Risk factors for lymphoproliferation and mortality in Sjögren's syndrome

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Sjögren's syndrome is a chronic inflammatory disease, primarily involving the exocrine glands. Its association with lymphoma is well documented. The salivary extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue type are the most common type of lymphoma in Sjögren's syndrome and constitute the major complication of the disease. These tumors are antigen-stimulated B-cell lymphomas and are characterized by localized stage, indolent clinical course and recurrence in other extranodal sites. This article reviews the literature and discusses the clinical, histopathological and therapeutic aspects of these tumors in Sjögren's syndrome. In addition, the predictive markers of lymphoma development and the mortality rate in Sjögren's syndrome are also highlighted.

Sjögren's syndrome (SS) is a slowly progressive, inflammatory autoimmune disease primarily affecting the exocrine glands. Autoreactive lymphocytic infiltrates invade the functional epithelium, leading to decreased exocrine secretions. Mucosal impairment is manifested as keratoconjunctivitis sicca (KCS), xerostomia, xerotrachea and vaginal dryness. Major salivary gland enlargement occurs in 60% of patients. In half of patients, the disease extends to extraglandular sites affecting the skin, lungs, kidneys, liver, peripheral nerves and muscles. The disease can occur alone (primary SS) or in association with other autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, and polymyositis (secondary SS). In addition, chronic hepatitis C virus (HCV) infection may also be implicated in the development of secondary SS in a specific subset of patients [1].

Clinical features

The disease usually runs a rather slow and benign course. Initial manifestations can be nonspecific and approximately 6 years can elapse from the initial manifestations to the full-blown development of the syndrome.

Glandular manifestations

Diminished tear production leads to the destruction of both corneal and bulbar conjunctival epithelium and a constellation of clinical findings termed KCS. Patients usually complain of a burning, sandy or scratchy sensation under the lids, itchiness, redness and photosensitivity. Physical signs include dilation of the bulbar conjunctival vessels, pericorneal injection, irregularity of the corneal image and, rarely, lacrimal gland enlargement.

Xerostomia, or dry mouth, is the result of the decreased production of saliva by the salivary glands. Patients report difficulty swallowing dry food, inability to speak continuously, changes in sense of taste, a burning sensation in the mouth, an increase in dental caries and problems in wearing complete dentures. Physical examination shows dry erythematous sticky oral mucosa, dental caries, scanty and cloudy saliva from the major salivary glands, and, on the dorsal tongue, atrophy of the filiform papillae. Parotid or major salivary gland enlargement occurs in 60% of primary SS patients. In many patients, salivary gland enlargement occurs episodically, whereas others have chronic, persistent enlargement. The swelling of parotid glands may begin unilaterally, but often becomes bilateral. Dryness may affect the upper respiratory tract as well as the oropharynx and cause hoarseness, recurrent bronchitis and pneumonitis. Loss of exocrine function may also lead to the loss of pancreatic function and hypochlorhydria. Patients may also experience dermal dryness and dyspareunia.

Nonexocrine systemic manifestations

Nonexocrine systemic manifestations are observed in approximately 50% of patients. They include both general constitutional symptoms such as low-grade fever, myalgias and arthralgias, as well as other organ involvement. The nonexocrine manifestations are divided into two major groups: periepithelial organ involvement, such as interstitial nephritis, and liver involvement and obstructive bronchiolitis,

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which is the result of lymphocytic invasion in epithelia of organs beyond the exocrine glands. These clinical features appear early in the disease and usually have a benign course. Extraepithelial manifestations, including palpable purpura, glomerulonephritis and peripheral neuropathy, are produced from an immune complex deposition as a result of the ongoing B-cell hyper-reactivity; they are usually observed late in the disease and are associated with increased morbidity and risk of lymphoma development.

Arthritis

Arthritis is observed in 50% of patients. Articular signs and symptoms include arthralgias, morning stiffness, intermittent synovitis and chronic polyarthritis, which may sometimes lead to Jaccoud's arthropathy. In contrast with RA, radiographs of the hands do not usually reveal erosive changes [2,3].

Skin involvement

Approximately 35% of patients present with Raynaud's phenomenon. This usually precedes sicca manifestations by many years. Patients with Raynaud's phenomenon present with swollen hands but, in contrast to those with scleroderma, they do not develop telangiectasias or digital ulcers [4]. Hand radiographs of these patients may show small tissue calcifications. Other skin manifestations include purpura, annular erythema and pernio-like lesions. Nonpalpable purpura is usually observed in patients with hypergammaglobulinemia, while palpable purpura is a manifestation of dermal vasculitis [5,6]. Annular erythemas have been described in patients with SS from Japan [7].

