HYPOTHESIS

Lymphomas complicating Sjögren’s syndrome and hepatitis C virus infection may share a common pathogenesis: chronic stimulation of rheumatoid factor B cells

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Abstract

Background—The occurrence of B cell non-Hodgkin’s lymphoma is a complication of Sjögren’s syndrome (SS) and, at least in some countries, of chronic hepatitis C virus (HCV) infection. Lymphomas occurring in both diseases share a number of characteristics: predominance of low grade, marginal zone histological type, frequency of mucosal localisation, possible transformation into a large B cell lymphoma, association with asymptomatic low level cryoglobulinaemia, absence of virus within lymphoma cells, but localisation of lymphomas in organs where the chronic viral infection is active in patients with HCV and where the autoimmune disease is active in patients with SS.

Hypothesis—It is 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). Then, that these RF B cells may become monoclonal and disseminate in other organs. The monoclonal secreted RF complexed with polyclonal IgG may cryoprecipitate. The following step would be a chromosomal abnormality (for example, trisomy 3 or bcl-2 translocation) which would confer to these cells a low grade B cell lymphoma compartment. A last event (for example, a mutation of p53) might transform this low grade B cell lymphoma into a high grade, large B cell lymphoma. The non-random utilisation of VH and VL by SS associated lymphoma B cells and the recent demonstration that these lymphoma B cells may display RF activity support the hypothesis that these lymphomas grow through an autotigen driven process.

Conclusion—The best preventive treatment of lymphoproliferations occurring in SS probably consists in decreasing the hyperactivation of autoreactive B cells when it is present, allowing the use of immunosuppressive drugs such as methotrexate or even tumour necrosis factor a antagonists, which in theory could favour other types of lymphoproliferation.

Lymphomas and Sjögren’s syndrome

Sjögren’s syndrome (SS) is an autoimmune disease characterised by a lymphocytic infiltration of salivary and lachrymal glands, leading to progressive destruction of these glands, and by production of autoantibodies.1 The occurrence of B cell non-Hodgkin’s lymphoma (NHL) represents a major complication in the evolution of SS in patients.2–3 The risk of lymphoma in patients with SS, which is equivalent for both primary and secondary SS, reached 6.4 cases/1000 a year (44 times greater than in a normal population) in 136 women with SS followed up for an average of 8.1 years.4 Comparable results (10–15% of lymphoma in patients followed up for more than 15 years) were obtained in several reports, including a small number of patients with NHL.5–7 Lymphomas complicating SS arise frequently in mucosal extranodal sites, not only the salivary glands but also the stomach and the lung. In an extensive study of 16 lymphomas occurring in patients with an underlying SS, we found a mucosal localisation in 13 patients (81%): parotid (seven cases), stomach (four cases), lung (three cases), skin (two cases), genital mucosa (one case).6 The same distribution was found: extranodal localisation in 80% of cases and salivary localisation in 55% of cases in a multicentre European study of 33 lymphomas.8

Most of the lymphomas described are low grade lymphomas, but various histological subtypes have been reported. A recent description of marginal zone B cell lymphomas (MZL), which encompasses both MALT lymphomas and their nodal counterpart: monocytoid B cell lymphomas (MBCL),9 allows a reinterpretation of the various histological subtypes of NHL described in patients with SS. Both variants (MALT and MBCL lymphomas) involve the marginal B cell compartment of lymphoid tissue, outside the follicular and mantle zones, share the same propensity for plasmacytic differentiation and a distinctive immunological phenotype, and often exhibit a similar chromosomal abnormality (trisomy 3 in 50% of cases).10 Furthermore, MZL can progress to high grade, large B cell
lymphomas. In the light of these data, a large number of reported NHL in patients with SS can be reclassified as MZL, either of low grade or of low grade transformed into high grade lymphomas. Our study of 16 NHL occurring in patients with SS provides arguments in favour of this interpretation.9

Earlier studies identified predisposing factors for the occurrence of NHL in patients with SS: parotidomegaly, low dose parotid irradiation, splenomegaly, lymphadenopathy, presence of a serum or urinary monoclonal component, and a decrease in serum polyclonal immunoglobulins.7 The possibility that detection of clonal B cells by polymerase chain reaction (PCR) may help to distinguish lymphoma from benign lymphoepithelial lesions remains controversial. In one study, 14/14 (100%) labial saliva gland (LSG) specimens of patients with SS exhibited oligoclonal or monoclonal immunoglobulin gene rearrangements by PCR; in one patient with lymphoma, tumour and LSG specimens obtained at the same time displayed different immunoglobulin gene rearrangements. However, in another study, monoclonal B cells were detected by PCR in only 11/76 (14%) LSG specimens of patients with SS6; four of these 11 patients subsequently developed extrasalivary lymphoma, and in each case the rearranged bands in the lip biopsy specimen and the lymphoma were of the same size.

