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Lymphoproliferative Disorders in Patients with Systemic Lupus Erythematosus

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1. Introduction

Lymphoproliferative disorders can develop in the setting of many immunosupressive conditions, and they have been well established following solid organ transplantation or allogeneic bone marrow transplantation (Blaes & Morrison, 2010). The incidence varies, depending on the type of organ transplanted, the degree of immunosuppression, the number of episodes of acute rejection and the patient's immune status to Epstein-Barr virus. The 2008 World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues defines monomorphic posttransplant lymphoproliferative disorders (PTLD) as lymphoid or plasmacytic proliferations that fulfill the criteria for one of the B-cell or T/NK-cell neoplasms recognized in immunocompetent patients. However, indolent B-cell lymphomas, such as extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), are specifically excluded from this category. Autoimmune and chronic inflammatory disorders are also associated with increased risks of non-Hodgkin lymphoma (NHL). Concretely in rheumatoid arthritis and systemic lupus erythematosus (SLE), an increased risk of malignant lymphomas has been described repeatedly, whereas the evidence is less consistent for other inflammatory disorders that display autoimmune phenomena, such as psoriasis, inflammatory bowel disorders and sarcoidosis. The risk of NHL in SLE patients is estimated to be 3- to 4-fold higher (Smedby et al., 2008a). Although the incidence of PTLD is thought to be bimodal and typically related to Epstein-Barr virus in the first year after solid-organ transplantation, the relationship between Epstein-Barr virus and NHL in SLE and other autoimmune diseases is not yet well established.

Because different NHL subtypes develop at different stages of lymphocyte differentiation, the incidence of specific NHL subtypes varies based on the type of autoimmune and inflammatory disorder as well as on the type and amount of autoimmune therapy. Data regarding the histology of the NHL that develops in patients with SLE suggest that these lesions derive from lymphocytes that have been exposed to antigen (Bernatsky et al., 2005a). Lymphoma development after the antigen-exposure stages of differentiation might suggest that chronic antigenic stimulation has a role in auto immunity-related lymphomas. From the lymphoma perspective, diffuse large B-cell lymphomas seem to display the most pronounced and general association with autoimmunity and inflammation, although certain specific T-cell lymphomas have been linked to distinct autoimmune conditions (e.g.

enteropathy-type T-cell lymphoma to coeliac disease) (Smedby et al., 2008b). Studies of lymphoproliferative disorders occurring in patients with SLE have shown an increased risk of marginal zone lymphoma, predominantly of the MALT type, and of diffuse large B-cell lymphoma (DLBCL) (Bernatsky et al., 2005b).
The mechanisms responsible for the association between lymphoma and SLE remain unknown. Exposure to immunosuppressive agents has been blamed for the elevated risk of lymphoma, but cases of lymphoma in patients with no history of having received immunosuppressive drugs have also been reported. The study of Bernatsky et al looking for the incidence of cancer in patients with SLE, reports that the highest relative risk of hematological malignancy occurred in the first year after diagnosis of SLE which indicates that cancer risk is not completely explained by cumulative doses of immunosuppressive drugs (Bernatsky et al., 2005b).

2. Objective

SLE is an autoimmune disease characterized by immune mediated attacks against the body's own tissues. The aetiology of the illness is unknown. In essence the fundamental rules of tolerance are violated and autorreactive B and T cell clones cooperate, proliferate and lead the production of pathogenic auto-antibodies. The development of lymphomas and autoimmunity involves an intrincate interplay among various pathogenic factors. Besides genetic abnormalities, a variety of environmental and microbial factors, as well as abnormal immune-regulatory processes and tolerance mechanisms can lead to autoimmunity and the generation of different lymphoma subtypes. Within germinal centers, naïve B cells undergo activation, proliferation, somatic hypermutation of rearranged V regions genes, isotype switching, and subsequent positive and/or negative selection by antigen. However, the germinal center exclusion of autorreaction is defective in SLE and the existence of a defective check point in the maintenance of peripheral B cell tolerance appears to be specific to patients with SLE. This is important because, some autorreactive B cells may initiate germinal center reactions and autorreactivity arises de novo in the germinal center through somatic mutations. Moreover, in patients with active SLE a marked B cell lymphopenia that affects naïve B cells leads to a relative predominance of memory B cells with multiple somatic mutations. Somatic mutations are introduced at a high rate in the germinal center and are implicated usually in single nucleotide exchanges. However, deletions and insertions may also occur. The involvement of the hypermutation machinery in deletions and insertions seem to be the main cause of generation of several lymphoproliferative disorders in these patients.
The aim of the present review is to summarize potential harmful steps in the development of lymphocytes, tolerance checkpoints (anergy, deletion, germinal centre exclusion, receptor editing and revision, memory check points, somatic hypermutation) and immune responses that induce the acquisition and proliferation of neoplastic lymphocytes in the contex of SLE. We also review the different subtypes of lymphoproliferative disorders associated with SLE and its management.

3. Development of B cell repertoire

B cells are derived from CD34+CD19-CD10+cells. The earliest lineage-committed B cell is the pro-B cell, which is characterized by a CD19+ phenotype (Wang et al., 1998). The pro-B

cell stage is defined by immunoglobulin (Ig) heavy chain rearrangement initiated via the recombinase activating genes RAG1 and RAG2 (Blom & Spits, 2006; LeBien & Tedder, 2008). In these cells, DH to JH gene rearrangements occur, often, but not always in both IgH alleles, which are located on chromosome 14 in humans (Cobett, et al., 1997; Ravetch, et al., 1981). In the next, step VH gene segment is rearranged to a DHJH (Cook & Tomlinson, 1995). If the first VH/DH/JH rearrangement is nonproductive, the B cell precursor has a second chance to generate a productive IgH gene rearrangement by using the second IgH allele. When heavy chain gene rearrangement is successful, then Ig class is expressed on the cell surface in association with μ heavy chain and the signal transducing molecules CD79a/b to form the pre-B cell receptor. This is accompanied by loss of CD34 and TdT expression and marks the transition to the pre-B-cell stage of development. Pre-B cells discontinue further IgH gene rearrangements, divide several times, and then initiate light chain gene rearrangements (Rajewsky, 1996). Internalization of the pre-B cell receptor and rearrangement of the light chains occur next, defaulting to the kappa gene. Lambda gene rearrangement and expression generally occur only if kappa gene rearrangement is unsuccessful. Successful light chain rearrangement induces the expression of sIgM composed by IgH and either κ or λ light chains. Failure to rearrange either the heavy or light chains induces apoptosis. If immature B cells react with self antigens, mechanisms of negative selection can induce apoptosis, receptor edition or anergy (LeBien, 2000).
Secondary B cell development is characterized by the migration of immature B cells to the spleen, where they differentiate into mature naïve B cells, now characterized by surface IgD in addition to IgM, CD21 and CD22, as well as a loss of CD10. Positive selection subsequently commences, with cells failing to react succumbing to cell death. Following this process, mature cells migrate to secondary lymphoid tissue whereupon they can further differentiate to plasma cells or establish a germinal center when they recognize an antigen (DiLillo, et al., 2008).

