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Epidemiology and environmental aspects of marginal zone lymphomas

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A B S T R A C T

Marginal zone lymphomas (MZLs) account for between 5% and 17% of all non-Hodgkin's lymphomas. MZLs consist of 3 different subtypes with extranodal being the most commonly reported, representing 50–70% of MZL, followed by splenic (20%) and nodal (10%). Median age at presentation varies between these lymphoma sub-types, ranging between 50 and 69 years, with an overall greater incidence noted in males compared to females.

Given the rarity of these lymphomas, epidemiologic data has been sparse, although it has been suggested the aetiology is multi-factorial including ethnicity and geographical factors. Other reported associations include autoimmune disease and infection, with *Helicobacter pylori* and *Campylobacter psittaci*, being the most commonly reported pathogens. Larger population studies are required to investigate the role of these environmental factors further as these can direct the future management of these lymphomas, through the use of more effective targeted treatments.

Introduction

Marginal zone lymphomas (MZLs) represent a group of lymphomas which originate from memory B lymphocytes normally present in a distinct anatomical location called the 'marginal zone' of the secondary lymphoid follicles [1]. Subsequently MZL cells are usually localised in spleen and mucosa-associated lymphoid tissues, and are rarely identifiable in lymph nodes. The International Lymphoma Study group separate MZL into three distinct sub-types depending on the site of involvement: (i) Extranodal MZL, (ii) Splenic MZL (with or without villous lymphocytes) and (iii) Nodal MZL (with or without monocytoid B cells) [2]. Extranodal MZL occur outside lymph nodes (eg in the gastrointestinal tract, thyroid, orbit, leptomeninges, spinal cord or skin), while mucosa-associated lymphoid tissue (MALT) lymphoma (MALToma) is the term used for extranodal MZL of MALT [3].

Although this classification suggests similarities of MZL cases within each of these sub-groups, there has been increasing evidence over the years of significant clinical, pathological and aetiological heterogeneity among MZLs occurring at different anatomical sites [4]. However, the relative rarity of these lymphomas has made it difficult to conduct epidemiological surveys and studies of pathogenesis. This review will present recent data highlighting the epidemiology and environmental factors related to these lymphomas, which can help to guide future diagnostic methods and therapies.

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Epidemiology

Incidence

MZL accounts for between 5% and 17% of all non-Hodgkin lymphomas (NHL) in adults. MALT lymphoma is the most frequent representing 50%–70% of MZL and 7%–8% of NHL [5]. These lymphomas can occur at any extranodal site and are commonly associated with chronic antigenic stimulation, either as a result of infection or autoimmune disease, with the stomach being the most common extranodal site followed by ocular/adnexal, lung, skin and salivary glands [2,6]. Splenic MZL (SMZL) accounts for 20% of all MZLs, while nodal MZL (NMZL) is the least common representing only 10% of MZLs [5,7,8].

Demographics: age and gender

In 2014, Khalil et al. published the largest population-based study analysing the incidence rates of MZL in the United States between 2001 and 2009 [9]. They noted that the incidence of extranodal MZL occurred equally among men and women. Interestingly, however, when they assessed by anatomical site, gender disparities became more apparent (Table 1). Notably, MZL incidence rates were significantly higher among males than females for the stomach, small intestine, skin and kidney, while the reverse was seen for MZL involving the salivary glands, soft tissue and thyroid [9]. MZL of the colon/rectum, lung and ocular/adnexal were the only anatomical sites to occur equally among the sexes. These gender differences were evident across all ages, with the overall median age for extranodal MZL cases being 66 years. In contrast, nodal MZL occurred at a slightly older median age (69 years) and the incidence of this MZL sub-type was significantly higher among males than females [9].

Splenic MZL is predominantly a disease of the elderly where the median age at presentation is 65 years, and nearly all patients are aged greater than 50 years [8]. There is a female predominance within this lymphoma sub-type, and the majority of patients often present with stage IV disease with bone marrow involvement [10,11].

When analysing these variables in relation to outcome, advancing age was shown to have an adverse prognostic significance in all MZL subtypes, while male sex was significant only for NMZL and MALT subtypes. The anatomical site of extranodal MZL has also been shown to have an impact on survival, with a worse prognosis associated with gastrointestinal and lung locations of origin, compared to ocular/adnexal, skin and thyroid [10].

Geography and ethnicity

There seems to be a geographical variability associated with marginal zone lymphomas, particularly the MALT sub-type (Fig. 1) [12]. For example, in 1992 Doglioni et al. compared the incidence of gastric lymphomas of MALT origin between the UK and Northeast Italy, noting a significantly higher number of cases presenting in the latter [13]. This was associated with a higher prevalence of gastritis secondary to *Helicobacter pylori* infection, which is thought to play a key role in the pathogenesis of this particular lymphoma sub-type and will be explored in more detail later.

Ocular/Adnexal lymphomas have also demonstrated geographical variability, with a large proportion of the MALT subtype occurring in Japan and Korea, which were characterised by a predominance of primary over systemic disease and young age at initial presentation [14]. Later studies suggested an association between.

Chlamydophila psittaci and ocular/adnexal lymphomas, where Ferreri et al. demonstrated a high prevalence of this infection in tumour tissue samples through polymerase chain reaction, with 80% of ocular/adnexal lymphoma samples shown to carry *C. psittaci* DNA in comparison to 0% in non-neoplastic orbital tissues [15]. Following on from this, another Korean

Table 1
Characteristics of patients with extranodal gastric MALT, extranodal MZL at other anatomical sites and Splenic MZL. NB: MALT = Mucosa-Associated Lymphoid Tissue; MZL = Marginal Zone Lymphoma; *H. pylori* = *Helicobacter pylori*; *C. psittaci* = *Chlamydophila psittaci*; *C. jejune* = *Campylobacter jejune*; *B. burgdorferi* = *Borrelia burgdorferi*; PPI = Proton Pump Inhibitor; IFN = Interferon [9–11,22].

Patient characteristics	Extranodal MZL (Gastric)	Extranodal MZL (Other anatomical sites)	Splenic MZL
Median age at presentation	66 years	66 years	65 years
Gender	Males > Females	• Small intestine; Skin: Males > Females • Ocular/Adnexal: Males = Females	Females > Males
Incidence rates (n per 1000)	3.8	0.1–1.4	1.6
Clinical features	• Asymptomatic • Gastritis • Ulceration • Weight loss	• Small intestine: Malabsorption syndrome; Diarrhoea • Ocular/Adnexal: orbital swelling; neurological compromise • Skin: generalized maculopapular rash; pruritus	• Splenomegaly • Weight loss • Infection • Fatigue • Bleeding
Associated pathogen	• *H. pylori*	• *C. psittaci*: Ocular/Adnexal • *C. jejune*: small intestine • B. burgdorferi: skin	• Hepatitis C
Recommended anti-infective therapy	• Triple eradication therapy (PPI, Amoxicillin and Clarithromycin) for 10–14 days	• *C. psittaci*: Doxycycline (3 weeks) • *C. jejune*: tetracycline or metronidazole • *B. burgdorferi*: cephalosporins or tetracyclines	• IFN-alpha ± Ribavirin

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