Case Report

Cutaneous T Cell Lymphoma in a Patient with Primary Biliary Cirrhosis and Secondary Sjögren's Syndrome

ARNE STROEHMANN, THOMAS DÖRNER, ANSGAR LUKOWSKY, EUGEN FEIST, FALK HIEPE, and GERD-RÜDIGER BURMESTER

ABSTRACT. We describe a patient with primary biliary cirrhosis (PBC) and secondary Sjögren's syndrome (SS) with pulmonary involvement who developed a cutaneous T cell lymphoma. The clinical course of secondary SS in PBC is thought to be less complicated than in progressive systemic scleroderma and SS. In contrast to secondary SS, the risk for developing non-Hodgkin's lymphoma is highly increased in patients with primary SS. Moreover, these lymphomas are usually of B cell origin. There are few reports of T cell lymphoma in primary SS. The occurrence of a T cell lymphoma in a patient with PBC and secondary SS indicates the necessity to investigate lymphoma in patients with secondary SS. (J Rheumatol 2002;29:1326–9)

Key Indexing Terms:
PRIMARY BILIARY CIRRHOSIS
SJÖGREN'S SYNDROME
T CELL LYMPHOMA
MYCOSIS FUNGOIDES

Primary biliary cirrhosis (PBC) is frequently associated with secondary Sjögren's syndrome (SS). The course of secondary SS in patients with PBC is similar to that seen in patients with rheumatoid arthritis (RA) and SS[1]. In this regard, the occurrence of pulmonary manifestations predominantly as lymphocytic interstitial pneumonitis has also been described. Most notably, an increased risk for the preferential development of B cell lymphoma is well documented for patients with SS[2]. To date, only a small number of cases of cutaneous T cell lymphoma occurring in SS have been described[3-6]. To our knowledge, this report describes the first case of T cell lymphoma in a patient with PBC and secondary SS.

CASE REPORT

A 51-year-old woman presented with a 5 year history of PBC with liver biopsy classified to stage II according to Ludwig, *et al*[7], along with characteristic laboratory, histological, and autoantibody findings. She had SS presenting repetitive periods of bilateral swelling of the salivary glands and sicca symptoms over a period of 5–6 years. The diagnoses of PBC and secondary SS were established at the same time and therefore distinction of a preceding disease is difficult. A salivary gland biopsy exhibited the characteristic immunohistopathological alterations with a focus score ≥ 2. As a complication of SS, she also developed pulmonary fibrosis, based on both radiographic findings and reduced diffusion capacity. For 5 years, administration of steroids and ursodesoxycholic acid as well as artificial tears resulted in a stable course.

She was admitted to our hospital with general malaise lasting 6 weeks, accompanied by a generalized maculous rash. She did not report fever, weight loss, or other symptoms. Shortness of breath, however, had increased in the previous 6 months. The itchy efflorescence had been resistant to treatment (antibiotics, antimycotics, local steroids, etc.) by her general practitioner.

On examination, she was in a reduced medical condition. Signs of early-stage exogenous Cushing's syndrome were apparent. Although predominantly localized on the legs, dry and squamous skin lesions were visible throughout the whole body that did not blanch on pressure (Figure 1). Schirmer's test was positive: left eye 3 mm/5 min, right eye 2 mm/5 min — similar results as obtained 5 years before. No lymphadenopathy was detectable. Further examination revealed bilateral end-expiratory crackles of both lungs and no heart murmur. The liver was enlarged by 3 fingers without clinical signs of ascites. Multiple tests for hepatic encephalopathy were negative.

Laboratory tests revealed an increased erythrocyte sedimentation rate (30 mm/h). Alanine transaminase (ALT) and aspartate transaminase (AST) were doubled (ALT 39 U/l, AST 29 U/l), alkaline phosphatase (AP) and glutamate dehydrogenase (GLDH) were increased 4-fold (AP 670 U/l, GLDH 12 U/l), and an 8-fold γ-glutamyl transpeptidase (248 U/l) was detected. In addition, hypergammaglobulinemia with doubled IgM (678 mg/dl) and normal IgG (1240 mg/dl) were measured. Bile acids, albumin, bilirubin, thromboplastin, ammonium, blood gas analysis, cholinesterase, and creatinine were all normal. She therefore fulfilled the criteria of Child A (5 points).