Pulmonary involvement

Manifestations from the respiratory tract and the pleura are frequent, but rarely clinically important. They can present either with dry cough secondary to dryness of tracheobronchial mucosa (xerotrachea) or dyspnea from airway obstruction or interstitial lung disease. The major finding of the disease is small airway obstruction, frequently associated with mild hypoxemia [8,9]. Chest radiography may reveal mild, interstitial-like changes. High-resolution computed tomography of the lungs in patients with abnormal chest radiography disclose wall thickening at the segmental bronchi [10–12]. Bronchial biopsy shows peribronchial and/or peribronchiolar mononuclear inflammation [13]. Lymphoma should always be suspected when lung nodules or hilar and/or mediastinal lymphadenopathy are present in chest radiographs. Interstitial disease in SS is rare. Pleural effusions are usually found in SS associated with other rheumatic disorders and not in primary SS [14].

Gastrointestinal & hepatobiliary features

Patients with SS often report dysphagia due to either dryness of the pharynx and esophagus or to abnormal esophageal motility [15,16]. Nausea and epigastric pain are also common clinical symptoms. Gastric mucosa biopsy specimens show chronic atrophic gastritis and lymphocytic infiltrates, similar to those described in minor salivary gland biopsies. Subclinical pancreatic involvement is rather common, as illustrated by the fact that hyperamylasemia is found in approximately 25% of SS patients [17]. Patients often present with hepatomegaly (25%) and antimitochondrial antibodies (AMA; 5%). In most of these patients, liver biopsy discloses a picture of mild intrahepatic bile duct inflammation [18,19].

Renal involvement

Clinically significant renal involvement is observed in approximately 5% of patients with primary SS. Patients may present either interstitial nephritis or glomerulonephritis. Interstitial nephritis is usually an early feature of the syndrome, while glomerulonephritis are a late sequelae. Subclinical involvement of the renal tubules can be seen in a third of patients, as it is attested by an abnormal urine acidification test. Renal biopsy typically reveals interstitial lymphocytic infiltration. Most of the patients present with hyposthenuria and hypokalemic, hyperchloremic distal renal tubular acidosis reflecting interstitial infiltration and destruction by lymphocytes [20–22]. Distal tubular acidosis may be clinically silent, but significant untreated renal tubular acidosis may lead to renal stones, nephrocalcinosis and compromised renal function. Membranous or membranoproliferative glomerulonephritis in SS has been described in a few patients [23]. Cryoglobulinemia, associated with hypocomplementemia, is a consistent serological finding in these patients.

Vasculitis

Found in approximately 5% of SS patients, vasculitis affects small- and medium-sized vessels and is manifest most commonly as purpura, recurrent urticaria, skin ulcerations and

mononeuritis multiplex. Uncommon cases of systemic vasculitis with visceral involvement affecting the kidneys, lung, gastrointestinal tract, spleen, breast and reproductive tract are described [24].

Neuromuscular involvement

Neuromuscular involvement includes peripheral sensorimotor neuropathy as a consequence of small vessel vasculitis and cranial neuropathy usually affecting single nerves such as the trigeminal or the optic nerve [25]. Many patients with primary SS complain of myalgias; however, muscle enzymes are usually normal or only slightly elevated. Polymyositis and inclusion body myositis have been described in SS.

Autoimmune thyroid disease

Autoimmune thyroid disease has been described in some cases of primary SS patients. Approximately 50% of SS patients present with antithyroid antibodies and an elevated basal thyroid-stimulating hormone level [26].

Lymphoproliferation

SS is particularly interesting for two reasons: first, it has a broad clinical spectrum extending from autoimmune exocrinopathy to extraglandular (systemic) disease; and second, it is a disorder in which a benign autoimmune process can lead to a malignant non-Hodgkin lymphoma (NHL). The interplay of inflammatory autoimmune diseases and lymphoproliferative disorders has been well recognized, and several models have been suggested to explain the increased rate of lymphoproliferation in autoimmunity and vice versa. Notably, among the diseases of immune deregulation, SS has the highest incidence of malignant lymphoproliferative disorders. We recently performed a meta-analysis to estimate the risk of lymphoma development in autoimmune diseases such as SS, SLE and RA. The meta-analysis demonstrated that lymphoma is more common in these autoimmune diseases than in the general population, and the risk is much higher in patients with SS [27].