4. Germinal centre reaction

Within germinal centers, activated B cells undergo the process of somatic hypermutation. Centrally proliferating B cells are referred to as centroblasts, which divide to form smaller centrocytes that migrate to periphery of the germinal center. Centroblasts first remove the surface immunoglobulin, then undergo several rounds of division and then re-express mutated immunoglobulin receptors as centrocytes. Centrocytes expressing BCR with increased affinity will be able to appropriately interact with germinal centre T cells and follicular dendritic cells and be positively selected. Surviving centrocytes subsequently depend on CD40-based interactions with T cells to facilitate differentiation into long lived plasma cells and memory B cells (MacLennan, 1994).

5. Tolerance B cell check points

B cell precursors undergo immunoglobulin gene rearrangements to generate a population of mature B cells bearing surface immunoglobulin (sIg) with a range of specificities. Random V/D/J gene assembly generates many self-reactive B-cell receptors (BCR). To avoid autoimmunity, B cells displaying self-reactive immunoglobulin are deleted centrally in the bone marrow and at subsequent check points in the periphery (Yurasov et al., 2005a) **(Fig. 1).** Self reactivity arising during V/D/J recombination could be corrected by receptor

editing, clonal deletion and anergy. In normal subjects the number of self reactive B cells decreases significantly as B cells progress though normal development. Nevertheless, central tolerance appears not enough to control self-reactive B cells in SLE patients. Significantly, the frequency of autoreactive antibodies declines from 75% in the bone marrow to 20% in the circulating naïve compartment (Yurasov et al., 2005b). However, several of these check points appear deficient in SLE patients (Yurasov S, et al., 2005b). In patients with SLE, mature naïve B cell compartment comprises 40% to 50% of autoreactive clones. This fact indicates that SLE patients have defects in censoring self reactive B cells early in development even in SLE patients in remission (Yurasov et al., 2006). Because signaling through the BCR is a primary mechanism for triggering deletion, anergy, or receptor edition abnormal BCR signaling is likely to play a role in breakdown tolerance (Kamradt & Mitchinson, 2001). Interestingly, circulating mature B cells from SLE patients demonstrate a heightened response to BCR crosslinking. Even more SLE patients have low levels of intracellular tyrosine kinase Lyn that can diminish BCR signaling through phosphorylation of inhibitory receptor such CD22 and FCRIIb (Flores-Borja, et al., 2005).

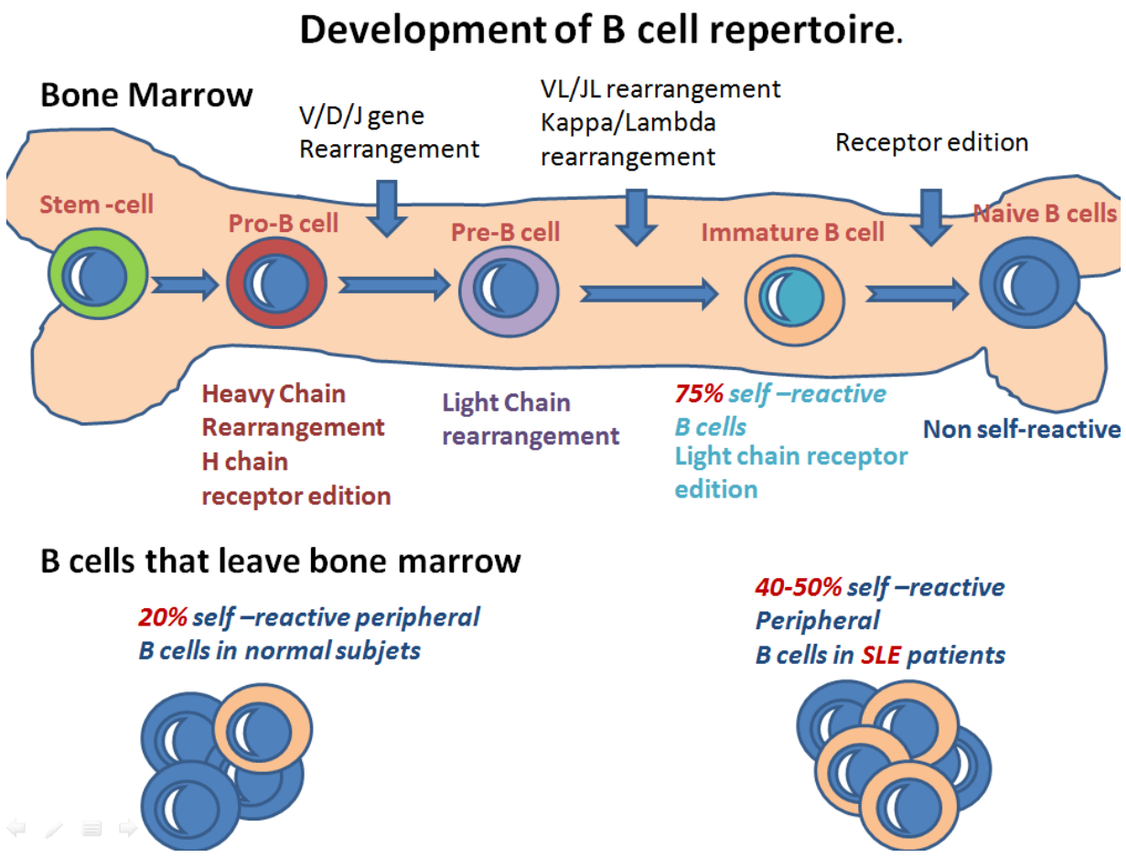

Fig. 1. Defective central tolerance in development of B cell repertoire in SLE.
Patients with SLE have increased numbers of self-reactive B cells. We speculate that defects in complement could contribute to this phenomena. We propose that although receptor edition works well in SLE patients if immature B cells cannot test their BCR with self-antigens it is possible that they mature to naive self-reactive B cells and leave bone marrow and migrate to secondary lymphoid organs.

