**RESUMEN**

El virus de la hepatitis C (VHC) posee un triple tropismo, hepatotropo, linfotropo y sialotropo. Los pacientes con infección por VHC pueden presentar diversas manifestaciones extrahepáticas que simulan las principales manifestaciones clínicas, inmunológicas e histológicas características del síndrome de Sjögren (SS) primario. Los pacientes VHC+ que presenten un síndrome seco pueden ser diagnosticados erróneamente como SS primario. De todas formas, existen diversas características clínicas e inmunológicas que pueden permitirnos diferenciar ambas situaciones. Los pacientes SS-VHC presentan una elevada frecuencia de crioglobulinemia e hipocomplementemia, así como una menor prevalencia de anticuerpos anti-Ro/SS-A y anti-La/SS-B comparado con pacientes con SS primario, así como un patrón de citocinas circulante Th2. Actualmente, la infección crónica por VHC, el SS, la crioglobulinemia y el linfoma B deben ser considerados como procesos estrechamente relacionados entre sí.

**KEY WORDS:** Virus / Síndrome de Sjögren / Virus hepatitis C / Linfoma / Crioglobulinemia.

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**ABSTRACT**

The hepatitis C virus (HCV) has a triple tropism: hepatotropism, lymphotropism and sialotropism. Patients with HCV chronic infection present some extrahepatic manifestations that may mimic the clinical, immunologic and histological manifestations of primary Sjögren’s syndrome (SS). HCV patients with sicca symptomatology and positive autoantibodies could be misdiagnosed as “primary” SS. Nevertheless, there are several clinical and immunological features that could help us to differentiate both processes. Patients with HCV-related SS present a higher frequency of cryoglobulinemia and hypocomplementemia and a lower prevalence of anti-Ro/SS-A and anti-La/SS-B antibodies compared with patients with primary SS, as well as a predominant peripheral Th2-cytokine response. Currently, HCV, SS, cryoglobulinemia, and B-cell lymphoma should be considered as closely related processes.

**KEY WORDS:** Viruses / Sjögren’s syndrome / Hepatitis C virus / Lymphoma / Cryoglobulinemia.

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**INTRODUCTION**

Sjögren’s syndrome (SS) is an autoimmune disease that mainly affects exocrine glands and that usually presents as a persistent dryness of the mouth and the eyes due to functional impairment of the salivary and lachrimal glands(1). In the absence of an associated systemic autoimmune disease, patients with this condition are classified as having primary SS. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands. The spectrum of the disease extends from an organ specific autoimmune disease (autoimmune exocrinopathy)(2) to a systemic process (muscloskeletal, pulmonary, gastric, haematological,
vascular, dermatological, renal and nervous system involvement(9).

A possible relationship between hepatitis C virus (HCV) and SS was postulated in 1992 by Haddad et al.(10). These authors reported the occurrence of characteristic histologic changes of SS in salivary glands of patients with HCV infection. Recently, two clinical studies, performed in large series of patients, described the clinical and immunological features of patients with SS and HCV infection(11). Furthermore, Koike et al.(11) reported the first experimental evidence of a direct link between SS and HCV infection. These authors described in a transgenic mouse carrying the HCV envelope genes the development of an exocrinopathy resembling SS in the salivary and lachrimal glands.

Systemic autoimmune diseases and lymphoma are closely related, with a bidirectional association. Lymphomas occur more frequently in the course of autoimmune diseases and rheumatic manifestations occur in the course of lymphocytic malignancies. Non-Hodgkin’s lymphoma (NHL) is the most serious complication during the evolution of primary SS. NHL has also been recently described in patients with chronic HCV infection. It is possible that the coexistence of HCV infection with SS in the same patient may favor the development of lymphoproliferative processes.