The spectrum of lymphoproliferation in SS includes an increased frequency of circulating monoclonal immunoglobulins (Ig) and/or free light-chains, presence of mixed monoclonal cryoglobulinemia (MMC), and a high frequency of NHL development [28–30]. The relationship between SS and lymphoma has been known since 1963 [31]. Kassan and colleagues, reported that patients with SS have a 44-fold greater relative risk of lymphoma development compared with age-matched women in the general population observed in the same period [32]. After 1 year, Zulman and colleagues proved that lymphoma cells infiltrating salivary gland lesions in SS patients were of B-cell origin [33]. In 1982, Schmid and colleagues, demonstrated that lymphoepithelial lesions in salivary gland biopsies of SS patients displaying areas of confluent lymphoid proliferation composed of plasmacytoid lymphocytes and plasma cells with cytoplasmic monoclonal IgMk, actually represented malignant lymphoma [34]. Subsequently, several reports supported the association of lymphoma with SS and recognized NHL as a major complication in the progression of the disease [35,36].

Clinical aspects: histopathology

Of all autoimmune diseases, SS best illustrates the autoimmune–lymphoproliferation-lymphoma sequence. The prevalence of NHL in SS patients is 4.3%, and usually develops later during the disease course. The median age at lymphoma diagnosis is 58 years and the median time from SS diagnosis to lymphoma diagnosis is 7.5 years [32,37]. Various histologic subtypes of NHL for patients with SS have been described in the literature, including follicle center lymphoma, lymphoplasmacytoid, diffuse, large B-cell lymphoma (DLBCL) and, in particular, mucosa-associated lymphoid tissue (MALT) lymphomas [32,37,38]. However, the majority of lymphomas in SS are extranodal marginal-zone B-cell lymphomas (MZLs) of the MALT type [37–39]. It is important to of note that cases classified in the past as immunocytomas probably belong to the MZL entity. The histological features of salivary MALT lymphoma, which, by definition, is a low-grade lymphoma, closely simulate those of Peyer's patch lymphoid tissue. More specifically, the histopathology includes:

- Reactive lymphoid follicles, with or without colonization by neoplastic cells;
- Marginal zone and/or monocytoid B cells (centrocyte-like cells) that infiltrate the overlying epithelium (lymphoepithelial lesions);
- Small B lymphocytes;
- Plasma cells (which may or may not be neoplastic).

The immunophenotype of MALT-type lymphoma is not specific and currently appears to be one of exclusion [40].

Neoplastic marginal-zone cells are expected to retain the homing pattern of their normal precursors, which explains the diverse distribution of

lymphoma of this type [38,41]. It has been postulated that this dissemination may be the result of the specific expression of a special homing receptor on the surface of the B-cells of MALT (integrin a4β7) that regulates the traffic of lymphocytes to the mucosal tissues by binding to the addressin MAdCAM-1 on the mucosal endothelium [42]. These lymphomas frequently arise in mucosal extranodal sites as well as in extranodal nonmucosal sites; in most of these sites, epithelium is present, usually columnar, suggesting that the property of these cells is homing to epithelia rather than to mucosa [41]. In our study, the MZLs in SS patients are primary low-grade and localized (Stage I and II) with extranodal manifestations (Table 1) [37]. The salivary glands are the most common site, but other extranodal sites can also be involved, such as the stomach, nasopharynx, skin, liver, kidney and lung. A total of 20% of patients had involvement of more than one extranodal site at diagnosis, indicating that these lymphomas preferentially migrate to other mucosal sites and emphasizing the need for complete staging procedures in SS patients with MALT lymphomas [37]. In addition, the lymphoma rarely involves peripheral lymph nodes, but frequently disseminates to locoregional lymph nodes. Presenting symptoms are caused by major gland enlargement, mainly of the bilateral parotid gland. The clinical picture in these patients is not characterized by the presence of B symptoms; bone marrow infiltration is very rare, whereas in disseminated disease, more than one extranodal site is usually involved [37]. Skin vasculitis and peripheral nerve involvement are also frequent nonexocrine manifestations. Furthermore, hematologic and serologic parameters, such as anemia, lymphopenia, monoclonal Igs and MMC, are particularly common in these patients [37].