On HEp-2 cells, antinuclear antibodies (ANA) stained positive at a titer of 1/2560, showing at least 2 distinct nuclear patterns (fine speckled and anticentromere pattern) and the typical cytoplasmic antimitochondrial antibody (AMA) pattern. On immunoblotting, the serum sample confirmed the 52 Ro/SSA protein, centromere A and B proteins, and AMA antigens. AMA-M2 antibodies, more specific for PBC, were positive in ELISA (650 U/ml). Repeatedly, anti-La/SSB antibodies were negative by ELISA and immunoblot.

In addition, IgM rheumatoid factor (RF), anti-smooth muscle antibodies

From the Department of Anaesthesiology and Intensive Care Medicine, Department of Medicine/Rheumatology and Clinical Immunology, and Department of Dermatology, Charité University Hospital, Humboldt University, Berlin, Germany.

A. Stroehmann, MD, Department of Anaesthesiology and Intensive Care Medicine; T. Dörner, MD, Associate Professor of Medicine; E. Feist, MD; F. Hiepe, MD, Professor of Medicine; G.R. Burmester, MD, Professor of Medicine, Department of Medicine/Rheumatology and Clinical Immunology; A. Lukowsky, PhD, Department of Dermatology.

Address reprint requests to Dr. A. Stroehmann, Department of Anaesthesiology and Critical Care Medicine, Charité University Hospital, Humboldt University of Berlin, 10117 Berlin, Germany.
E-mail: arne.stroehmann@charite.de

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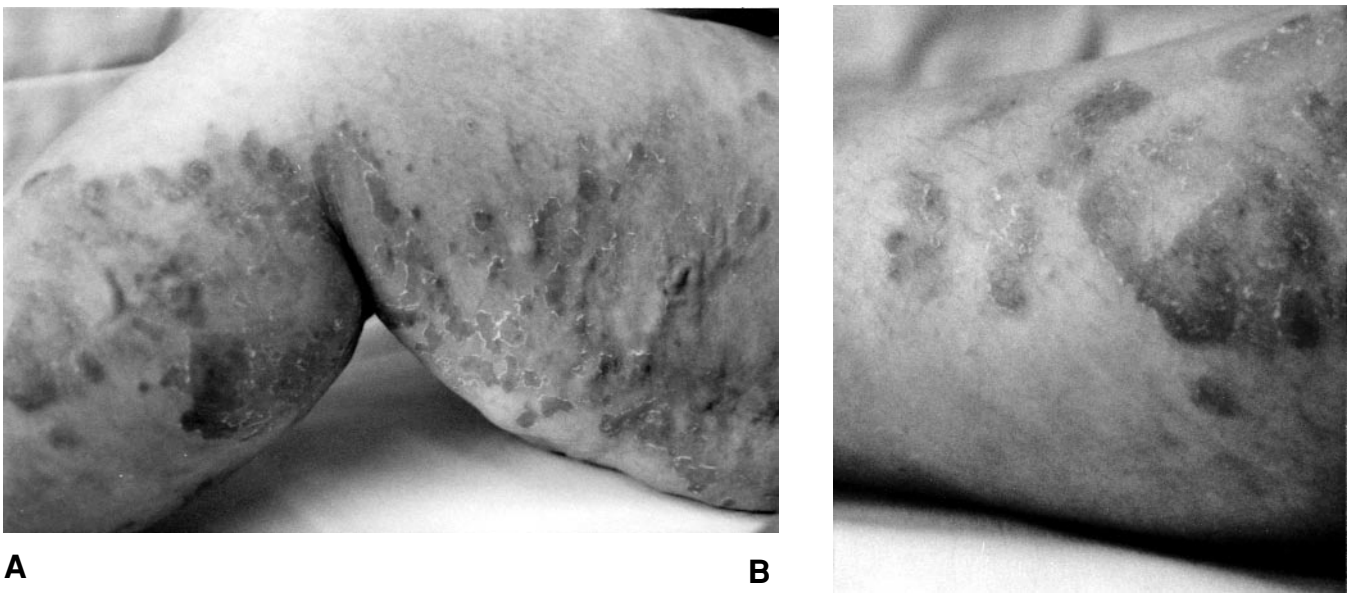

Figure 1. A. Dry and squamous skin lesions were predominantly localized on both legs (here the right leg) on admission. B. Detail of the lesions.