COMMON FINDINGS IN SS AND HCV INFECTION

Several studies described xerostomia and xerophthalmia in patients with chronic HCV infection(8,11). Several studies also analysed the histological characteristics of salivary gland biopsy in HCV patients, showing most of them lymphocytic infiltrates(11). Other studies analysed the morphologic and immunohistochemical features of lymphocytic infiltrates described in HCV patients, and reported highly similar features with primary SS(11). Autoantibodies may be detected in 20-40% of HCV patients, with antinuclear antibodies (ANA) and rheumatoid factor (RF) being the most frequent. In 2-40% of HCV patients, antinuclear antibodies, with primary SS described in HCV patients. These authors described a transgenic mice carrying the HCV envelope genes the development of an exocrinopathy resembling SS in the salivary and lachrimal glands.

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B-CELL LYMPHOMAGENESIS IN SJÖGREN’S SYNDROME

The incidence of malignant lymphoproliferations in SS is the highest among all autoimmune diseases, and primary SS is often considered to be a «crossroad» between autoimmune and lymphoproliferative disease. Interestingly, most lymphomas observed in patients with SS are of B-cell origin, despite the fact that the majority of cells infiltrating the salivary glands are T cells. Lymphoma is classically considered the main complication in the natural history of SS, although transversal studies reported that only 98 (4%) of 2311 patients with primary SS developed lymphoma(11) (Table I). Tzioufas et al. prospectively analysed the incidence of lymphoma, which is found in 7% of patients with primary SS followed over 5 years.

SS represents a pathological model of the evolution from polyclonal B lymphocyte activation to oligoclonal/monoclonal B cell expansion, which may culminate in the development of a malignant lymphoproliferative disease. The different phases of this process are usually marked by the appearance of antigen-driven activated B cell clones, which are commonly IgM-positive and with rheumatoid factor (RF) activity. However, the agent(s) able to trigger B cell proliferation is still unknown. Transition from an autoimmune benign proliferation to an overt lymphoproliferation may represent a multi-stage process involving B cells, whose final stage (lymphoma) is observed in a small percentage of patients with primary SS(11). The clinical heterogeneity of primary
SS originates distinct serological and immunogenetic subsets of patients with a differential risk of lymphoma development. Patients with negative immunologic markers probably have a lower risk for lymphoma development, while those with higher ESR, hypergammaglobulinemia and positive autoantibodies (reflecting an enhanced polyclonal B-cell activation), and especially those with circulating monoclonal Ig (reflecting an emerging monoclonal B-cell process) are those with the highest risk of lymphoma. Lymphomagenesis seems to be a slow, multi-stage process affecting a specific subset of patients with primary SS.

**Genetic alterations**

Several chromosomal abnormalities have been described in patients with SS and lymphoma. Patients with negative immunologic markers probably have a lower risk for lymphoma development, while those with higher ESR, hypergammaglobulinemia and positive autoantibodies (reflecting an enhanced polyclonal B-cell activation), and especially those with circulating monoclonal Ig (reflecting an emerging monoclonal B-cell process) are those with the highest risk of lymphoma. Lymphomagenesis seems to be a slow, multi-stage process affecting a specific subset of patients with primary SS.

**TABLE I. Prevalence of lymphoma in patients with primary SS: previous studies (Reference 18)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Patients with Lymphoma</th>
<th>% of Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talal and Bunim</td>
<td>58</td>
<td>5</td>
<td>8%</td>
</tr>
<tr>
<td>Block et al.</td>
<td>62</td>
<td>3</td>
<td>5%</td>
</tr>
<tr>
<td>Whaley et al.</td>
<td>171</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>McCutney et al.</td>
<td>136</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>Kelly et al.</td>
<td>100</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Patierno et al.</td>
<td>62</td>
<td>4</td>
<td>6%</td>
</tr>
<tr>
<td>Fakidis et al.</td>
<td>120</td>
<td>8</td>
<td>7%</td>
</tr>
<tr>
<td>Zulfic et al.</td>
<td>55</td>
<td>5</td>
<td>9%</td>
</tr>
<tr>
<td>Knuž et al.</td>
<td>31</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>Hernández et al.</td>
<td>39</td>
<td>4</td>
<td>10%</td>
</tr>
<tr>
<td>Trinitis et al.</td>
<td>103</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>Valesini et al.</td>
<td>295</td>
<td>9</td>
<td>3%</td>
</tr>
<tr>
<td>Davidson et al.</td>
<td>100</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Skopouli et al.</td>
<td>261</td>
<td>11</td>
<td>4%</td>
</tr>
<tr>
<td>Garinot et al.</td>
<td>80</td>
<td>6</td>
<td>7%</td>
</tr>
<tr>
<td>Pertovaara et al.</td>
<td>110</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>García Carrasco et al.</td>
<td>380</td>
<td>7</td>
<td>3%</td>
</tr>
<tr>
<td>Total</td>
<td>2111</td>
<td>98</td>
<td>4%</td>
</tr>
</tbody>
</table>