If the significance of the detection of an isolated B cell clone remains controversial, it is now established that the risk of lymphoma progression is high if the same B cell clone is detected in different tissues at different times.10 Recently, Moutsopoulos’s group showed that the main predisposing factor for the occurrence of NHL in patients with SS is the presence of a serum mixed cryoglobulinaemia,7 usually asymptomatic. Factors associated with cryoglobulinemia: low C4 level, purpura16 or, in another study, the presence of leg ulcers,17 were also associated with lymphoma. In patients without any of these factors, no risk of lymphoma was found.10

Different viruses have been implicated in the cause of some sicca syndromes, but viruses known to be present in other types of lymphomas (hepatitis C virus (HCV), Epstein-Barr virus, human herpes virus 8, or human T lymphotropic virus I) were not detected in lymphomas complicating SS.7 The possibility of activation of proto-oncogenes by translocation or mutations has been studied. Using PCR, we detected a t(14;18) major breakpoint region translocation in one of eight lymphomas tested.3 The t(14;18) translocation is usually not present in MZL.10 However, it has already been detected by two groups in a subset of Sjögren’s lymphomas.5 12 Pisa et al found the t(14;18) translocation in five of seven SS associated salivary lymphomas.4 It was not present, however, either in pre-lymphoma biopsy specimens from these patients, even though they exhibited oligoclonal B cell rearrangements, or in 50 salivary gland biopsy specimens of patients with SS. Interestingly, the t(14;18) translocation could be detected in bone marrow from a minor subset of patients with SS without lymphoma.19

Mutations in the tumour-suppressor activity gene p53 have been found in lymphomas and have been associated with progression of low grade MALT lymphoma to high grade.20 This inactivation of p53 activity is accompanied by an overexpression of the p53 protein, and in half of the cases by detection of serum anti-p53 antibodies. We detected serum anti-p53 antibodies in two of the 14 patients studied; both had a nodal MZL.21 Tapinos et al detected mutations of p53 in all of four studied salivary lymphomas and not at all in seven salivary gland biopsy specimens from patients with SS.22 Finally, using different sensitive cytogenetic techniques, Ihrler et al found no abnormalities in 12 benign salivary lymphoepithelial lesions from patients with SS, but detected complex chromosomal aberrations, particularly an increased prevalence of trisomy 18, in six of 13 salivary low grade MALT lymphomas and all of four salivary high grade lymphomas from patients with SS.23

Lymphomas associated with SS and HCV infection share common features

Despite the absence of a recurrent chromosomal alteration and of an associated virus, these lymphomas complicating SS probably have a common pathogenesis, in view of their frequency and their common localisations and histological subtypes. I propose that a key factor in understanding the pathogenesis of these SS associated lymphomas may be the sharing of a number of characteristics with lymphomas that complicate HCV infection. Indeed, even though it has not been confirmed in other countries to date, some Italian, American, and Japanese studies have reported a high prevalence (9–32%) of chronic HCV infection in patients with B cell NHL.24–26

Two subtypes of NHL complicating HCV infection must be distinguished: (a) lymphomas occurring in the long term evolution of symptomatic essential mixed cryoglobulinaemia (EMC). Most of these lymphomas are low grade lymphoplasmacytic B cell NHL, with bone marrow involvement. HCV RNA has been found in up to 98% of patients with EMC,27 and the occurrence of such B cell proliferations was known in these patients before it was shown that EMC was linked to HCV. (b) Another type of lymphoma seems to be more common in patients with HCV infection, frequently associated with asymptomatic cryoglobulinaemia and sharing a number of characteristics with SS associated lymphomas25—namely, low grade marginal zone histological type, frequency of mucosal localisation, possible transformation into large B cell lymphoma, association with asymptomatic low level cryoglobulinaemia, absence of virus within lymphoma cells in most cases but localisation of lymphomas in organs where the chronic viral infection is active.
Hypothesis of a common pathogenesis

In both HCV infection and SS, polyclonal B cell activation leads to secretion of rheumatoid factor (RF). In HCV infection, the triggers of RF production are probably complexes with HCV and anti-HCV IgG. In SS, the presence of RF is associated with other autoantibodies whose origin is unknown, but might also be the result of a chronic viral stimulation. Indeed, SS might be, at least in some cases, related to a known or unknown sialotropic virus. HCV itself may be detected in saliva and may lead to a sicca syndrome, different from autoimmune SS, but with histological lesions of salivary glands mimicking those of SS.

