

Diffuse Large B-Cell Lymphoma as a Sequela of Sjögren's Syndrome: A Case Report

Ildiko Fanny Horvath, Peter Szodoray and Margit Zeher*

Division of Clinical Immunology, 3rd Department of Medicine, Medical and Health Science Centre, University of Debrecen, 22 Moricz Zs. Street, 4032 Debrecen, Hungary

Abstract: We present a case of a 45-year-old woman with primary Sjögren's syndrome, who in 2005, one year after the onset of the systemic autoimmune disease developed chronic lymphocytic leukaemia, which eventually transformed - denoted as Richter's transformation - into diffuse large B-cell lymphoma in 2006. She had recurrent lymphadenopathy on the neck region from 2002. In September 2005 anaemia and elevated LDH enzyme levels were detected with persistent subfebrility and lymphatic node enlargement on her neck and axillary region. Chest and abdominal CT, biopsy from the lymphoid glands and crista biopsy were performed and B-CLL was diagnosed, therefore chlorambucil treatment was administered. After two cycles of chlorambucil the pulmonary involvement extended, the patient had high fever and the abdominal CT showed the appearance of multiple hypodens lesions in the liver. Based on the histological evaluation of the hypodens lesions of the liver, the diagnosis of diffuse large B-cell lymphoma has been established, therefore 8 cycles of R-CHOP treatment were administered. The patient has been in complete remission since then.

Conclusion: The main message of this case report is that lymphadenopathy, the decrease of serum immunoglobulin levels and autoantibody titres, as well as the predominance of monoclonal gammopathy point to the possibility of malignant transformation in patients with Sjögren's syndrome.

INTRODUCTION

The frequent association between autoimmune diseases and non-Hodgkin's lymphoma (NHL) has been described previously and could be explained - at least partially - that the immunoproliferative disorders in these patients are probably multi-causal (genetic predisposition, toxic immunosuppressant therapies). Sjögren's syndrome (SS) is associated with an increased risk of NHL (4- to 40-fold and higher risk for primary disease than for secondary disease). A 1000-fold increased risk of parotid gland marginal zone lymphoma, diffuse large B-cell and follicular lymphomas have been described [1-3]. NHL is considered to be the most serious complication of SS. The risk of developing NHL, which is equivalent to both primary and secondary SS, is estimated to be 44 times higher than that of in a healthy population [3]. NHLs in SS patients occur chiefly in salivary glands and in other mucosa-associated lymphoid tissues (MALT), as well as in lymph nodes and bone marrow. The evolution from benign lymphocytic infiltration characteristic of SS to malignant NHL is probably a multi-step process. However, the underlying molecular events are still unknown [4-8]. Although the exact pathomechanism is unknown, there are clinical predisposing factors for the occurrence of NHL in SS patients such as parotid gland's enlargement, splenomegaly, lymphadenopathy, palpable purpura and laboratory parameters (e.g. presence of low levels of complements, mixed cryoglobulinemia, decrease in serum polyclonal

immunoglobulins, or the presence of serum or urinary monoclonal components) [1-8]. In SS each subtype of NHLs has been reported, the most common types of them are the extra-nodal B-cell type mucosa-associated lymphoid tissue (MALT) lymphomas (28-fold increased risk compared to the normal population) and the aggressive diffuse large B-cell lymphomas (11-fold increased risk compared to the normal population). Thus, the association between SS and MALT lymphomas is well-defined and known, we believe that in SS, diffuse large B-cell lymphomas should get more attention because of their frequent occurrence in this systemic autoimmune disease. However, the common features of their pathomechanisms still need to be explored. [9-12]. The main elements of common pathomechanism between SS and NHLs are the following: chronic antigen stimulation in the exocrine glands, high level of B-cell activating factor (BAFF), major genetic aberrations which may lead to failure in the apoptotic system, which generally leads to uncontrolled proliferation [9-14]. Richter's syndrome is the transformation of a chronic lymphocytic leukaemia (CLL) into a diffuse large B-cell lymphoma. This evolution is an unusual and serious complication of CLL with an incidence of 1-10% of all CLL cases [15]. CLL and the diffuse large B-cell lymphoma (DLBCL) are very different forms of malignant lymphoproliferative diseases with different aggressiveness, morphological characteristics and surface markers such as many types of clusters of differentiation molecules (CDs) for example CD5, CD19, CD23 in B-CLL and CD20 in DLBCL [15].