Other authors found increased levels of EBV-DNA in saliva of SS patients with pseudolymphoma and increased levels of antibodies against EBV early antigen in their sera, and some reports detected EBV in lymphomatous tissues. The recent isolation of a new member of the herpes virus family (Human Herpes Virus-6, HHV-6) from patients with lymphoproliferative diseases prompted several authors to examine HHV-6 in tissue samples and saliva from patients with primary SS who developed NHL. Jarrett et al. analysed tissue samples from a SS patient with B-cell lymphoma and detected HHV-6-specific DNA sequences. Fox et al. found HHV-6 DNA in lymph node samples of 1/14 patients with SS. A possible relationship between Helicobacter pylori and gastric lymphomagenesis has been recently postulated in patients with SS. Lymphoid accumulation in the gastric mucosa is common in SS but evidence for an antigen-driven B-cell expansion has not been demonstrated. De Vita et al. described a low-grade gastric lymphoma concomitantly with H. pylori infection in a patient with SS. After H. pylori eradication, a dramatic regression of gastric lymphoma into chronic gastritis was observed. Multiple molecular analyses showed expansion of the same B-cell clone in synchronous gland lymphomas. Analysis of bcl-2 translocations in tissue biopsies may aid to the diagnosis of lymphoma, although a negative result did not rule out malignancy. Mucosa-associated lymphoid tissue (MALT) and monocytoid B-cell lymphomas (MBC) may exhibit a chromosomal abnormality, the trisomy 3, in 50% of the cases. Finally, mutations of the tumour-suppressor activity gene p53 have been associated with progression of low-grade MALT lymphoma to high-grade, and Guo et al. described a defective repair of O6-methylguanine-DNA in patients with primary SS and lymphoma.
and metachronous lymph node, parotid, and gastric lesions before and after *H. pylori* eradication. Other authors (35) studied gastric tissue in patients with SS in order to define whether the presence of MALT in the stomach was associated with several infectious agents, and found that *H. pylori* infection is not more frequent among patient with SS than in controls, and that MALT may occur in the stomach even in the absence of *H. pylori* infection. Other studies performed in SS patients with simple dyspepsia indicate that clonality may persist for up to six months after eradication of *H. pylori* (36). Although *H. pylori* may play an important role in the local boosting of B-cell lymphoproliferation, the underlying B-cell disorder seems to be a non-malignant process (34).

### Monoclonal selection/overexpansion

The benign lymphoepithelial lesions of SS are composed by a majority of CD4 T-cell lymphocytes and a minority of B-cell lymphocytes that are often oligoclonal (37,38). While circulating B cells from patients with SS do not spontaneously secrete increased amounts of immunoglobulins, B cells infiltrating the epithelial cells of exocrine glands produce large amounts of immunoglobulins with RF activity. Previous studies indicated that polyclonally activated B cells are mainly localised in the affected exocrine glands in patients with primary SS (39). Moutsopoulos et al. (40) found in B-cells from minor salivary gland biopsies of patients with SS a common idiotype with monoclonal Ig from patients with B-cell lymphoma, suggesting thus that neoplastic transformation in primary SS may start in the exocrine glands (27). Association between serum IgMk monoclonality and an increased proportion of k-positive plasma cells in salivary glands of patients with SS (40) also indicates that affected exocrine glands are the main area of monoclonal B-cell activity.