Table 1. Sjögren's syndrome patients with low-grade extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type.

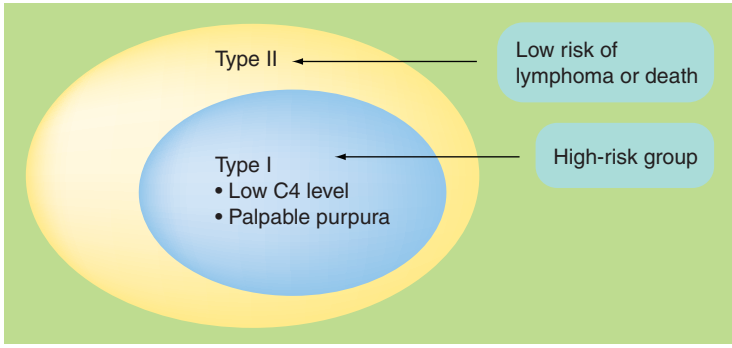
Clinical characteristic	Positive (%)
Performance status (Grade 0–1)	85
B symptoms (fever, night sweats and weight loss)	15
Clinical stage (localized disease)	61
Involvement	
Nodal	15
Extranodal	46
Both	39
Splenomegaly	7
Bone marrow infiltration	7
Bulky disease	7
Low-risk group (IPI)	68

HCV-associated SS patients with B-cell lymphoma are clinically characterized by a high frequency of cryoglobulinemic-related manifestations, including vasculitis, rheumatoid factor (RF) positivity and MMC, together with a predominance of MALT lymphomas involving organs in which HCV replicates (exocrine glands, liver and stomach) [1]. Thus, lymphomas in SS and HCV patients share several characteristics, such as a predominance of low-grade MZL, the frequency of mucosal involvement and a close association with cryoglobulinemia. Furthermore, SS lymphomas and HCV-associated lymphomas bear Ig with RF reactivity and present a restricted use of B-cell antigen receptor gene segments, suggesting a common pathogenesis of these lymphomas and also indicating the significant role of B-cell antigen receptor in their development [43–47].

Lymphomas in SS patients tend to evolve toward a less differentiated cell type [37]. Transformation of MALT lymphoma to DLBCL is heralded by the emergence of increased transformed blasts that form sheets or clusters, and finally form a confluence effacing the preceding MALT lymphoma. The majority of high-grade lymphomas in salivary glands are DLBCLs. It is not known how many of the DLBCLs arise from pre-existing MALT lymphomas and how many are of nodal type or represent transformation of follicular lymphomas. Immunohistochemical, karyotypic and genotypic studies have provided convincing proof that the supervening large-cell lymphomas arise from the same clone as the low-grade lymphomas. Thus, the majority of the high-grade lymphomas in SS patients may represent blastic-variance of MZLs [48].

During transformation, the clinical picture is characterized by further nodal and extranodal dissemination [37]. Although dissemination of MALT lymphoma in SS patients is associated with good prognosis, the histologic transformation to high-grade presents poor prognosis. Therefore, it is crucial to identify *de novo* and secondary DLBCLs in SS patients since the median overall survival is estimated to be only 1.8 years [37]. Therefore it can be concluded that NHLs in SS fall into two main categories; the first relating to the majority of patients who develop indolent extranodal MZLs and the second category relating to those developing high-grade aggressive lymphomas, such as *de novo* or secondary DLBCLs, which are only occasionally encountered in SS.

Figure 1. Patients with low C4 levels and palpable purpura have greater risk of lymphoma development.