According to our best knowledge there is no example or case-report which explains the association between Sjögren's and Richter's syndrome. The main aim of this work is to

*Address correspondence to this author at the Division of Clinical Immunology, 3rd Department of Medicine, Medical and Health Science Centre, University of Debrecen, 22 Moricz Zs. Street, 4032 Debrecen, Hungary; Tel: 36-52-414-969; Fax: 36-52-414-969; E-mail: zeher@iibel.dote.hu

examine this very rare type association of NHL lymphomas to SS while showing its clinical characteristic and special laboratory findings of this association.

CASE DESCRIPTION

In 2002 a 39-year old female accountant attended our clinic with persistent lymphadenomegaly on her neck region. Two biopsies from the lymph node conglomerate were performed between 2002 and 2004. Without evidence of malignancy, the histological evaluation showed immunoreactive diffuse hyperplasy. The patient had no family history of malignancy or autoimmune disorders. In her past medical history there were no significant illnesses before 2002. After 2002 the patient attended our out-patient clinic for control every three months and other symptoms (xerophthalmia, xerostomy, vasculitis with palpable purpura) gradually developed which suggested the onset of a systemic autoimmune disease. In our out-patient clinic there is a general practice that we check our patients every 6 months to observe the changes of symptoms or laboratory parameters of systemic autoimmune disease. Those cases where any dysfunctions suggesting manifestation of lymphoproliferative disorders had been found are checked every 3 months. Positive laboratory findings were: rheumatoid factor (RF)-, anti-beta2 glykoproteins (IgG-, IgM) and anti-cardiolipin (CL IgG-, A-, M isotypes too) autoantibody positivity, low level of complements (C4, C1q) and reduced (0.06 ml/min) saliva production with sialometry. The patient had objective xerostomy and xerophthalmia with positive results of diagnostic tests such as Schirmer's-test and sialometry; she had elevated levels of anti-SS-A and anti-SS-B, and minor salivary gland biopsy was performed to fulfil the histological diagnostic criteria for SS. Finally, the patient fulfilled the diagnostic criteria for primary SS according to the corresponding diagnostic criteria in February 2005 [16]. In September 2005 we observed lymphadenomegaly in the axillary regions and the neck, as well as predominantly increased body temperature (37.0-37.5 °C). We found high levels of lactate-dehydrogenase (LDH was 603 IU/L, normal value: 230-460 IU/L) and 10.4 g/dL normochrom, normocytic anaemia (haemoglobin, normal value: 12.0-16.0 g/dL). In order to screen for haematological/lymphoproliferative ma-

lignancy, crista biopsy (a method which is used to take bone-marrow sample from the region of crista iliaca posterior superior for histological examination for correct haematological diagnosis) was performed. Complementary genetic measurements were assessed and we found heavy chain of immunoglobulin (IgH) and T-cell receptor (TCR) polyclonal gene-redistribution. We could not confirm paraprotein in serial sera samples. Chest- and abdominal computer tomography (CT) were performed to determine the extent of the malignant process. The chest X-ray revealed multiple round shadows perihilary and a large consolidation with necrotic parts (the diameter of this consolidation was 60 mm) in the space above the left side of diaphragm, near the heart. On the chest CT a 4x5x6 cm lesion was apparent, while the abdominal CT showed numerous enlarged lymph nodes with retroperitoneal appearance, as well as moderate splenomegaly. These findings suggested lymphoma. The patient had primary Sjögren's syndrome mainly with sicca symptoms and associated clinical symptoms and specific laboratory findings of vasculitis as extra-glandular manifestations until the onset of lymphatic node enlargements, as first signs of lymphoma-development. We did not find any other extra-glandular features, such as lung or kidney involvement. The first biopsy from the axillary lymph node suggested B-cell type CLL (B-CLL) with anti-CD5 positive small lymphocytic lymphoma (Fig. 1). In September 2005, according to present classification system, RAI3 stage of B-CLL was diagnosed with lymphocytosis, lymphatic node enlargement, splenomegaly and anaemia, therefore chlorambucil treatment was administered. During the next check-up in March 2006, we repeated the chest CT and we found that the diameter of the consolidation increased (from 6 to 8 cms) and this solid structure transformed to a multilocular-cystic lesion and new small (1-1.5 cm) round shadows appeared in the upper lobes of the right and left lungs (Figs. 2, 3). After 2 cycles of chlorambucil the pulmonary involvement extended. The repeated abdominal CT showed multiple, hypodens lesions in the liver and besides the known lymph node enlargement in the retroperitoneal region, new abnormal lymph nodes appeared along the great vessels (aorta and celiac trunc) of the abdomen and in the hile of the liver. In March 2006 we found 80 g/L hypochrom, microcytic anaemia (mean cell volume