However, B-cells from other organs rather than salivary glands may also be carefully evaluated for the presence of B-cell monoclonal expansion. To better characterise prelymphomatous stages of B-cell lymphoproliferation, De Vita et al. (40) studied multiple tissue lesions (synchronous from different tissues and metachronous from the same tissue) of 6 consecutive patients with SS who had an associated lymphoproliferative disorder, and evaluated the persistence and dissemination of the same B-cell clone, as well as estimated size of expanded B-cell clone(s) during the disease. Local overexpansion of the same B-cell clone was detected in multiple sites by molecular analyses of synchronous biopsy specimens. In contrast, bands of different molecular weight were observed in synchronous biopsy samples from different tissues in the majority of SS patients, indicating different dominant B-cell clones in different microenvironments. Analysis of metachronous biopsies showed that B-cell clonal overexpansion was frequently multifocal and fluctuating in SS, since different clones predominated not only in different tissues (synchronous biopsy tissue), but also in the same affected tissue at different times (metachronous biopsies). The authors provided conclusive evidence that clonal B-cell expansion is a frequent event in SS, but may be either oligoclonal or monoclonal, either smaller or larger in size, either fluctuating or established, or either localized or disseminated. These different events conceivably imply a different risk of lymphoma progression, though they may all occur under the same pathologic diagnosis of lymphoproliferative lesion.

In SS patients, lymphomagenesis may follow a multi-step aetiopathogenic process (Fig. 1). The first step may be an exogenous infectious agent (EBV, HCV...) that induces an antigenic stimulus, which may be related to viral antigenic products or cross-reactive autoantigens (molecular mimicry). This stimulus may enhance the activity of specific helper T cell clones that cause polyclonal activation of B-cells, with production of different types of autoantibodies, soluble immune complexes or cryoglobulins. In a subsequent phase, some B cell clones may selectively proliferate, inducing production of monoclonal immunoglobulins (usually IgMk with RF activity), which can be detected in serum and in

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**Figure 1. Lymphoproliferation in Sjögren’s syndrome: a multi-step aetiopathological process.**
type II cryoglobulins. Minor populations of B cells or T cells may clonally expand in salivary gland tissues of SS patients. A persistent B-cell proliferation in these salivary gland tissues may eventually lead to the emergence of a neoplastic clone, may be a particular B-cell or T-cell clone with an underlying karyotypic alteration, that escapes immunologic control and finally evolves into a NHL.

B-CELL LYMPHOMAGENESIS IN HCV INFECTION

The association between HCV and lymphoma has been postulated in recent years. In 1994, the presence of HCV ongoing replication in both serum and peripheral lymphocytes was first demonstrated in one-third of unselected patients with B-cell NHL, regardless of their different grades of malignancy. Subsequent studies confirmed this higher incidence of HCV infection in NHL, although recent studies described lower prevalences. Additional support for the possible association of clonal B-cell expansion and HCV infection has been provided by Franzin et al., who found a high frequency of clonal B-cell expansion in HCV-infected patients, even in the absence of cryoglobulinemia.

B-cell activation

Persistence of HCV or other viruses may cause continuous B cell stimulation in the host, with an hyperproduction of polyclonal Ig and RF, thus inducing the formation of cryoglobulins. Continuous HCV viral replication may be representative of enhanced and/or long duration immune pressure in response to chronic HCV infection, with subsequent selection of oligoclonal or monoclonal RF-secreting B-cells. Chronic stimulation of the immune system by IgG-HCV complexes or by the infectious agent directly, leads to monoclonal expansion of B cells expressing the corresponding RF in peripheral blood and in bone marrow biopsies. RF also plays an important role in immune complex formation. The antigens involved may be autologous denatured Ig, HCV genomic sequences, or other unknown factors.