During central tolerance in bone marrow, receptor editing appears to be the preferred mechanism to establish early B cell self-tolerance (Tiegs et al., 1993; Gay et al., 1993; Halverson et al., 2004). Self reactive BCR can apparently be purged by receptor editing, a mechanism through which antigen binding in bone marrow induces continued rearrangement of immunoglobulin gene segments; this process results in a change in the specificity of a previously autorreactive BCR (Melamed, et al., 1997). Interestingly, although receptor editing works well in patients with SLE, it is possible that it could be insufficient to avoid the development of self-reactive B cells (Dörner, et al., 1999) and subsequent emigration to lymph nodes or spleen. However, the basic question as to whether receptor editing is increased or decreased during lupus requires further study (Luning-Prak et al., 2011). Interestingly, receptor edition can contribute to generating lymphoproliferative disorders (Chiorazzi, et al., 2005; Wang, et al., 2008; García-Muñoz et al., 2009; Hatzidimitriou, et al., 2009).

There are also data showing that regulatory checkpoints exist for B cells in the periphery in germinal center and in the late stages of B cell differentiation to memory or long-lived plasma cells (Cappione A 3rd et al., 2005; William et al., 2006)

Germinal center exclusion of self reactive B cells (9G4 B cells) that express self-reactive antibodies encoded by the IGVH 4-34 gene is an important peripheral checkpoint to avoid interaction of autoreactive B cells with T cells and subsequent generation of autoantibodies. For this reason, 9G4 B cells are present only in 5-10% of the naïve B cell in healthy donors as well as in the IgM memory compartment and these cells participate in less than 1 % of germinal centers of tonsil biopsies. However, germinal center exclusion is defective in SLE patients and evaluation of lymphoid tissue from tonsillar biopsies and spleens reveals that the frequency of germinal center 9G4 B cells in this population is 15% to 20% (Cappione A 3rd et al., 2005). The expression of *IGHV4-34* heavy chains in antibodies is synonymous of autoreactivity against N-acatyllactosamine (NAL) determinants expressed by the iI blood group antigen and other self glycoproteins including CD45 (Silberstein et al., 1991; Pugh-Bernard et al., 2001. Cappione AJ, et al., 2004). Importantly, antibodies against anti-B cell CD45 and a significant fraction of anti-native double stranded DNA (anti-DNA) use *VH4-34* heavy chain and are detected in patients with SLE (Pugh-Bernard et al., 2001) and represent about 10-45% of total serum IgG in this patients. However, *IGHV4-34* antibodies are virtually undetectable in healthy sera because *IGHV4-34* cells are censored at multiple check points during B cell development to avoid autoimmunity (Pugh-Bernard et al., 2001).

Preventing the generation of self-reactive memory B cells or long lived plasma cells is another important peripheral checkpoint to stay away from autoimmunity. B cells expressing self reactive antibodies and broadly bacterially reactive antibodies are continuously removed from the repertoire in the transition from naïve to IgM memory B cells and selection against self reactive antibodies is implemented before the onset of somatic hypermutation (Tsuiji et al., 2006). This checkpoint is supported by data showing a decrease in frequency of autoreactive IgM+ memory B cells to 2% from 20% in the mature naive B cell population in healthy individuals (Tsuiji et al., 2006). Even when dysfunction of this checkpoint in SLE is not yet determined, the fact that memory B cells with IGHV4-34 have been detected in patients with SLE (Odendhal et al., 2000) provides indirect support for some deficiency in this checkpoint.

The presence of extensive somatic mutations seen in autoantibodies derived from SLE patients strongly supports the notion of germinal center maturation of pathogenic, self reactive B cells and support defects at several check points.

6. Lymphomagenesis in SLE

Chronic immune stimulation by self antigens and infectious agents together with genetic variations of TNF-α and IL-10 expression have been suggested to explain lymphomagenesis in SLE (Dias et al., 2011; Bertansky et al., 2009). However, the mechanism underlying the association between SLE and lymphoma remains unexplained. Lymphoproliferative neoplasm could arise from precursor B cells development and in pre-germinal center, germinal center or post germinal center differentiation**.** During development and maturation of B cells, they can acquire mutations, deletions or translocations that direct the generation of lymphomas. Rearrangements of V/D/J genes, receptor editing, somatic hypermutation, and class switching are responsible for DNA strand breaks that lead chromosomal aberrations that are in part responsible for lymphomagenesis (Küppers et al.,1999). A reasonable hypothesis is that the accumulation of clonally expanded self-reactive B cells that recognize self-antigens in the lymph nodes may predispose these B cells to DNA breaks, facilitating tumorigenesis (Xu et al., 2001). In support of this viewpoint, lymph nodes of patients with SLE have extensive necrosis with apoptotic debris (self antigens), with numerous plasma cells within germinal centers. On the one hand, these histopathologic features suggest that in lymph nodes it is possible that self reactive B cells can suffer somatic hypermutation, class switching and receptor edition/revision induced by apoptotic bodies increasing the risk of suffering DNA breaks and translocations. On the other hand, B cells with self-reactive specificity are likely to present self peptides to autoreactive T cells (Chan et al., 1999). In this context, T cells contribute to rescuing and supporting the maturation of self-reactive B cells to plasmatic B cells or memory B cells. Significantly, during this process it is possible that some cells acquire translocations and DNA alterations that contribute to development of lymphoma. In addition, in combination with recognition of self antigens in lymph nodes, self reactive B cells also recognize self antigens in bone marrow and acquire translocations or genetic alterations during B cell development. Autoreactive B cells may suffer receptor editing and V/D/J gene recombination in bone marrow. Recent evidence shows that L chain receptor editing occurs not only in bone marrow with a pre-B/immature B cell phenotype but also in immature/transitional splenic B cells. Nevertheless, editing at the H chain locus appears to occur exclusively in bone marrow cells with pro-B phenotype (Nakajima et al., 2009). Receptor editing appears to work well in patients with SLE. However, a feature of SLE is an increased production of self-reactive B cells that migrate from bone marrow to secondary lymphoid organs. This implies that other mechanisms or defects are necessary to maintain central tolerance in bone marrow. Significantly, defects in elimination of apoptotic cells and defects in complement components have been proposed to explain impaired central tolerance in bone marrow (Carrol, 2004). Interestingly, this model suggest that autoantigens from apoptotic cells are presented to immature B cells by immune complexes containing C1q, C4b and IgM in bone marrow. In support of this model Tripodo, et al., discovered C1q production by bone marrow stromal cells, an important part of complement that is involved in clearance of apoptotic cells (Tripodo et al., 2007).