Predictive factors of lymphoma development

Given that SS patients are at higher risk of developing lymphoma, several investigators have attempted to establish predictive factors for this progression. In 1971, Anderson and colleagues, demonstrated that a decrease in the level of serum Ig and disappearance of RF coincided with the time of progression to lymphoma [49]. Kassan and colleagues, demonstrated that patients with lymphadenopathy, splenomegaly, parotid gland enlargement and previous low-dose irradiation or chemotherapy had an increased risk of lymphoma development [32]. Our department found that the presence of MMC was the most significant factor in predicting the risk of lymphoma development. The cross-reactive idiotypes 17109 and G6 were also correlated with lymphoma development [50]. It was also suggested that the evidence of monoclonal paraproteinaemia, and urinary free light-chains could identify patients with a particular risk of later lymphoma development [51]. In another study, aiming to identify simple but reliable clinical and serological markers of an increased risk for lymphoproliferation, we demonstrated that lymphoma development was associated with the presence of palpable purpura, low C4 and MMC [52]. Patients with low C4 levels and MMC have a more than seven-times greater risk of developing lymphoma and those with palpable purpura five-times greater, as compared with patients without these risk factors [52]. In the European multicenter study that included 765 SS patients, lymphadenopathy, skin vasculitis, peripheral neuropathy, anemia and lymphopenia were significantly more frequent in those who developed NHL than in the general SS population [37]. Ioannidis and colleagues confirmed that the lymphoproliferative disease was independently predicted by parotid gland enlargement, palpable purpura and low C4 levels. Patients without any of these factors were at negligible risk of developing lymphoma during the follow-up period [53]. According to this study, our department suggested a predictive classification of SS into two distinct categories, each carrying a varying risk of lymphoma development. Patients with low C4 levels and/or palpable purpura are classified as high-risk (Type I SS), while those without (80% of all primary SS diagnoses) are classified as low-risk (Type II SS) with negligible potential for lymphoma development (Figure 1). Notably, Ramos-Casals and colleagues demonstrated that lymphoma was associated with low C3, C4 and CH50 levels in univariate analysis, although low C4 levels alone were an independent significant variable in multivariate analysis [54]. Others have suggested that leg ulcers, which may also be manifestations of vasculitis, as well as $CD4^+$ T lymphocytopenia, are predictive of lymphoma development [36,55]. Therefore, a $CD4^+$ lymphocytopenia is not only a sign of HIV patients but a stronger predictor of lymphoma development in SS. Finally, high serum β2-microglobulin levels, low serum IgM levels and the disappearance of a previously positive RF are other biological predictors of NHL development in SS [56]. These data suggest that, although some clinical parameters may herald the imminent onset of lymphoma, few reliable markers are available to predict this progression (Table 2). Patients with these risk factors constitute a separate subgroup that should be monitored and managed closer than other SS patients.

There has been speculation that in SS, abnormal persistence of autoreactive peripheral lymphocytes due to defective Fas/Apo-1-mediated apoptosis, and antigen-driven sustained lymphoproliferation by exoantigen or autoantigen, may provide a preferential milieu for lymphoma development [45,57]. A different cause of lymphocyte persistence, but with similar outcomes, is illustrated by the forced overproduction of B-lymphocyte stimulators (BLyS), which act during maturation of B lymphocytes. Analysis of BLyS plasma levels in SLE, primary SS and RA has shown that BLyS is higher in patients than in controls [58–60]. It has also been shown that patients with SS have a higher incidence and higher levels of B cell-activating factor of the TNF family (BAFF) serum levels in comparison to SLE patients [61,62]. Furthermore, patients with active SLE have decreased numbers of $CD19^+/CD27^-$ naive B cells and increased numbers of $CD19^+/CD27^+$ memory B cells [63], in contrast to patients with SS who are characterized by a significant reduction in the number of the peripheral

Table 2. Predictors of lymphoma development.

Clinical	Serological
Splenomegaly	Mixed monoclonal cryoglobulinemia
Persistent enlargement of parotid glands	Low levels of C4
Lymphadenopathy	Cross-reactive idiotypes (17.109, G6)
Pulpable purpura	
Leg ulcers	

$CD27^+$ memory B cells due to their accumulation in the salivary glands [64]. Given the vigor with which Ig genes are modified during immune responses, it is plausible to hypothesize that some of the critical transforming events are the product of an intense ectopic germinal center reaction in SS. In this regard, patients with SS with an increased risk of NHL are characterized by splenomegaly, lymphadenopathy, mixed MMC and parotid swelling, all indicators of an extensive B-cell proliferation predisposing to an increased likelihood of genetic aberrations.