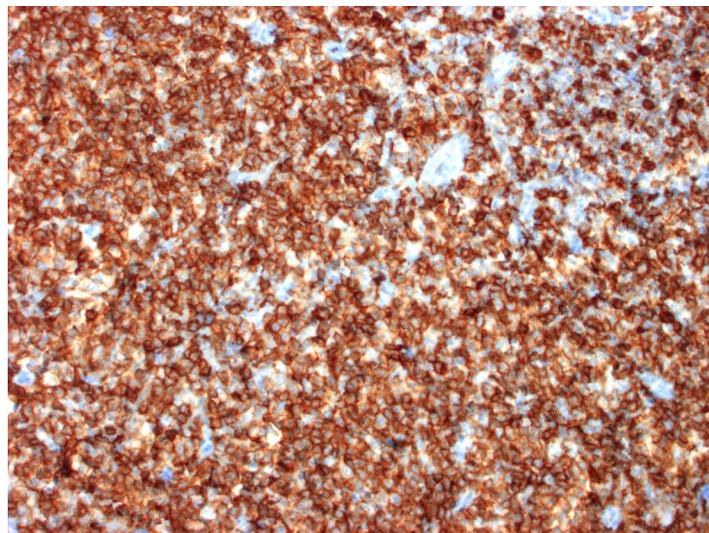


Fig. (1). The biopsy from the axillary lymph node suggested small lymphocytic lymphoma (anti-CD5 staining, 20x).

[MCV] 76,3 fL [normal value: 80-99 fL], mean cell haemoglobin [MCH] 22.9 pg [normal value: 27-31 pg], mean cell haemoglobin concentration [MCHC] 300 g/l [normal value: 315-355 g/L], elevated C-reactive protein (CRP 111.69 mg/L [normal value < 5 mg/L]), elevated liver enzymes (LDH 548

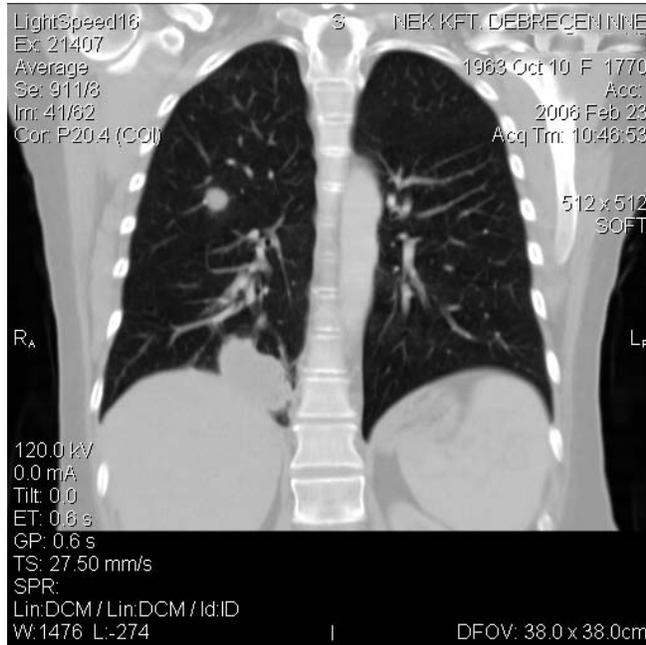


Fig. (2). The chest X-ray showing multiple round shadows perihilar and a large consolidation with necrotic parts (the diameter of this consolidation was 60 mm) in the heart-diaphragm square.

