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Clinical features and management of non-gastrointestinal non-ocular extranodal mucosa associated lymphoid tissue (ENMALT) marginal zone lymphomas

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A B S T R A C T

Extranodal mucosa associated lymphoid tissue (ENMALT) marginal zone lymphomas may arise at any site of the body. The most frequent localizations other than gastrointestinal and eye are salivary gland, skin, lung and thyroid. These lymphomas usually arise in a setting of inflammation due to a persistent infection or autoimmune diseases such as Sjogren syndrome in salivary MALT lymphomas and Hashimoto's thryroiditis in thyroid lymphomas. They affect middle-aged patients with a female predominance when lymphoma arises in certain locations. Patients often present with localised stage I or II although disseminated disease may be present at diagnosis or relapse in a third of the cases. Biopsy of the affected site is mandatory to establish the diagnosis and a full work-up staging is recommended. The clinical course is indolent and prognosis is good despite that recurrences following response to therapy are frequent. Surgery, radiotherapy and/or Rituximab based regimens are effective in these lymphomas.

Introduction

Isaacson and Wright first introduced the term of mucosa associated lymphoid tissue (MALT) lymphoma in the early 80's to describe a form of extranodal B-cell lymphoma that originates from mucosa-associated lymphoid tissue (MALT) [1]. They emphasized their slow evolution, their tendency to remain localized and their setting in an inflammatory background due to infection or autoimmunity. Extranodal MALT (ENMALT) lymphomas may arise at any anatomical localization in the body and stomach is the most frequent site; in around a third of the patients, multiple sites may be involved at presentation [2]. There is no definitive evidence of a microorganism or bacterium responsible for triggering ENMZL lymphomas other than gastrointestinal or eye. Although the role of possible triggers in the development of other ENMZL is debatable, a retrospective Italian study on 172 patients with non-gastric MALT lymphomas has shown a high prevalence of infection by hepatitis C virus (HCV). The overall prevalence of HCV was 35% and it was more common in cutaneous (43%) and salivary gland (47%) MALT lymphomas [3]. According to Ann Arbor staging most patients present with stage I and II disease. For the initial staging of patients with ENMALT lymphomas the European Society of Medical Oncology (ESMO) recommends the following: clinical history and physical examination, full blood cell count, renal and liver biochemistry, lactate dehydrogenase (LDH) and B2 microglobulin,

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serum protein immunofixation, serology for immunodeficiency virus (HIV), HCV and hepatitis B virus (HBV), computed tomography (CT) scan of the chest, abdomen and pelvis and bone marrow aspirate and trephine biopsy. In addition, particular tests are recommended for specific sites of localization such as lung, skin, salivary glands and thyroid [4]. So far, a definitive MALT lymphoma specific prognostic index has not been firmly documented. The only information available comes from the International Extranodal lymphoma Study Group (IELSG) that has devised a prognostic model based on data from 393 patients with MALT lymphomas entered into a prospective randomised clinical trial. The combination of three factors: age>70 years, raised LDH and stage>II allowed to stratify the patients in three groups: no adverse factor, 1 adverse factor and >1 adverse factor with significant differences in the 5 year progression free survival (PFS) (75%, 63% and 29%) as well as overall survival (OS) (99%, 94%, 74%) [5]. This scoring requires validation in other series of patients. The clinical course of ENMALT lymphomas is indolent, most patients respond to local therapies and despite of local or systemic recurrences prognosis is good.

In this review we will focus exclusively on the clinical manifestations, outcome and treatment of ENMALT lymphomas other than gastrointestinal and ocular as the latter are the topic of chapters x and xx (Table 1).

Primary salivary gland marginal zone lymphoma

Clinical features

This is the most common non-gastric MALT marginal zone lymphoma. It represents 5–10% of all salivary tumours and it is the most frequent lymphoma subtype of the salivary glands [6]. It is strongly associated with autoimmune diseases such as Raynaud syndrome, rheumatoid arthritis or esclerodermia and particularly with Sjogren Syndrome and sialadenitis. A retrospective analysis on 584 patients with Sjogren syndrome documented that 53 of them developed a lymphoma over a 30 year period and 31 (59%) of these lymphomas corresponded to MALT lymphomas of which 74% [23] were primarily arising on the salivary glands [7]. The median time from the diagnosis of Sjogren syndrome and the lymphoma development was 11 years. Although no microorganism has been identified in salivary gland MALT lymphoma, its association with autoimmunity strongly suggests the role of chronic antigen stimulation in the pathogenesis of this lymphoma. It affects adults with a median age of 55–60 years and has a marked female predominance with male/female ratios ranging from 1/3 to 1/4 [6,8–10]. The higher incidence of this lymphoma in females may not be unexpected as Sjogren syndrome is significantly more common in females. In addition, there is a high prevalence of HCV infection which appears to be mutually exclusive of Sjogren syndrome [10]. The parotid gland is the most commonly affected followed by the submandibular gland; involvement of sublingual or minor salivary glands is less frequent [6,9]. Patients often present with a unilateral, rarely bilateral swelling of one of the salivary glands but involvement of different salivary glands has also been documented (Fig. 1A). The majority of patients have localised (stage IE) or regional disease (stage IIE) whilst disseminated disease is rare. Contrast enhanced CT scan shows localised nodules within the gland or diffuse mild enhancement of the gland with or without the presence of cysts; calcifications are rare [11]. The value of a whole body positron emission tomography (PET)-CT scan has not been demonstrated. A complete work-up for lymphoma staging according to the ESMO guidelines is recommended to evaluate the extend of the disease. In addition, ESMO recommends an ear/nose/throat examination and ultrasound as well as investigation of serum anti-SSA and anti-SSB antibodies [4]. Cytology and/or flow cytometry on needle aspirates are not sufficient to establish the diagnosis. A tissue biopsy is mandatory to rule out other lymphomas that may manifest primarily in the salivary glands such as follicular lymphoma or diffuse large B-cell lymphoma (DLBCL).

Outcome and treatment

The clinical outcome is favourable and transformation to a DLBCL or the coexistence of a large cell lymphoma with the low-grade marginal zone lymphoma is rare [6,9,12]. A retrospective analysis on survival using the US National Cancer Institute's Surveillance Epidemiology End Results (SEER) database has documented an OS of 95% at 5 years, 85% at 10 years and 78% at 15 years and an outcome more favourable for patients with localised disease (98% at 5 years) compared with those with disseminated disease (88% at 5 years) [8]. A multicenter study of the Rare Cancer Network on 63 patients documented an OS of 81.7% and a disease specific survival (DSS) of 93% at 5 years. Prognostic factors with an adverse effect in survival were advanced stage (stage IV), residual tumour after treatment and relapse [9]. In another study on 33 patients,

Table 1
Primary extranodal mucosa associated lymphoid tissue (MALT) marginal zone lymphomas other than gastrointestinal and ocular.

Primary salivary gland ENMZL (SGALT)
Primary cutaneous ENMZL (SALT)
Primary thyroid ENMZL
Primary lung ENMZL (BALT)
Primary breast ENMZL
Others: primary central nervous system and urogenital ENMZL

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