Treatment & prognosis

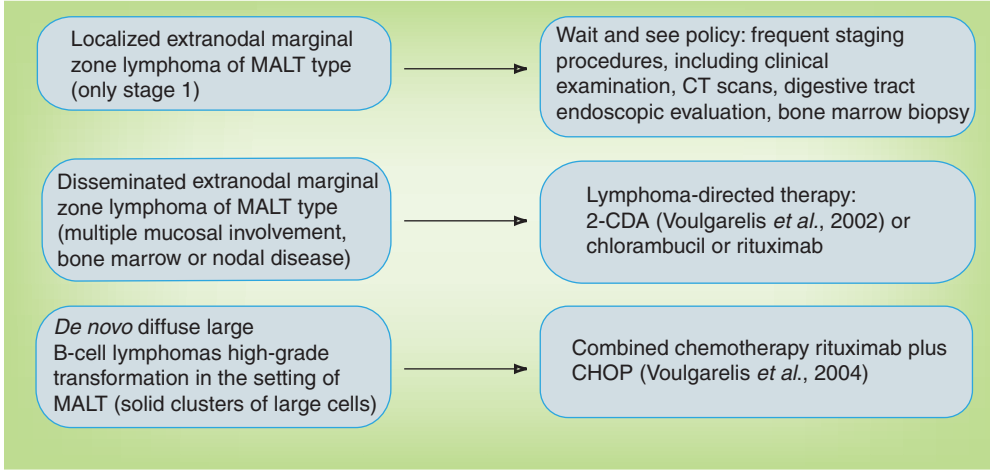
MALT lymphomas are clinically indolent diseases. In a few series that have been published, non-SS patients with nongastric MALT lymphomas appear to have a good outcome with a 5-year overall survival rate ranging from 86 to 100%. As demonstrated in our study, patients with indolent salivary MALT lymphomas usually have a quite uncomplicated course with a median overall survival of 6.4 years [37]. In our study, patients were managed according to the current policy of each institution at the time of diagnosis. Noticeably, at a median follow-up of 6 years, treated and untreated patients with MALT lymphoma demonstrated the same overall survival. In contrast, patients with aggressive DLBCL who were all treated with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) had significantly worse survival.

As the histologic grade is a very important prognostic factor for overall survival, the treatment of SS-associated NHL depends on the histologic grade of the lymphoma [37]. Thus, in patients with localized low-grade lymphoma affecting the exocrine glands, a wait-and-watch policy should be undertaken, and if lymphoma is disseminated patients may be treated with single-agent chemotherapy (Figure 2). In a recent study we identified the achievement of complete response (CR) in 75% of the patients with SS-associated B-cell lymphoproliferation during 4 years of follow-up and improvement in some SS features after 2-chloro-2-deoxyadenosine therapy (oral symptoms, parotidomegaly, salivary flows, hyposthenuria and disappearance of cryo/urine monoclonal bands) [65].

By contrast, combined chemotherapy is recommended for patients with low-grade lymphoma transforming to high-grade, and those with high-grade lymphoma. Over the last 15 years, a number of aggressive induction regimens have been evaluated in a pilot single-institution study that included patients with high-grade lymphomas. However, when these regimens were subsequently compared with CHOP in large randomized trials, patients treated with CHOP had comparable complete remission rate and overall survival. Consequently, the majority of patients with aggressive NHL in SS receive an anthracycline-containing regimen, such as CHOP. Unfortunately, the median survival is estimated to be only 1.8 years in these patients. The presence of B symptoms and a large tumor diameter (7 cm) are additional independent death risk factors [37]. This observation, together with data indicating that rituximab plus CHOP (R-CHOP) had a significant clinical effect in DLBCL, increasing both response rate and survival compared with CHOP alone, prompted us to use this regimen in six SS patients with aggressive NHL [66,67]. The major point of our study was that R-CHOP induced sustained CR in all SS patients with aggressive B-cell NHL for a follow-up period of 2 years. Moreover, the extranodal manifestations of the patients, such as peripheral neuropathy and skin vasculitis, disappeared after eight cycles of R-CHOP. The remission of these symptoms and signs was accompanied by a decrease of the circulating MMC, as well as an increase in C4 levels [67]. Thus, R-CHOP appears to be effective in controlling both the autoimmune and neoplastic process in these patients.

In SS patients with high risk factors, such as palpable purpura, low C4 and MMC, a strong predisposition appears to exist for the development of lymphoproliferation. In such cases, the use of monoclonal antibodies targeting the CD20 antigen resulting in the depletion of activated B lymphocytes, could be adopted as an effective therapeutic approach in preventing the lymphomatous potential of intense B-cell activation.

Figure 2. Our policy for the management of indolent lymphomas is presented.



2-CDA: 2-chloro-2-deoxyadenosine; CHOP: Cyclophosphamide/doxorubicin/vincristine/prednisone; CT: Computerized tomography; MALT: Mucosa-associated lymphoid tissue.