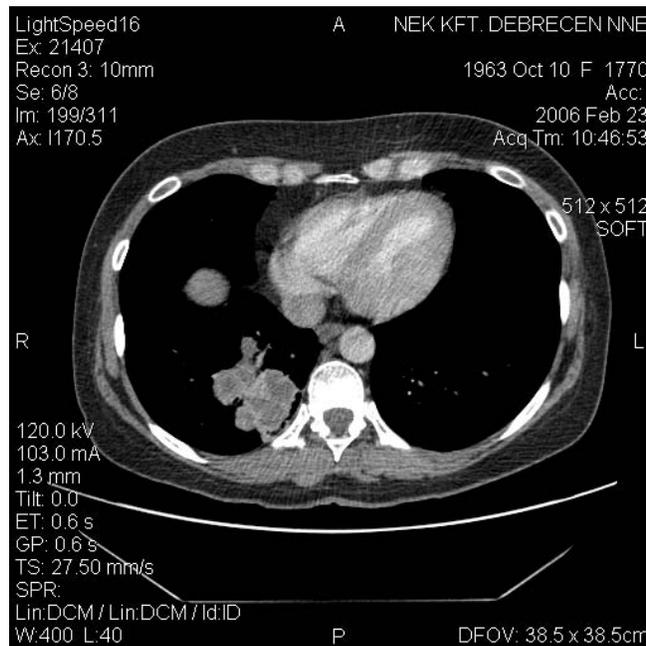


Fig. (3). The solid structure of the lesion in the heart-diaphragm square subsequently transformed to a multilocular-cystic lesion and new small (1-1.5 cm) round shadows appeared in the right and left upper lobes of the lungs in March 2006 (chest CT).

IU/L [normal value: 230-460 IU/L], gamma-glutamyl-transferase [GGT] 337 IU/L [normal value: 7-50 IU/L], alkaline-phosphatase [AP] 624 IU/L [normal value: 200-280 IU/L]). In April 2006, liver biopsy was performed and the immuno-histochemical evaluation showed CD20 positive diffuse large B-cell type lymphoma (DLBCL), stage IV/B (Figs. 4, 5), suggesting poor prognosis. There were no bone marrow involvement. Immune-chemotherapy was started with R-CHOP (rituximab, cyclophosphamide, vincristine, adriablastin, methylprednisolone). Rituximab was administered at a dose of 375 mg/m² given at the beginning of each treatment cycle of chemotherapy with 21-day intervals. For the patient's 1.79 m² body surface 700 mg of rituximab with 1350 mg cyclophosphamid, 2 mg vincristin, 90 mg adriablastin, 80 mg methylprednisolone was administered. From April 2006 to January 2007 she received 8 cycles R-CHOP therapy. At present, twelve months after the completion of her therapy the DLBCL is in complete remission and the extraglandular signs of SS are in inactive clinical stage with the administration of 250 mg per day oral dose of hydroxychloroquine and 6 mg per day methyl-prednisolone.

DISCUSSION

The association of NHL with SS has been described in detail previously [1-12] although the underlying pathogenic background is still unknown. Richter's syndrome denotes the development of aggressive lymphoma that arises in patients with CLL. Richter's transformation is a very rare entity which occurs in approximately 1-10% of CLL patients. Treatment options for these patients are limited and include combination chemotherapy with or without the addition of monoclonal antibodies and stem cell transplantation [17, 18]. In this work we showed an important case of this rare syndrome, with a positive outcome. To the best of our knowledge the association between Richter's syndrome and SS has not been described previously. The pathogenesis of NHL in SS is an intricate multi-step process, including B cell monoclonal proliferation, driven by oncogenic and/or infectious agents, as well as cytokines. Various predictive factors such as persistent enlargement of parotid glands, adenopathy, splenomegaly, palpable purpura, low levels of various complements, mixed cryoglobulinemia, monoclonal gammopathy, and decrease in serum polyclonal immunoglobulines suggest potential lymphoma evolution [1-8]. Several genetic aberrations of MALT lymphoma have been identified, some of which appear to play an important role in the pathogenesis of the disease. For example the mutation of *MALT1* gene with translocation mechanism t(11;18)(q21;q21) is considered to be specific for MALT lymphomas. This translocation results in the synthesis of the *API2-MALT1* fusion protein, which can activate nuclear factor-KB, a transcription factor for a number of survival-related genes. Up-regulation of these molecules promotes cellular proliferation and resistance to apoptotic signals. Another translocation of t(14;18)(q32;q21) involving *IGH* and *MALT1* in patients with MALT lymphomas has been reported, too. Although the potential function of this particular translocation in the pathogenesis of MALT lymphomas has not yet been elucidated, these findings together with the data published on t(11;18)(q21;q21) suggest *MALT1* rearrangements in up to 50% of all patients with MALT lymphoma. The NHLs in SS are usually B-cell neoplasms in which the clonally rearrangements of the im-