We speculate that the impaired elimination of apoptotic cells in bone marrow and lymph nodes could contribute to persistent autoantigenic overstimulation leading to refractoriness of autoimmunity and increased risk of chromosomal alterations and lymphomas **(Fig. 2).**

7. Hypothetical immunologic mechanisms implicated in generation of lymphomas in patients with SLE (Fig 2)

Deficiency in self-antigen retention induced by defects in complement components or impaired clearance of apoptotic B cells will possibly lead to an increased release of self-reactive B cells from bone marrow to periphery. On the one hand, defects in the complement system might produce deficient presentation of antigens in bone marrow and diminish the

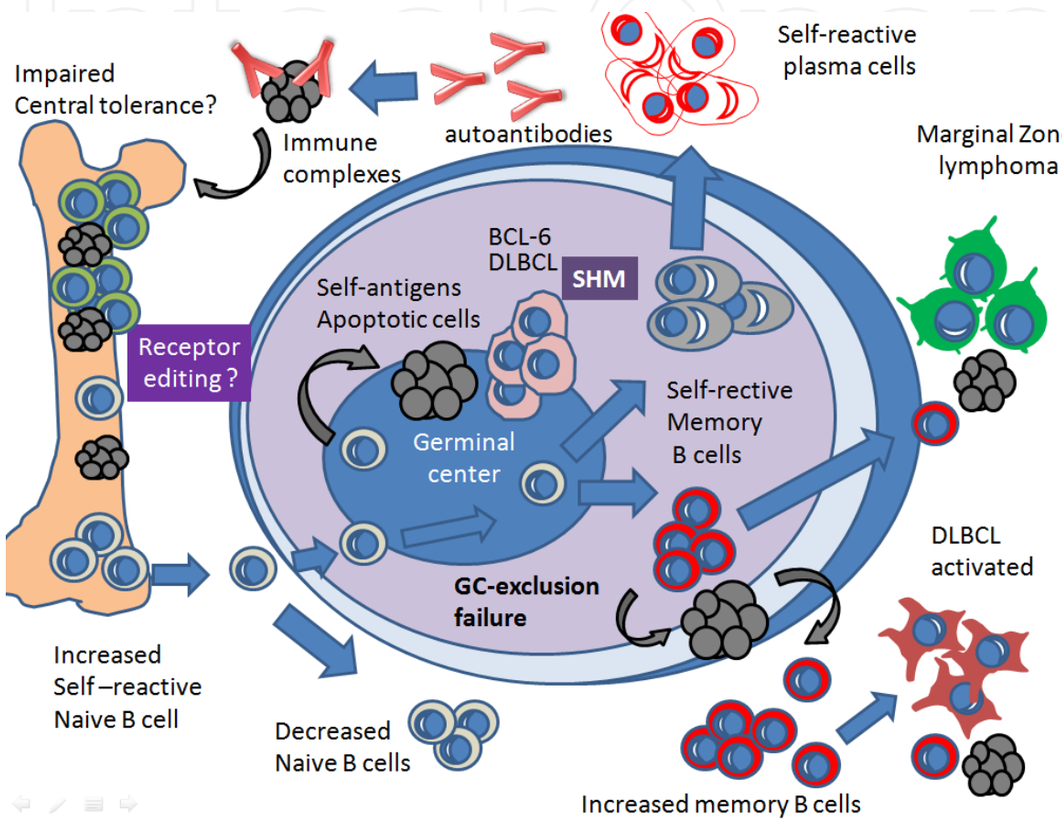

Fig. 2. Lymphoma development in patients with SLE.
Impaired clearance of apoptotic cells in concert with insufficiency in germinal centre exclusion of self-reactive B cells might induce constant stimulus of these B cells. Naive self-reactive B cells recognize auto-antigens and become memory B cells and plasma cells that produce auto antibodies. Continuous activation of memory B cells raises the risk of transformation into DLBC (activated subtype) and marginal zone B cell lymphomas. SLE activity and decrease in complement components could contribute to a defect in both central tolerance and clearance of apoptotic cells.

protection of receptor edition mechanism. On the other hand, impaired clearance of apoptotic cells in bone marrow induces increased stimulation of immature self-reactive B cells that could suffer increased receptor edition in bone marrow or avoid tolerance. Importantly, receptor edition also can produce polyreactive B cells or a simple change in recognition from an auto-antigen for others that recognize the new edited BCR in an immature B cell. These two mechanisms could be implicated in generation of mantle cell lymphoma (García-Muñoz et al.,2009) or chronic lymphocytic leukemia with unmutated

IGHV genes (Hadzidimitriou et al. 2009). Increased variable region gene recombination and heavy or light chain receptor edition in self-reactive B cells of patients with SLE in bone marrow could in theory contribute to lymphomagenesis. Self reactive B cells that leave bone marrow, enter germinal centres because germinal center exclusion is defective in patients with SLE. Within germinal centers, self-reactive B cells recognize self-antigens from apoptotic cells and suffer somatic hypermutation, receptor revision, and class switch-recombination. Some of this self-reactive B cells can be converted into memory B cells or plasmatic B cells that produce autoantibodies and return to the sites of antigen stimulation. During this process self-reactive B cells can acquire translocations, deletions or mutations that make a subtype of lymphoma. Germinal center derived lymphomas are derived by transformation from either variable region gene recombination (BCL-2-IgH) in follicular lymphoma, somatic hypermutation (BCL-6) in diffuse large B cell lymphoma, or class switching in c-myc sporadic Burkitt´s lymphoma (Küppers et al.,1999). **(Fig. 3)** Post-germinal center B cell lymphomas are marginal zone lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia and plasmacytoma and are derived from memory B cells and plasma cells (Jaffe ES et al., 2008) **(Fig. 3)**. Interestingly, post-germinal center derived lymphomas are commonly associated with antigen stimulation by self-antigens or infectious agents (Suarez et al., 2006). In a study of 24 patients with malignant lymphoma and rheumatic diseases including SLE the majority of diffuse large B cell lymphomas exhibited activated phenotype and EBV associated lymphoma comprised only a small fraction (Kojima et al., 2006).

8. Lymphoma and SLE; Therapy

8.1 Lymphoma subtypes in SLE patients

Patients with SLE have an increased risk to develop lymphomas specially diffuse large B cell lymphoma (Löfstrom et al., 2007; Bernatsky et al., 2005; Bernatsky et al., 2006: King & Costenbader, 2007; Lin et al., 2003; Rossi et al., 2011; Biasiotta et al., 2010; Simon et al., 2007) and marginal zone lymphomas (Maeda et al., 2008; Gonzalez et al., 2009; Tektonidou, 2010) however, several subtypes have been reported.

