas

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ABSTRACT

Extranodal marginal zone B-cell lymphomas (EMZLs) of the mucosa-associated lymphoid tissue (MALT) are indolent lymphomas which can present at any extranodal site. The most frequent localizations (other than stomach) are ocular adnexa, salivary gland, skin, lung and thyroid. Chronic inflammation and antigenic stimulation are a potential risk for the development of MALT lymphomas. While Helicobacter Pylori (HP) is known to be associated with gastric MALT lymphoma and antibiotic therapy is effective in the setting of HP-positive, other microorganisms (such as Chlamydophila Psittaci, Campylobacter Jejiuni, Borrelia Burgdoferi) have been implicated in the pathogenesis of non-gastric MALT lymphomas. However, antibiotic therapy has not been extensively investigated for the non-gastric type, except for ocular adnexal MALT lymphoma, which could benefit from an upfront treatment with doxycycline. Surgery, radiotherapy, Rituximab alone or in combination with chemotherapy and "chemo-free" approaches, including lenalidomide, have shown efficacy in the treatment of non-gastric MALT lymphomas.

1. Introduction

Among MZL group, the extranodal of MALT type represents approximately 7–8% of all non-Hodgkin lymphomas (NHLs); median age at diagnosis is around 60 years old [1]. MALT lymphomas may virtually involve all epithelial tissues and mucosal sites, even those normally devoid of lymphoid tissue. Environment, autoimmune disorders and infectious agents may have a role in the development of EMZLs: in fact, chronic inflammatory processes in extranodal sites are accompanied by a lymphoid population which could become clonal over time. The most frequent sites include the stomach, salivary glands, skin, ocular adnexa, lung, thyroid, upper airways, small bowel, colon and breast [2]. The anatomic site and the site-specific biologic and genetic differences could have a prognostic impact on outcome, influencing treatment approaches. Non-gastric EMZLs generally show an indolent course, despite frequent relapses [3]. The management of non-gastric EMZLs is heterogeneous, including "watch and wait" approach after surgical resection or biopsy, antibiotic therapy, radiotherapy, chemotherapy with or without immunotherapy.

This review summarizes clinical and therapeutic aspects of non-gastric EMZLs, especially focusing on current evidence for the management and site-directed treatment.

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2. Biology of non-gastric MALT lymphomas

Non-gastric EMZLs may result from chronic immune stimulation by either autoimmune disorders (such as Hashimoto thyroditis, Sjögren syndrome, Chron's disease) or infectious agents such as Helicobacter Pylori (HP), Chlamydophila Psittaci (CP), Campylobacter Jejiuni (CJ), Hepatitis C virus (HCV). Chronic inflammation and antigenic stimulation are potential risk factors for the development of MALT lymphomas, since local chronic antigen-driven stimulation leads to the origin of organized lymphoid tissue, inducing clonally expanded lymphocytes. The majority of patients with autoimmune disorders present more frequently extra-gastric lymphomas (salivary glands and ocular adnexa) [4].

The pattern of somatic hypermutation of IGHV genes in nearly all cases of MALT lymphomas suggests an antigen-driven mechanism of clonal expansion [3]. Moreover, different immunogenetic profile seems to be associated with anatomical sites: IGHVH1-69 in salivary gland lymphomas; IGHVH4-34 in orbital adnexal lymphomas; IGHV3 and IGHV4 families in pulmonary lymphomas; IGHVH1-69 or IGHVH4-59 in cutaneous lymphomas [3,5].

Various microorganisms may have an etiologic link to non-gastric MALT lymphomas arising in other anatomical sites: for example, CP has been implicated in the pathogenesis of ocular adnexal MALT lymphoma [6], *Borrelia Burgdoferi* (BB) for cutaneous MALT lymphoma [7], CJ for the small bowel [8] and A*chromobacter xylosoxidans* (AX) for the lung lymphoma [9]. Moreover, HCV infection can also have a causative role in the development of MZLs, including the MALT type [10,11], showing notable geographic discrepancies [12].

3. Clinical presentation of non-gastric MALT lymphomas

Symptoms and signs are different and related to the primary anatomic site: diarrhoea, cough, appearance of skin lesions or any other symptom according to the involved organ. B-symptoms are extremely rare, and adverse biological prognostic factors such as high lactate dehydrogenase (LDH) or β2-microglobulin levels are infrequently elevated [13]. Monoclonal gammopathy occurs in about one third of MALT lymphomas [14] which might have some association with advanced stage and bone marrow involvement [15,16]. The frequency of paraproteinemia seems to be mainly dependent on the primary MALT localization [13]. MALT lymphomas generally show a low tendency to spread outside the primary origin site; conversely, extragastric MALT lymphomas show a higher tendency for multiple MALT involvement compared to gastric ones [13].

4. Diagnosis

The diagnosis should be made according to the current WHO classification by histopathological evaluation of biopsy [17,18]. The presence of lymphoepithelial lesions is not pathognomonic for MALT lymphoma, since they can also be found in reactive conditions or even in other extranodal lymphomas. Therefore, a confirmed diagnosis by an expert hematopathologist is essential for differential diagnosis in order to avoid overtreatment in case of benign conditions and rule out a potential associated large B cell lymphoma [3]. MALT lymphoma usually remains localized within the primary site for a long time: it could present as multifocal lesions within the same organ, but it is not considered as a dissemination of disease [3]. Dissemination to other sites is not frequent, reported in up to one-quarter of cases, and it is more common in non-gastric compared to gastric MALT lymphomas [3,19–21]. Because of the risk of occult disseminated disease, an accurate and extensive staging is required, independently of presentation site [18].

5. Prognostic assessment

MALT lymphoma generally shows an indolent course with frequent relapses which tend to involve the original or other mucosal sites, sparing lymph node and bone marrow [22]. Involvement of these latter has been associated with shorter overall (OS) and event-free survival (EFS) [16], showing a worse outcome compared to dissemination to multiple mucosal sites, as demonstrated by the retrospective survey of the International Extranodal Lymphoma Study Group (IELSG) [2]. Overall, non-gastric MALT lymphomas have a poorer prognosis compared to the gastric type.

To date no consistent accepted prognostic markers have been identified for non-gastric MALT lymphoma. Outcome differs for each different site, but also even within the same involved organ, reflecting the different biology and genetics of EMZL development [23]. An example of this is the MALT lymphoma of salivary glands: those that result from a history of Sjögren syndrome has a better survival compared to those without [3,24].

Retrospective studies have suggested survival could not be affected by different initial treatment strategies [2,19,20]. In this context, treatment is often chosen according to clinician's experience and patient's preference. However, un unmet need is to identify high risk patients and to improve their outcome. Therefore, a MALT lymphoma-specific index may be able to guide and modulate therapeutic strategies, according to the risk, reserving more intensive treatment to patients at increased risk of progression or death. With these purposes, Thieblemont C. et al. [25] recently proposed a MALT-lymphoma prognostic index (called MALT-IPI), generated from the dataset of the IELSG19 prospective clinical trial and validated in a large external series of more than 600 MALT lymphoma patients. The MALT-IPI with three parameters (age $\geq$ 70 years, elevated LDH level, Ann Arbor stage III or IV) is able to stratify patients in three risk groups showing significantly different EFS, progression-free survival (PFS), cause-specific (CSS) and OS.