Under pressure of chronic antigen stimulation, RF repertoire is remodelled, and progressively includes non-specific, somatically mutations of RF similar to those observed in chronic autoimmune diseases such as rheumatoid arthritis.

Association of HCV with WA mRF suggests that HCV stimulates the proliferation of WA XId-positive B cells. CD5+ B cells usually produce germline genes that encode the WA mRF. Monoclonal IgMk cells infiltrating the liver and bone marrow of patients with type II cryoglobulinemia have been identified as CD5+, whereas circulating IgMk monoclonal cells are CD5-. Experimental studies showed that the CD5 antigen is a lineage marker for primordial B cells arising predominantly in the peritoneal cavity, and, in humans, CD5 seems to be a marker for a T cell-independent B cell developmental pathway. Recently, CD81 was identified as an HCV receptor on B-lymphocytes, providing a mechanism by which B cells are infected and activated by the virus. Zackerman et al. have demonstrated the association of increased CD81 expression and expansion of CD5+ B-cells with the production of RF and mixed cryoglobulins in HCV-infected patients, suggesting that overexpression of CD81 and expansion of CD5+ peripheral B-cells may play a role in the development of HCV-associated autoimmune and lymphoproliferation.

A peculiar tropism of HCV infection for specific tissues has been observed. HCV-RNA has been detected in peripheral blood cells (mainly lymphocytes, but also neutrophils and monocytes), as well as in different organs such as liver, stomach, bone marrow and salivary glands. The role of these cells as HCV reservoirs and effectors of tissue damage is strongly suspected, and the possibility that HCV acts as a local trigger of B-cell proliferation in these «privileged» reserves of the virus should be considered. A recent study showed that HCV not only colonize gastric MALT, but also may increase the risk of development of MALT.

Recent studies are focused on the role of the HCV-E2 envelope protein in B-cell lymphomagenesis. The high similarity found between antibodies with RF activity and anti-HCV E2 antibodies suggested that HCV, alone or complexed with IgG, could play a pathogenetic role as exogenous trigger in certain stages of B-cell lymphoproliferation and in certain subsets of B-cell NHL. Quinn et al. cloned the B-cell receptors from HCV-associated lymphomas, that were further expressed as soluble immunoglobulins. These immunoglobulins were tested for their ability to bind the HCV-E2 envelope glycoprotein. One of 2 lymphoma immunoglobulin test cases bound the E2 protein in an identical manner to human anti-E2 antibody. Moreover, it bound E2 from multiple viral genotypes, suggesting reactivity with a conserved E2 epitope. These findings support the hypothesis that some HCV-associated lymphomas may be originated from B cells that were initially activated by the HCV-E2 protein.

Role of cryoglobulins

Since the development in 1989 of a test for the detection of HCV antibodies, it has been established that almost all cases of mixed cryoglobulinemia (MC), previously called essential, are related to chronic HCV infection. At present, several findings suggest a close association between HCV and MC, including the presence of anti-HCV antibodies in...
a high proportion of MC patients, the presence of HCV-RNA sequences in serum and plasma samples, bone marrow cells and peripheral blood mononuclear cells (PBMC) from cryoglobulinemic patients and, finally, the presence of anti-HCV antibodies and specific HCV-RNA sequences in cryoprecipitates (50). Detection of HCV-RNA in the PBMC of MC patients (58) may suggest a correlation between this phenomenon and the pathogenesis of cryoglobulinemia. Infection of circulating lymphocytes by HCV could trigger the mono- or polyclonal B-cell proliferation, which is responsible for the production of immune complexes, including mixed cryoglobulins, and the consequent vasculitis (59). However, De Maddalena et al. (60) did not observe any difference in positivity between the PBMC collected from MC patients and those from non-cryoglobulinemic HCV infection. This suggests a tropism of HCV for PBMC, regardless of the presence of a cryoglobulinemic syndrome. Detection of HCV genoma in circulating lymphocytes (58) suggests a direct involvement of the immune system in the pathogenesis of clonally-serological features of MC. It has long been known that lymphomas may develop in some patients with MC, usually after a long-term follow-up period (59). In patients with type II MC, the appearance of non-Hodgkin’s B cell lymphoma has been recorded after a mean period of 6 years from disease onset (61,62). In all cases, circulating HCV markers were present, and viral RNA was detectable in both fresh and cultured PBMC from cryoglobulinemic patients (59,62). Thus, HCV-related proteins, genomic HCV sequences, and ongoing viral replication have been identified in PBMC and lymph node cells from patients with type II MC and neoplastic lymphoproliferation (61,62). HCV-lymphotropism could explain the appearance of a benign B-cell expansion in MC, which at some point may switch over to evident B-cell malignancy (59). Since HCV cannot be integrated into the host genome, it may be hypothesized that HCV is involved in the oncogenesis through indirect mechanisms (59,62). Several studies analysed the immunological characteristics of HCV-related cryoglobulinemia and B-cell lymphoma (59,62,64,66,67) (Table II).