8.2 Highly aggressive B cell lymphomas

Burkitt lymphoma is a highly aggressive B cell malignancy typically characterized by a rapid proliferation rate and the translocation of c-myc [t(8;14), t(8;22) or t(2;8)]. The typical immunophenotype of Burkitt lymphoma is sIg+, CD10+,CD19+, CD20+, TdT -, Ki-67+ (90-100% of cells), bcl-2 -, bcl-6 + (Ferry, 2006) Patients with Burkitt lymphoma often present with symptoms of a rapidly enlarging abdominal mass and B symptoms. Bone marrow involvement is found in up to 70% of patients, and leptomaningeal spread is common (Perkins et al., 2008). Data from patients with SLE and Burkitt lymphoma are scarce, however: some case reports or case series include patients with SLE that develop this rare malignancy (Posner et al., 1990; Bernatsky et al., 2005). The treatment of Burkitt lymphoma is based on intensive chemotherapy. Some highly effective regimens include CODOX-M (cyclophosmphamide, vincristine, doxorubicin, high dose methotrexate) alternating with IVAC (ifosfamide, etoposide and high-dose cytarabine)(Magrath et al., 1996.) or Hyper-CVAD (hyper fractioned cyclophosphamie, vincristine, doxorubicin, dexametasona) (Thomas et al., 2006) both plus Rituximab.

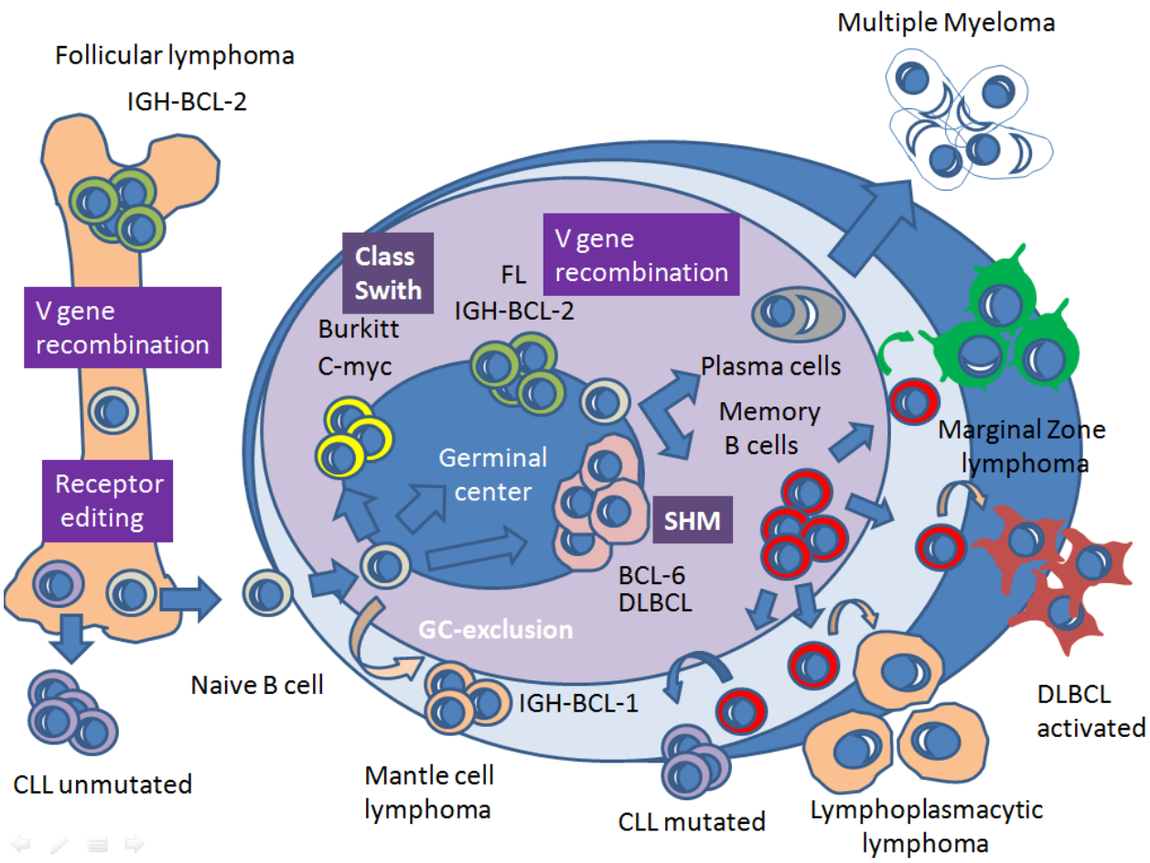

Fig. 3. Origin of Non Hodgkin B cell lymphomas and mechanisms related to their development

During development B cells can acquire translocations, deletions or mutations that make a subtype of lymphoma. Pre-germinal center derived lymphomas are CLL unmutated and mantle cell lymphoma and some follicular lymphomas. Germinal center derived lymphomas are derived by transformation from either variable region gene recombination (BCL-2-IgH) in follicular lymphoma, somatic hypermutation (BCL-6) in diffuse large B cell lymphoma, or class switching in c-myc sporadic Burkitt´s lymphoma. Post-germinal center B cell lymphomas are marginal zone lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia and plasmacytoma and are derived from memory B cells and plasma cells.

8.3 CD5+ B cell lymphomas

CD5+ B cell lymphomas comprises Mantle Cell lymphoma (MCL) and Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL). Sometimes patients with SLE develop this subtypes of lymphomas (Munzert et al., 1997; Lugassy et al., 1992).

8.3.1 Mantle cell lymphoma

MCL can have a varied initial presentation and clinical course. Most patients are diagnosed when they already present an advanced stage disease. Common sites of involvement include lymph nodes, spleen, bone marrow gastrointestinal tract and the lymphoid tissue of

Waldeyer´s ring. MCL is characterized by the translocation t(11;14)(q13;q32) which leads to the overexpression of cyclin D1. Mutation analysis of the rearranged immunoglobulin´s heavy chain variable region (IGHV) genes shows a major subset with unmutated IGHV and a smaller subset displaying mutated IGHV genes (Swerdlow et al., 2008). The treatment of MCL is by intensive chemotherapy with R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin and Dexametasone) alternating with R-MA (Rituximab plus high-dose methotrexate and cytarabine) (Romaguera et al., 2005) followed by consolidation with myeloablative chemotherapy with autologous stem cell transplant in selected patients in first complete remission (Dreyling et al., 2005). However, other less intensive treatment options include R-CHOP (Howard OM, et al., 2002), Bendamustine (Rummel et al., 2005) and Bortezomib (Fisher et al., 2006).