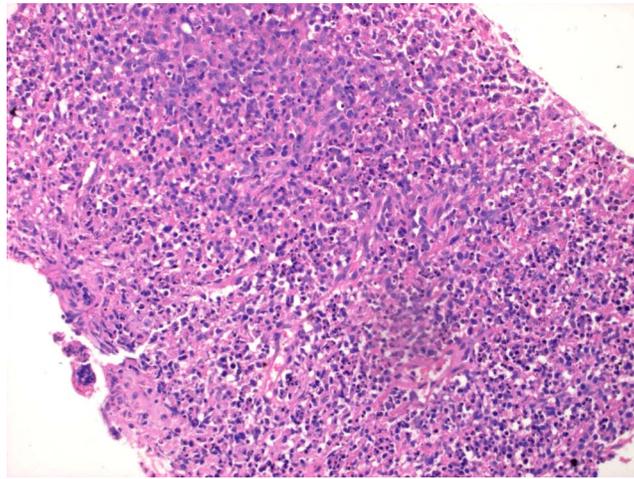


Fig. (4). Liver biopsy showing CD20 positive diffuse large B-cell type lymphoma (DLBCL) (H.E. staining, 20x).

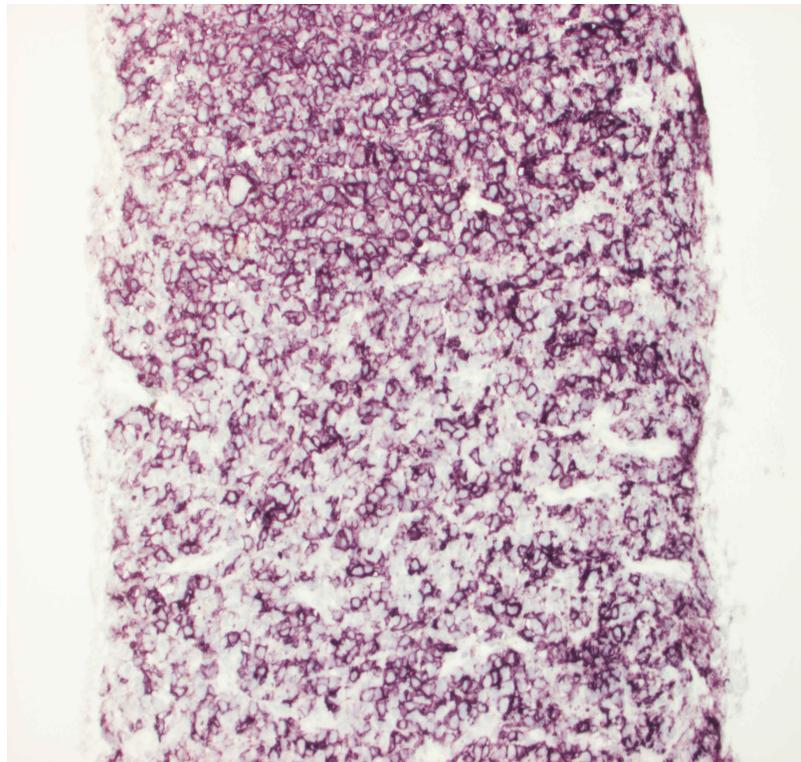


Fig. (5). Immunohistochemistry showing CD20 positive infiltrating cells (anti-CD20 staining, 20x).