**TABLE II.** Immunological characteristics of patients with HCV-related cryoglobulinemia and B-cell lymphoma

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Sex (female)</th>
<th>Mean age</th>
<th>Cryog. Symptoms n (%)</th>
<th>ANA+ n (%)</th>
<th>RFe n (%)</th>
<th>Hypocom n (%)</th>
<th>Associated SAD n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silvestri et al. (44)</td>
<td>19</td>
<td>10(53)</td>
<td>61 yr</td>
<td>5 (26)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sansonno et al. (64)</td>
<td>12</td>
<td>7 (58)</td>
<td>68 yr</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>La Civita et al. (62)</td>
<td>14</td>
<td>10 (71)</td>
<td>60 yr</td>
<td>14 (100)</td>
<td>5 (36)</td>
<td>7 (50)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>De Vita et al. (67)</td>
<td>35</td>
<td>20 (57)</td>
<td>65 yr</td>
<td>5 (14)</td>
<td>15 (43)</td>
<td>13 (37)</td>
<td>2 (6)</td>
<td>–</td>
</tr>
<tr>
<td>De Re et al. (66)</td>
<td>16</td>
<td>11 (69)</td>
<td>64 yr</td>
<td>9 (56)</td>
<td>–</td>
<td>13/16 (94)</td>
<td>–</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>


**TABLE III.** Differential aspects of SS secondary to HCV in comparison with primary SS

- Higher mean age of SS-HCV patients
- Lower frequency of parotidomegaly
- Hepatic involvement in the majority of patients
- Higher frequency of cryoglobulinemia
- Higher frequency of hypocomplementemia
- Lower frequency of anti-ENA autoantibodies
- Differentiated pattern of Th1/Th2 cytokines

**CLINICAL IMPLICATIONS**

**Differential aspects of HCV-related SS**

Most of the published studies support the existence of SS in chronic HCV patients but, in medical practice, could we differentiate it from primary SS? In our patients with HCV-related SS, we observed several differences when compared to primary SS (64) (Table III). HCV-SS patients presented a higher mean age, a lower prevalence of parotidomegaly and a higher prevalence of hepatic involvement. Patients also showed a different immunologic pattern compared with primary SS patients, with a lower frequency of anti-Ro/SSA antibodies and a higher prevalence of cryoglobulins and hypocomplementemia. We recently described a different pattern of circulating cytokines in HCV-SS patients (predominant Th2 response) compared with primary SS patients (predominant Th1 response) (66). A poor Th1 response (low levels of IL-2) and an enhanced Th2 response (high levels of IL-6 and IL-10), with high levels of sIL-2, was present in those patients with HCV-SS. This cytokine pattern is clearly different from that...
observed in patients with primary SS. We also analyzed the correlation of circulating cytokines with the main clinical and immunologic SS features and we found higher levels of IL-6 and IL-10 in SS patients with liver involvement. Thus, our results suggest that the monocyte/macrophage function (source of IL-6, IL-10 and TNFα) may be chronically stimulated in patients with HCV-related SS, probably as a consequence of the cellular reactivity against viral infection.