8.3.2 Chronic lymphocytic leukemia/small lymphocytic lymphoma

CLL/SLL is an indolent B cell malignancy, which is believed to originate in memory antigen-experienced B-cells. Tumors usually involve not only the peripheral blood and bone marrow but also lymph nodes, spleen and liver. The diagnosis of SLL is typically applied if the presentations predominantly nodal and the diagnosis of CLL is made when the principal involvement is bone marrow and blood. CLL remains an incurable tumor and clinical features have very variable presentation, course, and outcome. Risk markers and stratification in CLL can be divided in two different entities. High risk phenotype usually expresses unmutated immunoglobulin heavy variable genes (Hamblin et al.,1999) CD38 surface marker (Damle et al.,1999), zeta-associated protein 70 (ZAP-70)(Crespo et al., 2003) and chromosomal aberrations as 17p (the site of the tumor protein p53) or 11q23 deletions (the site of the ataxia telangiectasia mutated ATM)(Dörner et al., 2000). Low risk phenotype habitually expresses mutated IGVH, lack CD38 and ZAP-70 and has a normal karyotype or 13q14 deletion. Additional adverse predictive factors include advanced Rai (Rai et al., 1975) and Binet clinical staging (Binet et al., 1981), usage of VH3-21 independent of VH mutation status (Throsélius et al., 2006) and short lymphocyte doubling time (Montserrat et al., 1986). There is no evidence that early treatment of asymptomatic patients benefits them. The current advice is that patients who are asymptomatic should be managed by watchful waiting until they present symptoms or International Workshop on Chronic Lymphocytic Leukemia indications for treatment are met (Hallek et al., 1996). First line treatment includes chlorambucil, fludarabine, Bendamustine or fludarabine plus cyclophosphamide, either alone or in combination with Rituximab (Hallek, 2010) . The choice of therapy is influenced by co-morbidities and status performance of patients.

8.4 Follicular lymphoma

Coexistence of follicular lymphoma (FL) and SLE has previously been reported (Löftröm et al., 2007; Suvajdzic et al., 2011). FL is a neoplasm composed of follicle center (germinal center) B cells (typically both centrocytes and centroblast) which usually has at least a partial follicular pattern. FL is genetically characterized by the translocation t(14;18)(q32;q21) and BCL-2 rearrangements.

FL involves lymph nodes, spleen, peripheral blood and Waldeyer ring. FL may occasionally be primary in extranodal sites. Most patients have widespread disease at diagnosis, including peripheral and central (abdominal and thoracic) lymphadenopathy and

splenomegaly. Despite widespread disease, patients are usually otherwise asymptomatic (Harris et al., 2008). Multiple treatment options exist for patients with newly diagnosed FL, ranging from observation only to a variety of combined chemoimmunterapy regimens (Bendandi, 2008; Cheson et al., 2011).

8.5 Diffuse large B-cell lymphomas

Studies specifically investigating lymphoma and SLE have noted that DLBCL are the most common histology when lymphoma occurs in these patients (Gayed et al., 2009). This aggressive subtype makes up 30% of lymphomas in the general population, but in SLE groups, it accounts for between 38% and 53% of lymphomas (Smedby et al., 2006; Bernatsky et al., 2005a). Although DLBCL can occur at any age, it is, in general, a disease of middle-aged and older adults. Unlike indolent Iymphomas that are almost always widely disseminated at diagnosis, DLBCL present as early-stage disease in approximately 30% of cases. Clinically, presentation with a rapidly enlarging symptomatic mass is very common, with B symptoms (fever, unexplained weight loss > 10% over 6 month interval, or night sweats) in one-third of the cases. Extranodal disease in DLBCL can be present in up to 40% of cases; common sites include the gastrointestinal tract, bone, and CNS.

With the application of microarray techniques, three subgroups of DLBCL with distinctive gene-expression profiles have been identified on the basis of hierarchical clustering: germinal-center B-cell-like, activated B-cell-like, and type 3 DLBCL (Rosenwald et al., 2002). A number of recent studies have attempted to define germinal-center and non-germinal center phenotypes in DLBCL, using immunohistochemistry markers such as bcl-6, CD10 for germinal center and MUM1, IRF4 and CD38 for post-germinal center. In general, a germinal center immunophenotype, particularly including Bcl-6 expression, has been associated with a better prognosis (Lossos et al., 2004).

8.5.1 Therapy

For nearly 20 years anthracycline-based chemotherapy has been the mainstay of treatment, because of its proven efficacy, the CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) regimen being the gold standard of therapy for aggressive NHL. Application of this treatment resulted in curing 30% of patients with DLBCL. The standard chemotherapy regimen has changed little in the past three decades, but a variety of strategies have been tested to identify regimens that might increase the disease-free survival rate for aggressive lymphomas. Monoclonal-antibody therapy has been added to the armamentarium and represents an advance in therapeutic options. The anti-CD20 monoclonal antibody rituximab has been combined with the chemotherapy regimen of CHOP in an attempt to improve outcomes; increased remission and survival have been reported with no additional toxicity (Friedberg JW & Fisher RI., 2006).

8.5.2 Limited stages

Classically, external beam radiation therapy was employed as a single modality in the therapy for localized DLBCL, with prolonged disease-free survival of approximately 35%. However with the success of anthracycline based chemotherapy in treating advanced stage DLBCL, the combination of CHOP with radiotherapy emerged as the strategy of choice for treating localized DLBCL (Miller et al., 1998). Several cooperative groups have developed clinical assays in order to elucidate which is the best chemotherapy regimen to

combine with radiotherapy in these patients. The SWOG group showed advantage for progression-free survival (PFS) and overall survival (OS) in patients receiving 3 cycles of CHOP followed by involved field radiation (40-50 Gy) versus those who received 8 cycles of CHOP alone (Miller et al., 2001). Results worsened with the acquisition risk factors. Similar results in advantage for disease-free survival but not for OS were published for the ECOG group of patients receiving 8 cycles of CHOP followed by radiotherapy consolidation (Horning et al., 2004). The GELA group has also addressed this issue in several clinical trials suggesting no advantage for patients receiving radiotherapy and a short course of chemotherapy compared to those receiving standard chemotherapy (Reyes et al., 2005). Recent reports about the addition of rituximab showed advantages in PFS and OS to the historical experience without rituximab therapy (Persky, 2008). Nowadays, R-CHOP rather than CHOP would be recommended for these patients. However, no data exist to support the use of three courses of R-CHOP chemotherapy with radiation consolidation for limited stage disease. In view of the activity of R-CHOP in more advanced disease and in spite of the lack of a randomized trial to demonstrate its superiority in the setting of three rather than six courses, most clinicians prefer to use R-CHOP rather than CHOP.