munoglobulin genes have been found. Recently data suggest that certain mutations in the genes of Fas (one of the cell-surface receptors involved in cell death pathway) and Fas ligand (Fas-L) can play important role in the pathogenesis of autoimmune-related lymphoproliferation. As stated in other findings the expression of Bcl-2 (one of the anti-apoptotic proteins) and the relative decrease of Bax (with pro-apoptotic effect) together with an increasing Bcl-2/Bax ratio in cells may explain their resistance to apoptosis, resulting in a prolonged life-span and the perpetuation of conditions which may lead to the development of lymphomas [19-24]. The common genetic background of the association of SS and Richter's syndrome has not been described previously in the literature. SS can associate with any type of NHL. Its association with DLBCL has been found to become more

frequent. In this report we described a severe case with the second most frequent type of NHL in SS, fortunately with a favourable outcome owing to modern chemotherapy. The treatment of SS associated NHL depends on the type of the lymphoma itself. Rituximab has been used in the treatment of NHL since 1997. The first observations on the additional therapy using monoclonal antibodies in DLBCL were published by Coiffier *et al.* in 2002 and they reported better remission rate with rituximab opposed to CHOP combination alone [25]. Further successful treatments in DLBCL with added rituximab therapy have been described previously [26-29]. The exact mode of action of rituximab (anti-CD20 monoclonal antibody) is unclear, although the following effects have been proposed. The Fc portion of molecule mediates antibody-dependent cellular cytotoxicity (ADCC) and

complement-dependent cytotoxicity (CDC), which are general regulatory effects on the cell cycle. The rituximab increases MHC II and adhesion molecules lymphocyte function-associated antigens [LFA]-1 and LFA-3, it elicits shedding of CD23, it downregulates the B-cell receptor and it induces apoptosis of CD20+ cells [30]. The combined effect results in the elimination of B cells (including the cancerous ones) from the body, allowing the repopulation with healthy B cells developing from lymphoid stem cells. We could confirm these data on the beneficial effect of added rituximab therapy with our patient who is in complete remission over one year.

We believe that the regular follow-up of patients with SS is of significant importance and the laboratory/radiological and clinical check-ups for malignant transformation are necessary. With the administration of biologicals along with regular cytostatic agents in SS patients with lymphoma a better outcome can be achieved, and life expectancies become more favourable.