Predictive factors for lymphoma development

Clinical factors

Several investigators attempted to establish predictive factors for developing lymphoma in SS (Table IV). In 1978, Kassan et al. showed that lymphadenopathy, splenomegaly, parotidomegaly and previous exposure to cytotoxic agents were more often observed in those SS patients who developed lymphoma. More recently, Valesini et al. confirmed that lymphadenopathy and splenomegaly are risk factors for developing NHL, although some retrospective studies failed to support these findings.

Zufferey et al. described that the presence of extraglandular manifestations at the time of SS diagnosis was seen in all the patients who developed lymphoma. Purpura of the lower limbs is an extraglandular manifestation that has often been reported in SS patients with lymphoma and was found in 3 out of 5 patients with lymphoma many years before the development of lymphoma. In contrast, Valesini et al. found that patients who developed lymphoma showed a lower prevalence of ocular symptoms, arthralgia and anti-Ro/SSA antibodies. We also found that patients with a younger onset of SS (before the age of 35) have a higher prevalence of lymphadenopathy, RF and monoclonal immunoglobulins, as well as a higher prevalence of lymphoproliferative disease, thus conferring to the age at onset of SS an important prognostic value.

Immunological markers

In 1971, Cummings et al. described an important reduction of hypergammaglobulinemia was frequent just before the development of lymphoma. Other authors described decreases in previously elevated serum IgM and IgM-RF levels, but this finding has not been confirmed in some subsequent studies. Some authors also described elevated serum levels of beta2-microglobulin and soluble IL-2 receptor as laboratory markers of lymphoma development. Recently, Ioannidis et al. described that low C4 and palpable purpura were predictive factors of mortality and lymphoma development.

TABLE IV. Clinical and immunological findings suggesting malignant lymphoproliferation in primary Sjögren’s syndrome

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Immunological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent enlargement of parotid glands</td>
<td>Lowered serum IgM</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Negative rheumatoid factor (having been positive)</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>High serum β2-microglobulin</td>
</tr>
<tr>
<td>Mediastinal or hilar lymph nodes</td>
<td>Monoclonal gammopathy</td>
</tr>
<tr>
<td>Lung nodules</td>
<td>Mixed cryoglobulinemia</td>
</tr>
<tr>
<td>Persistent fever</td>
<td>Cross-reactive idiotypes (17-109, G6, SF18/2)</td>
</tr>
</tbody>
</table>

In 1986, Walters et al. described that urinary monoclonal free light chains may be of aid to the diagnosis of malignant lymphoma, and studies of RF from SS patients showed that the presence of cross-reactive idiotypes (CRI) 17-109 and G6 are associated with NHL. In a recent study, Tzioufas et al. prospectively investigated whether the presence of mixed monoclonal cryoglobulinemia and the monoclonal RF CRI may serve as predictive factors for lymphoma development in primary SS. In a series of 103 consecutive patients with SS followed for a period of 5 years, 7 patients developed lymphoma. Six of these 7 patients (86%) had cryoglobulinemia before the appearance of lymphoma, as compared to 12/96 (12%) of the remainder. The CRI 17-109 and G6 also correlated with the development of lymphoma. A step-wise multiple comparison analysis revealed that both of these CRI were linked to the presence of monoclonal mixed cryoglobulinemia.