8.5.3 Advanced stages

After rituximab was found to have activity in B cell NHL, the GELA group conducted a randomized trial to compare CHOP alone vs. R-CHOP in elderly patients (60 to 80 years old) with DLBCL. Chemotherapy courses were given every 3 weeks. Patients were randomly assigned to receive either eight cycles of CHOP every 21 days or eight cycles of R-CHOP. They concluded that the addition of rituximab to the CHOP regimen increases the complete remission rate and prolongs event-free and OS in this group of patients, without a clinically significant increase in toxicity (Coiffier et al., 2002). Once the GELA group proved the superiority of R-CHOP-21, Pfreundschuh et al. decided to conduct the trial known as MabThera International Trial (MInT) to evaluate CHOP-21, R-CHOP-21, CHOEP-21 and R-CHOEP-21 in patients aged 18–60 years with favorable prognosis (0-1 adverse risk factors according to age-adjusted International Prognostic Index). They concluded that rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis DLBCL (Pfreundschuh et al., 2006). The addition of rituximab to CHOP seems to eliminate the advantage of CHOEP over CHOP. This study also proved for the first time that rituximab when added to CHOP or CHOEP is effective in patients younger than 60 with favorable IPI. Following these results, the RICOVER-60 trial was developed to asses whether six courses were as effective as eight cycles and whether the addition of rituximab to CHOP-14 could improve outcome of patients treated with the CHOP-14 regimen. Conclusions of this study were that six cycles of R-CHOP-14 significantly improved event-free, PFS and OS over six cycles of CHOP-14 treatment. The other major conclusion of this study was that six cycles of chemotherapy with or without rituximab was as effective as eight cycles (Pfreundschuh et al., 2008). The RICOVER trial has been criticized for not including an arm with R-CHOP-21. As CHOP-14 is superior to CHOP-21, and R-CHOP-14 is superior to CHOP-14, it is logical to think that R-CHOP-14 should also be superior to R-CHOP-21. However, many investigators refuse to accept that R-CHOP-14 is the gold standard for treatment of DLCL until a randomized study with a control arm of R-CHOP-21 is carried out (Cabanillas, 2010).

8.5.4 Special considerations in DBCL and SLE therapy

When treatment options for DLBCL in the context of SLE are considered, special caution should be taken in order to manage the prognostic factors related to the tumor (e.g. histology, genetics and stage) as well as patient-specific factors (e.g. age, comorbidity, and general health status), because many lymphoma treatments are gruelling, particularly for old or frail individuals (Sehn et al., 2007). Patients with SLE often have both the hematopoietic reserve reduced and the immune function altered due to immunossupressive drugs thus being therapy-related infections a major problem in these patients. In this particular subset of patients with SLE and DLBCL, aggressive surveillance, prophylaxis, and treatment of infections are essential to prevent morbidity and mortality. Granulocyte colony stimulating factors (G-CSF) are largely used in the treatment of hematologic disorders to improve the myelosuppression indirectly induced by the chemotherapy regimen. G-CSF reduces the depth and duration of neutropenia in lymphoma patients and thus allows the design of more dose intense chemotherapy regimens which were shown to improve outcome particularly in patients with DLBCL (Lionne-Huyghe et al., 2006).

Besides, many SLE patients have deteriorated the glomerular filtration rate and a delay in drug excretion, needing the adjust of cytotoxic drugs to creatinine clearance. For this reason, management of tumor lysis syndrome in these patients can also be problematic. In order to avoid these problems, patients with SLE and renal impairment should be handled following chemotherapy schedules with a prephase treatment, in the same way on which are treated very aggressive lymphomas and elderly patients (Pfreundschuh, 2004, 2010). Sufficient fluid intake must be ensured, and appropriate supportive measures must be provided, including frequent electrolyte controls and allopurinol or even rasburicase administration to prevent hyperuricemia and tumor lysis syndrome.

SLE is associated with high cardiovascular morbidity and mortality. Clinically silent pulmonary hypertension, right ventricular dysfunction and myocardial perfusion defects usually asymptomatic are common in SLE patients (Plazak et al., 2011). A careful evaluation by means of echocardiography preferably with tissue doppler study and lung function test should be part of the pre-treatment studies to prevent anthracycline toxicity (Buss et al., 2010). Recommendations for therapy should be similar to elderly DLBCL patients. R-CHOP should be administered with close functional monitoring or even excluded if they present with cardiac-failure New York Heart Association > 2 and/or an ejection fraction < 50% or have a forced expiratory volume in 1 second (FeV1) level < 50% or a diffusion capacity < 50%. If cardiomyopathy is the only limiting condition, doxorubicin should be replaced by liposomal doxorubicin under close monitoring of the cardiac function. (Pfreundschuh, 2010; Zaja et al., 2006)

8.6 Marginal zone lymphoma

The marginal zone of lymphoid tissues is a unique B-cell compartment that contains B cells with a high surface density of IgM and complement receptor 2, and which exhibits a rapid activation and immunoglobulin secretion in response to blood-borne T-independent (Weill et al., 2009). This micro-anatomic compartment is well developed in lymphoid organs such as spleen, mesenteric lymph nodes and mucosa-associated lymphoid tissue or MALT where circulation of antigens occurs. Marginal B-cell lymphomas (MZL) are a well categorized group of indolent B-cell NHL that arise from the marginal zone of lymphoid tissues. The WHO-classification of tumors of hematopoietic and lymphoid tissues distinguish three different MZL types: extranodal, splenic and nodal (Isaacson et al., 2008).

Despite its common cell origin these three subtypes display differences in their frequency and clinical presentation and features according to the organ where the lymphoma arises. Extranodal MZL, also known as low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (or MALT lymphoma) is the most common MZL subtype accounting for approximately 70% of all MZLs (Isaacson et al., 2004, 2008). These subtypes can arise at virtually any extranodal site and are commonly associated with chronic antigenic stimulation, either as a result of infection (eg, Helicobacter pylori in the stomach) or autoimmune disease. Splenic MZL accounts for approximately 20% of all MZLs. (Matutes et al., 2008). Patients typically present with an enlarged spleen, involvement of abdominal lymph nodes, and bone marrow disease. Liver and leukemic involvement are not infrequent. Nodal MZL is the least common, representing approximately 10% of all MZLs. (Arcaini et al., 2009). Patients with nodal MZL, by definition, have lymph node-based disease without involvement of the spleen or extranodal sites.