Mortality of SS

Although few studies have been reported that have investigated the mortality rate in primary SS, lymphoma development appears to be a major complication of this disease and is consistently associated with the presence of hypocomplementenia and MMC [52–54].

The morbidity and mortality rate was evaluated in a prospective cohort study of 261 SS patients, amongst whom 11 patients displayed lymphoproliferative disorders: nine cases of B-cell lymphoma, one case of chronic lymphocytic leukemia and one case of Waldenstrom's macroglobulinemia [52]. Hence, from time of diagnosis, the lymphoproliferative disorder incidence rate per 1000 person-years follow-up was 12.2 (95% confidence interval [CI]: 6.1–21.8). During follow-up, 11 of the 261 patients died, three due to lymphoma. Lymphoproliferative disorders were correlated with low C4 levels, MMC and purpura, with low C4 level at diagnosis constituting the strongest mortality predictor [52]. The age- and gender-standardized mortality ratio (SMR) indicated that the observed mortality rate (11.8 per 1000 patient-years follow-up) was 2.07-times grater than that of the general Greek population (95% CI: 1.03–3.71). However, if high-risk patients are excluded from the analysis, the SMR decreases to 1.02, similar to the rate expected in the general population. This particular study was extended to include a total of 723 SS patients [53]. The resulting SMR rate was estimated at 1.15 (95% CI: 0.86–1.73). Low C4 levels again presented as the main defining mortality predictor.

Further study of 484 SS patients with a median 7-year follow-up resulted in 34 deaths, six of which were due to lymphoproliferative disease [68]. Mortality predictor markers in this study were defined by low C3 and C4 levels. The SMR was 1.17 (95% CI: 0.81–1.63) compared with lymphopreliferative disease cause-specific SMR of 7.89 (95% CI: 2.89–17.18), a very similar result to the previous study. Yet, another study of 218 SS patients demonstrated the association of low C4 levels with a low survival rate due to lymphoproliferative disease [54].

On balance, these studies suggest that systemic manifestations as well as the serological profile of SS determine outcome with low levels of C4, C3, CH50 and cryoglobulinemia constituting the strongest predictors of lymphoproliferative disorders and mortality in SS.

Conclusion

SS patients with high risk factors, such as palpable purpura, low C4, $CD4^+$ lymphocytopenia and MMC constitute a separate subgroup that should be monitored more closely than other SS patients. A strong predisposition appears to exist in these patients for the development of lymphoproliferation, especially for low-grade salivary gland MZLs. Therefore, the clinical follow-up of SS patients should include routine complement determination, as well as serum immunoelectrophoresis in order to detect the possible emergence of a monoclonal B-cell population, susceptible to lymphoma development.

Future perspective

To gain a better understanding of the whole lymphomagenesis in SS, it would be valuable to determine the specific antigen recognized by these lymphomas. It is important to identify clinical features at the time of the initial presentation that possibly predispose histologic progression and parameters that addresses the efficacy of treatment in presenting high-grade transformation. Anti-CD20 therapy is promising in the reduction of the incidence of lymphoma development in high-risk groups.

Executive summary

Epidemiology

- The prevalence of non-Hodgkin's lymphoma (NHL) in Sjögren's syndrome (SS) patients is 4.3% and usually develops later in the disease.

Clinical presentation

- Physicians takinfg a first examination of an SS patient displaying clinical signs such as significant enlargement of the salivary glands, lymphadenopathy, splenomegaly, skin vasculitis and peripheral neuropathy, should consider the presence of NHL.

Predictors of lymphoma development

- Among the clinical and serological parameters that have been associated with lymphoma development in SS patients, the presence of palpable purpura, low C4, $CD4^+$ lymphocytopenia and mixed monoclonal cryoglobulinemia constitute the main predictive markers and patients displaying these risk factors should be monitored closely.

Pathology

- NHLs in SS fall into two main categories, the first relating to the majority of patients who develop indolent extranodal marginal-zone B-cell lymphomas and the second category relating to those developing high-grade aggressive lymphomas, such as *de novo* or secondary diffuse, large B-cell lymphoma (DLBCL), which are only occasionally encountered in SS.

Treatment

- SS patients with indolent salivary mucosa-associated lymphoid tissue lymphomas usually have quite an uncomplicated clinical course with a median overall survival of 6.4 years. The combination of rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone has a significant clinical effect in DLBCL.

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