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Marginal zone lymphoma: Associated autoimmunity and auto-immune disorders

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A B S T R A C T

Large epidemiological studies have shown a consistent increased risk for developing lymphoma in the setting of autoimmune disorders (AID). It is known that this link appears to be stronger for some AID and certain non-Hodgkin lymphoma subtypes e.g. Sjögren's syndrome and extra-nodal marginal zone lymphoma of the salivary gland, and thyroid MALT lymphoma in a background of Hashimoto's thyroiditis.

B and T-cell hyperactivity due to chronic antigenic stimulation and the consequent presence of acquired lymphoid tissue seems to play a key role in the pathogenesis of AI-related lymphomas. Advanced age at diagnosis, prolonged disease course and disease severity are thought to increase the risk of lymphoma development in AID patients. There is increasing evidence that AI-related lymphomas constitute a different spectrum of entities indicating a different pathobiology with specific clinical features and treatment implications.

This chapter will provide a general overview on the epidemiological aspects of the NHL-AID association focussing on marginal zone lymphomas – one of the NHL subtypes mostly implicated in the synchronous/metachronous association with AID. We will review the possible biological mechanisms involved and the risk factors in each autoimmune condition related to this lymphoma.

Introduction

The incidence of non-Hodgkin lymphoma (NHL) has greatly increased over the past decades [1], but the lymphomagenesis processes are still poorly understood with few risk factors consistently identified [2,3]. The most compelling elements contributing to lymphoma development are (1) severe immune perturbation (inherited or acquired); (2) Effect of infectious agents in the context of immune dysfunction (suppression/deregulation of T-cells with consequent EBV-driven B-cell proliferation); (3) Infectious agents (*Helicobacter pylori*, Hepatitis C virus) and (4) Autoimmune disorders (AID) [4–6].

AID and NHL are very broad and heterogeneous groups of diseases. The first affects 5–9% of the world population and includes more than 80 chronic illnesses widely portrayed by immune system dysfunction and loss of tolerance to self-antigens. B-cell NHL is the 10th most common cancer worldwide accounting for approximately 3–4% of the total [7]. Both sets of diseases seem to emerge as a result of a multistep process involving the loss of important regulatory checkpoints in normal B-cell proliferation [8].

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Numerous reports show convincing specificity in the association between AID and lymphomas [2,6,8–13]. However, as both are rare diseases data are more solidly reported for certain systemic AID e.g. Sjögren syndrome (SS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Hashimoto's thyroiditis (HT), immune thrombocytopenic purpura (ITP) and autoimmune haemolytic anaemia (AIHA). These seem to be closely related to B-cell lymphomas, mainly diffuse large B-cell lymphomas (DLBCL) and marginal zone lymphomas (MZL), while gastrointestinal/cutaneous autoimmune conditions tend to be associated with the development of T-cell lymphomas [2,10,14–16].

This chapter will provide a general overview on the epidemiological aspects of the NHL-AID association and will focus on MZL – one of the B-cell NHL subtypes mostly implicated in the synchronous/metachronous association with AID. Review the main proposed mechanisms/pathways involved and the risk factors in each autoimmune condition related to this lymphoma will be included.

NHL & autoimmune diseases: main epidemiological aspects

The first report of an association between an AID and lymphomas was made in 1966 [16]. Since then several studies emerged focussing on this close relationship, possible mechanisms involved and risk magnitude [2,12]. The rarity of both diseases is a limiting factor for accurate epidemiological investigations. Additionally, most studies tend to report a higher risk of lymphoma in the first year after the diagnosis of an AID, which brings up reverse causality (paraneoplastic inflammation) as an additional potentially confounding factor. Furthermore, there is a tendency to over select patients with more advanced/aggressive disease since the data are collected mainly from hospital registries overlooking patients affected by less severe illnesses [2,8,9,12].

Despite the low incidence of AID and lymphoproliferative disorders in the general population recent studies managed to bring together significant population data in large pooled analyses [2,8,12] (Table 1). Smedby et al. [2] published the largest cohort with self-reported AID and risk of NHL by subtypes. It included 29,423 participants from 12 countries in Europe, North America and Australia. This study revealed further evidence for an increased risk of NHL development associated with a history of AID and showed that this association is stronger for some NHL subtypes and with only certain AID. It also confirmed the increased risk of NHL in SS (almost 7-fold) and the striking association with parotid gland NHL with a 250-fold increase in risk and more specifically with parotid gland MALT lymphoma (1000-fold increase in risk).

SLE was found to present close to 3-fold increase in the risk of NHL confirming previous findings in the literature [12,17,18]. Patients with SLE were at an increased risk of MZL, mainly ENMZL (MALT type) and of DLBCL [18]. Interestingly, the risk of NHL was not found to be increased in RA overall, conflicting with most reports that associate RA with an increased risk especially of DLBCL [19–21]. On the other hand, there was a moderate risk associated to RA patients treated with corticosteroids or immunosuppressants endorsing the effects of therapy as a possible aiding factor in this association [2,15].

The most recent large-scale cohort study was published in 2014 and included patients diagnosed with AID from 1964 to 2010 in Sweden. This study further corroborated previous findings linking these two entities and reported as a novel finding the strong association of NHL with polymyositis, primary biliary cirrhosis, myasthenia gravis, Behçet disease, rheumatoid fever, ulcerative colitis, polymyalgia rheumatica and chronic rheumatic heart disease [12].

Marginal zone lymphomas and autoimmune diseases

MZL accounts for approximately 8% of all NHL with 3 distinct subtypes described in the 2008 WHO classification of haematological malignancies: extranodal marginal zone of mucosa-associated lymphoid tissue (ENMZL), splenic marginal zone lymphoma (SMZL) and nodal marginal zone lymphoma (NMZL). This group of lymphomas is thought to originate from memory B-cells typically seen in a distinct micro-anatomic compartment called marginal zone of the secondary follicle [22–24].

The precise aetiology of many marginal zone lymphomas has yet to be elucidated, but is believed to involve sustained antigenic stimulation (infectious, auto-antibodies, etc) triggering a wide range of genetic and molecular abnormalities culminating in uncontrolled B-cell proliferation and neoplastic transformation [25,26]. The chronic activation and deregulation of the immune system set the crucial background not only for B-cell expansion but for local auto-antibody production i.e. a microenvironment exposed to constant antigen-driven stimulation and lacking normal regulatory mechanisms may favour the development of both diseases [27].

The strongest associations with MZL include SS, HT, SLE, RA, ITP and AIHA. The prototype of the association MZL-AID is salivary gland lymphoma (ENMZL) arising in a background of SS.

Sjögren Syndrome

The prevalence of SS in the general population is around 3% making it the third most common systemic AID. It is far more common in women with a ratio of 9:1 and median age of onset is between 40 and 60 y. It is characterised by chronic inflammation of the exocrine glands, mainly lachrymal and salivary glands with an extensive lymphoid infiltrate forming acquired lymphoid follicles, which are believed to be a risk factor for lymphoma development [28]. There is consequent destruction of the epithelium and loss of its function leading to specific symptoms e.g. xerostomia and keratoconjunctivitis [27,29,30].

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