8.6.1 Therapy

Therapy of patients with MZL and SLE should not differ from that administered to patients without the latter condition. While some patients obtain cure of MALT lymphoma with an antibiotic treatment of the infectious causing agent, as occurs in the case of the infections for *H. pylori*, other patients require treatment with radio chemotherapy and immunotherapy (Martinelli et al., 2005; Zucca E & Dreyling M., 2008). Approximately 75 % of patients with gastric MALT lymphoma achieve a remission following the elimination of H. pylori with antibiotics (Du & Isaccson, 2002; Wundisch et al., 2005). The interval of histological regression following this treatment is variable, ranging from 1 to 25 months. In the cases both of persistent infection or resistant lymphoma, a second attempt with the antibiotic therapy is usually recommended (Psyrri et al., 2008). Although antibiotics have demonstrated efficacy in early stages of disease, its use is also recommended in patients with advanced stages, in those without apparent infection for *H. pylori*, as in those with primary non-gastric disease. However, a therapeutic consensual guide for these patients has not yet established, much less for patients with the rare condition of MALT lymphoma and SLE.

In addition, the therapeutic role of treatments against infectious pathogens in non-gastric MALT lymphoma is less defined. The therapeutic application of antibiotics against B. Bugdorferi in cutaneous MALT lymphoma has been described, as well as the treatment against *C. psittaci* in MALT lymphoma of ocular adnexa (Bertoni & Zucca, 2005; Ferreri et al., 2005). However the association of these pathogens with MALT lymphoma seems to show a marked geographical variation and the antibiotic effectiveness of the treatments has not been confirmed yet (Husain et al., 2007).

Treatment with the anti-CD20 monoclonal antibody rituximab, chemotherapy and radiation therapy as single agents or in combination are alternative therapies for patients failing to treatment with antibiotics. Rituximab has demonstrated efficacy in gastric MALT lymphoma without *H. pylori* evidence, in cases of refractory disease, in relapses and in advanced disease as well as in localized disease in non-gastric MALT lymphoma (Martinelli et al., 2005; Thieblemont & Coiffier, 2006). The combined administration of rituximab with chemotherapy increases the efficacy of the monoclonal antibody.

The regimens of chemotherapy include alkylating agents, commonly used in low-grade lymphomas, analogues of purines, like the fludarabine, whose use combined with rituximab

has proven to be efficacious in patients with gastric and non-gastric MALT lymphoma (Levy et al., 2002). Recently, the combination of bendamustine (a new agent combining the alkylating and the purine analogue properties) with rituximab has demonstrated a great efficacy in achieving remission in MALT lymphoma of any origin with a very successful toxicity profile (Kahl et al., 2010). Anthracycline based regimes are occasionally used for young patients with aggressive gastric disease and for refractory patients to conventional treatments.

Splenic MZL is a disease with a relatively indolent course, but the optimal treatment strategy and outcome of splenic MZL remains undefined. Patients without a marked lymphocytosis, anemia or thrombocytopenia may not require treatment. However there is a significant group of patients who die from the lymphoma in a short interval of time (Chacón et al., 2002). Before rituximab, the recommended treatment for splenic MZL with symptomatic splenomegaly or threatening cytopenia was splenectomy, since chemotherapy had limited efficacy. Responses to splenectomy occurred in approximately 90% of patients (Sagaert X & Tousseyn T, 2010). Chemotherapy with CHOP and purine analogues such as fludarabine or pentostatine demonstrated objective responses (Franco et al., 2003). Presently, treatment of such patients with rituximab administered as a single agent or in combination has shown remarkable responses with an overall survival comparable to that reported following splenectomy (Bennett M & Schechter GP., 2010). Rituximab in combination with purine nucleosides may provide further improvement in PFS; however, confirmatory prospective trials are necessary.

As shown, in MZL chronic infections and autoimmune diseases such as SLE induce a chronic antigenic stimulation in B lymphocytes, through BCR. This constant stimulation induces the molecular NF-κB way, which probably plays a role in the initiation of the development of subsequent lymphoma (Thome, 2004; Ngo et al., 2011) Regarding therapy we can speculate with the future utility of drugs interacting the NF-κB way such as proteosome inhibitors (O'Connor, 2005).

8.7 Other lymphomas

Interestingly, a wide variety of lymphomas types with low prevalence has been reported in SLE patients. These subtypes include lymphoplasmacytic lymphoma (Papadaki et al., 2003), intravascular lymphoma (Sanchez-Cano et al., 2007), Franklin´s disease (García-Muñoz et al., 2008.), subcutaneous panniculitis-like T cell lymphoma (Pincus et al., 2009.), ALK-negative T cell anaplastic large cell lymphoma (Suvajdizc et al.,2003), peripheral T cell lymphoma (Löfström et al., 2007) and T cell leukemia/lymphoma (Frisch Stork et al.,2009).

9. Conclusions

SLE has an excess of lymphoma unrelated to immunosuppressive therapy. The mechanisms underlying the association between SLE and lymphoma remain unknown, but it is possible that impaired clearance of apoptotic cells in bone marrow and lymph nodes induces amplified stimulation of self-reactive B cells, increasing the risk to DNA damage and lymphomagenesis. Patients with SLE have shown an increased risk of marginal zone lymphoma, predominantly of the MALT type, and of DLBCL. Treatment of lymphoproliferative disorders in SLE does not differ from that administered to patients without SLE. Because the outcome is dependent on treatment, patients with SLE and suspected lymphoma should be evaluated jointly by both a rheumatologist and a hematologist with experience in lymphoproliferative disorders.

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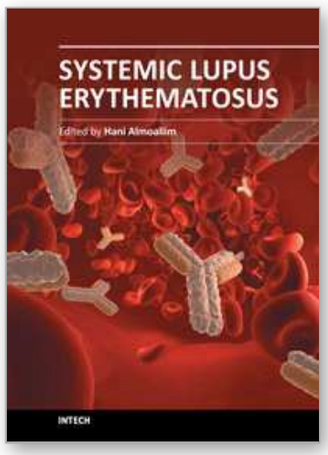

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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