REFERENCES

- [1] Ekström Smedby K, Vajdic CM, Falster M, *et al.* Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 2008; 111: 4029-38.
- [2] Valesini G, Priori R, Bavoillot D, *et al.* Differential risk of non-Hodgkin's lymphoma in Italian patients with primary Sjogren's syndrome. *J Rheumatol* 1997; 24: 2376-80.
- [3] Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LT. Lymphoma and other malignancies in primary Sjogren's syndrome. A cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis* 2006; 65: 796-803.
- [4] Royer B, Cazals-Hatem D, Sibilia J, *et al.* Lymphomas in patients with Sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. *Blood* 1997; 90: 766-75.
- [5] Karin Ekström S, Henrik H, Johan A, *et al.* Autoimmune and chronic inflammatory disorders and risk of Non-Hodgkin Lymphoma by subtype. *J Natl Cancer Inst* 2006; 98: 51-60.
- [6] Zulman J, Jaffe R, Talal N. Evidence that the malignant lymphoma of Sjögren's syndrome is a monoclonal B-cell neoplasm. *N Engl J Med* 1978; 299: 1215-20.
- [7] Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. *Arthritis Rheum* 1999; 42: 1765-72.
- [8] Mariette X. Lymphomas in patients with Sjögren's syndrome: review of the literature and physiopathologic hypothesis. *Leuk Lymphoma* 1999; 33: 93-9.
- [9] Tonami H, Matoba M, Kuginuki Y, *et al.* Clinical and imaging findings of lymphoma in patients with Sjogren syndrome. *J Comput Assist Tomogr* 2003; 27: 517-24.
- [10] Smedby KE, Baecklund E, Askling J. Malignant lymphomas in autoimmunity and inflammation a review of risks, risk factors, and lymphoma characteristics. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2069-77.
- [11] Trejo O, Ramos-Casals M, López-Guillermo A, *et al.* Hematologic malignancies in patients with cryoglobulinemia: association with autoimmune and chronic viral diseases. *Semin Arthritis Rheum* 2003; 33: 19-28.
- [12] Talal N, Bunim JJ. The development of malignant lymphoma in the course of Sjögren's syndrome. *Am J Med* 1964; 36: 529-40.
- [13] Szodoray P, Jonsson R. The BAFF/APRIL system in systemic autoimmune diseases with a special emphasis on Sjögren's syndrome. *Scand J Immunol* 2005; 62: 421-8.
- [14] Jonsson MV, Szodoray P, Jellestad S, Jonsson R, Skarstein K. Association between circulating levels of the novel TNF family members APRIL and BAFF and lymphoid organization in primary Sjögren's syndrome. *J Clin Immunol* 2005; 25: 189-201.
- [15] Ghofrani M, Tantiwongkosi B, Smith AS, Wasdahl DA. Richter transformation of chronic lymphocytic leukemia presenting as a dural-based non-hodgkin lymphoma mass. *AJNR* 2007; 28: 318-320.
- [16] Vitali C, Bombardieri S, Jonsson R, *et al.* Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-558.
- [17] Swords R, Bruzzi J, Giles F. Recent advances in the diagnosis and therapy of Richter's syndrome. *Med Oncol* 2007; 24: 17-32.
- [18] Tsimberidou AM, Keating MJ. Richter's transformation in chronic lymphocytic leukemia. *Semin Oncol* 2006; 33: 250-6.
- [19] Abbondanzo SL. Extranodal marginal-zone B-cell lymphoma of the salivary gland. *Ann Diagn Pathol* 2001; 5: 246-54.
- [20] Farmer JP, Lamba M, Jordan DR, Gilberg S, Bence-Bruckler I, Burns BF. Lymphoproliferative lesions of the lacrimal gland: clinicopathological, immunohistochemical and molecular genetic analysis. *Can J Ophthalmol* 2005; 40: 151-60.
- [21] Streubel B, Huber D, Wöhrer S, Chott A, Raderer M. Frequency of chromosomal aberrations involving *MALT1* in mucosa-associated lymphoid tissue lymphoma in patients with Sjögren's syndrome. *Clin Cancer Res* 2004; 10: 476-80.
- [22] Royer B, Cazals-Hatem D, Sibilia J, *et al.* Lymphomas in patients with Sjögren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. *Blood* 1997; 90: 766-75.
- [23] Bahler DW, Miklos JA, Swerdlow SH. Ongoing Ig gene hypermutation in salivary gland mucosa-associated lymphoid tissue-type lymphomas. *Blood* 1997; 89: 3335-44.
- [24] Takacs I, Zeher M, Urban L, Szegedi G, Semsei I. Diagnostic value of the detection of t(14;18) chromosome translocation in malignant hematological and immunopathological diseases using polymerase chain reaction. *Acta Med Okayama* 2000; 54: 185-92.
- [25] Coiffier B, Lepage E, Briere J, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346: 235-42.
- [26] Vose JM, Link BK, Grossbard ML, *et al.* Phase II study of rituximab in combination with chop chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 2001; 19: 389-97.
- [27] Pfreundschuh MG, Trumper L, Ma D, *et al.* Randomized intergroup trial of first line treatment for patients (60 years with diffuse large B-cell non-Hodgkin's lymphoma with a CHOP-like regimen with or without the anti-CD20 antibody rituximab—early stopping after the first interim analysis. *Proc ASCO* 2004; 556.
- [28] Voulgarelis M, Giannouli S, Tzioufas AG, Moutsopoulos HM. Long term remission of Sjögren's syndrome associated aggressive B cell non-Hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) *Ann Rheum Dis* 2006; 65: 1033-7.
- [29] Simon Zs, Tarr T, Ress Zs, Gergely L, Kiss E, Illes A. Successful rituximab-CHOP treatment of systemic lupus erythematosus associated with diffuse large B-cell non-Hodgkin lymphoma. *Rheumatol Int* 2007; 28: 179-83.
- [30] Szodoray P, Alex P, Dandapani V, *et al.* Apoptotic effect of rituximab on peripheral blood B cells in rheumatoid arthritis. *Scand J Immunol* 2004; 60: 209-18.