Therefore, I make the assumption that in both diseases the first event of lymphomagenesis is the chronic stimulation at the site of the disease of polyclonal B cells secreting RF (fig 1). A consequence of this polyclonal activation of autoimmune B cells might be the increased frequency of bcl-2 rearrangement in peripheral blood leucocytes, described both in SS and in HCV infection. Then, these RF B cells may become monoclonal and disseminate into other organs. The monoclonal secreted RF complexed with polyclonal IgG may cryoprecipitate. This state could be reversible if the chronic stimulation of RF B cells is stopped. The following step would be a chromosomal abnormality (for example, trisomy 3, translocation of bcl-2 or mutation of p53), which would confer to these cells a low grade B cell lymphoma compartment. The mucosal localisation of these abnormal RF B cells, with a less effective control by T cells than in lymph nodes or bone marrow, might favour their survival. A last event (for example, a mutation of p53) might transform this low grade lymphoma into a high grade large B cell lymphoma.

Testing the hypothesis

If this hypothesis is correct, most of the B cell lymphomas associated with SS or HCV should have a surface immunoglobulin with RF activity. This assumption is suggested by the non-random utilisation of VH and VL by SS associated lymphoma B cells: seven VH genes have been sequenced and used exclusively VxIII genes (Humkv325, Humkv328, or Vg). These genes (51p1, Humkv325, and Humkv328) are known to be used preferably by B cells secreting RF. The same restriction of VH and VL genes has been found in lymphomas complicating HCV infection. Recent estimates indicate that there are approximately 51 VH and 32 Vx functional segments in the average human genome. Therefore, the probability of chance selection alone of three of five lymphomas that coexpress the 51p1, VH, and Humkv325 gene segments is extremely low. Moreover, analysis of mutations seen in VH genes of lymphomas complicating either SS or HCV infection, suggests an antigen driven process for the growth of these lymphomas.

Nevertheless, these points are not sufficient to prove that SS associated lymphoma B cells have RF activity. Indeed, it is admitted that, if these VH and VL genes are often used by B cells secreting RF, they are also overused in the expressed normal repertoire. Further support that these lymphoma B cells display RF activity comes from their sequence which often starts with the same amino acids as CDR3 from RF—glycine - aspartate - tyrosine—and whose length is usually the same as the length of CDR3 from RF: 14-15 aa. However, to demonstrate definitively the RF activity of lymphoma B cells, it was necessary to transfec heavy and light chain variable genes in a non-secretory myeloma cell line, and show that the secreted immunoglobulins have RF activity. These experiments were recently performed by Pasquali’s group who demonstrated an RF activity of membrane immunoglobulin of two lymphomas complicating SS.

Conclusion: therapeutic consequences

In conclusion, the chronic stimulation at the site of the disease of autoimmune B cells (for example, RF B cells) may be the first event of lymphomagenesis in both autoimmune diseases and chronic infections (like HCV or Helicobacter pylori infection).

In HCV infection the best preventive treatment of lymphoproliferations may be antiviral treatment. Indeed, it has been shown recently that an effective treatment of HCV infection with interferon α and ribavirin induced a

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Figure 1  Pathogenic hypothesis suggested owing to shared characteristics between lymphomas complicating HCV infection and Sjögren’s syndrome. HCV = hepatitis C virus; Bλ = B lymphocyte; pc = polyclonal; mc = monoclonal; RF = rheumatoid factor.
dramatic decrease of t(14–18) positive cells present in the blood of these patients, cells which may represent an activated reservoir of autoimmune pre-lymphomatous cells. Accordingly, we have recently described six patients with both chronic HCV infection and splenic marginal zone lymphoma with villous lymphocytes in complete or very good partial remission after antiviral treatment with interferon α.

In Sjögren’s syndrome, in the absence of a known cause of the disease, the best preventive treatment of lymphoproliferations is probably to decrease the hyperactivation of autoreactive B cells when it is present, allowing the use of immunosuppressive drugs such as methotrexate or even TNFα antagonists, which in theory could favour other types of lymphoproliferations that do not share any common characteristic with SS associated lymphomas.

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