Triple association between SS, HCV and NHL

The occurrence of B cell NHL is a complication of SS and, at least in some countries, of chronic HCV infection. In SS and HCV patients, lymphomas share several characteristics, such as a predominance of low grade marginal zone histological type, frequent mucosal localization, a possible transformation into a large B cell lymphoma, a close association with cryoglobulinemia and the localization of lymphomas in organs where HCV or SS are active. Lymphomagenesis in both diseases may be induced by the chronic stimulation of polyclonal B cells secreting RF at the site of the disease. SS might be, at least in some cases, related to a known (HCV, herpes virus) or unknown sialotropic virus that infects salivary glands, leading to chronic damage of these glands.
The immunologic characteristics of patients with NHL have scarcely been analysed. De Vita et al. characterized B-cell lymphomas in 35 consecutive HCV patients and found a definite clinical picture of MC or SS preceding NHL onset in 5 patients. When comparing the primary sites of NHL involvement at onset in patients with primary extranodal NHL according to the presence or absence of HCV infection, liver and salivary involvement were significantly more frequent in HCV patients. Primary localization in these organs is extremely uncommon in unselected series of B-cell NHL without HCV infection. We performed an exhaustive review of the main series of patients with NHL or SS searching for additional patients with the triple association between SS, HCV and lymphoma. We found 21 cases, most incompletely described. The autoimmune diseases diagnosed in all these patients were sicca/SSjögren syndrome associated to HCV infection. Haematologic neoplasia consisted of B-cell NHL in all patients and extranodal involvement was only detailed in 4 cases (parotid gland in 2, liver in 1 and stomach in 1). The presence of cryoglobulins was determined in 17 patients and was positive in 10 (59%), and hypocomplementemia was detected in 6/9 (67%). These data indicate a greater presence of the triple association between SS, HCV and NHL than previously suspected, suggesting the need for an exhaustive study of patients with «idiopathic» NHL searching for associated, silent SS and/or chronic HCV infection.

In a recent review, Mariette proposed that in both diseases the first event of lymphomagenesis is the chronic stimulation at the site of the disease of polyclonal B cells secreting rheumatoid factor (RF). The monoclonal secreted RF complexed with polyclonal IgG may cryoprecipitate. The following step would be chromosomal abnormalities, evolving into a low grade B cell lymphoma. A last event, such as a mutation of p53, might transform a low grade B cell lymphoma into a high grade B cell lymphoma. The triple association between SS, HCV and lymphoma suggests an important role of associated autoimmune and/or chronic viral diseases in the pathogenesis of B-cell lymphoproliferations and reinforces the suspected links between autoimmunity, infection and cancer.

### Table V. Triple association between systemic autoimmune diseases, HCV infection and hematologic malignancies: previous reports

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
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<th>SAD</th>
<th>Hematologic malignancy</th>
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<td>La Civita et al.</td>
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<td>Selva et al.</td>
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<td>Caramaschi et al.</td>
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CONCLUSIONS
HCV chronic infection may mimic the main clinical, immunologic and histologic features of primary SS, which could lead to the misdiagnosis of primary SS in HCV patients. However, SS-HCV patients present certain immunologic features that may allow to differentiate it from primary SS, such as a higher prevalence of cryoglobulinemia and hypocomplementemia, and a lower prevalence of anti-Ro/SS-A and anti-La/SS-B antibodies. Thus, HCV infection has been recently considered as exclusion criteria for the diagnosis of primary SS(90). HCV should be considered as a virus with a triple tissue tropism (hepatotropism, lymphotropism and sialotropism)(90), and this could explain the greater prevalence of sicca syndrome, cryoglobulinemia and lymphoproliferation observed in patients with chronic HCV infection. This triple association may have important therapeutic implications. Manette(90) has suggested that the best preventive treatment of lymphoproliferations occurring in SS probably consists in decreasing the hyperactivation of autoreactive B cells when it is present. Antiviral therapies should also be considered. Recently, it has been shown that the treatment with interferon of HCV patients with splenic villous lymphoma leads to regression of the lymphoma(92). Treatment with interferon of HCV patients with splenic villous lymphoma leads to regression of the lymphoma(92). Other therapeutic agents, such as 2-chloro-2-desoxyadenosine(93) or riloximab(94) may play an important role to treat B-cell lymphoma in SS-HCV patients. The closely association between NHL, SS and HCV should be considered as an interesting example of aetio-pathogenic overlap between autoimmunity, infection and lymphoproliferation.

REFERENCES