(SMA), and anti-parietal cell antibodies (PCA) were positive. The patient's complete HLA phenotype was A1, A33(19); B8, B14; Cw8; Bw6; DR1, DR17(3); DR52, DQ1, DQ2. HTLV-1/-2 antibodies were negative on immunoblot and ELISA.

Abdominal ultrasonography revealed a diffuse, inhomogenous, nonnodular, and irregular vascular texture of the liver. At least 3 lymphoma within the hepatoduodenal ligament (maximal diameter 20 mm) were found, whereas portal flow (color coded duplex sonography) and architecture of the gall bladder and choledochal duct appeared normal. All these hepatic findings were consistent with liver cirrhosis, as previously diagnosed histologically. Thoracic computed tomography (CT) scans revealed fibrotic transformations, especially of the lower parts of the lung. These findings had been stable for the last 5 years.

Histological investigation of the skin lesions revealed mycosis fungoides-like lymphoid infiltrates, almost exclusively formed by T cells (Figure 2). The proliferation rate was roughly 20%. Molecular analysis of the γ-T cell receptor (TCR-γ) revealed a monoclonality in the skin specimen in contrast to the polyclonal finding in the peripheral blood (Figure 3). Taken together, these histological and molecular findings were very consistent with an early stage of an erythematous form of mycosis fungoides.

After the diagnosis of mycosis fungoides was established, the patient was transferred to the Department of Dermatology of our hospital, where she received treatment with acitretin and PUVA. Under this therapy the skin lesions disappeared completely, and the condition remains stable 2 years later. She was discharged to the outpatient department.

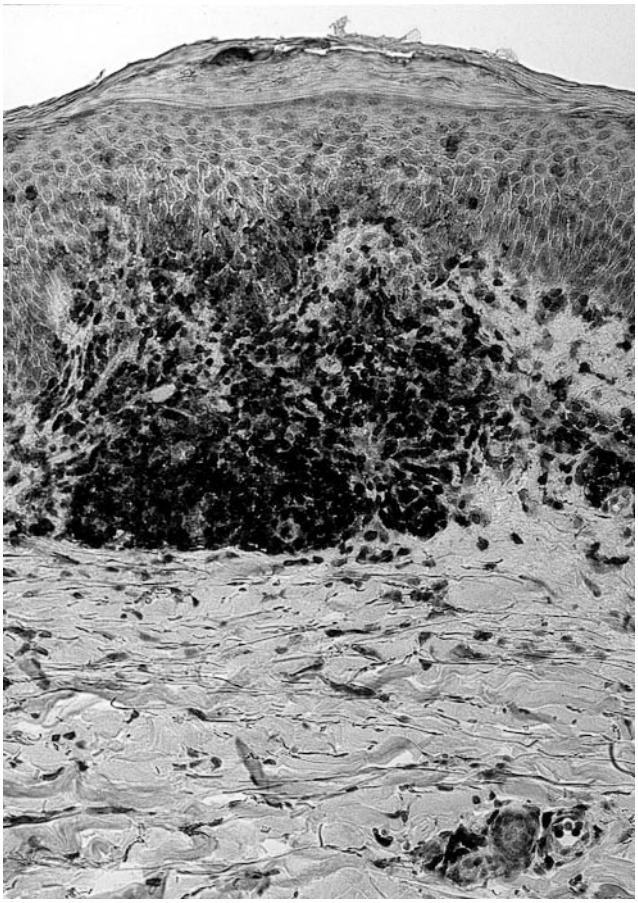

Figure 2. Low power photomicrograph of biopsy specimen (860.4 × 688.4 μm) prepared from the skin lesions. Lesional skin sections were paraffin embedded and stained for CD45 RO (clone UCHL-1). As CD45 RO is specific only for T cells, the infiltration of T cells into the stratum reticulare could be seen clearly.

DISCUSSION

Clinical and laboratory data indicate this patient had primary biliary cirrhosis associated with a secondary SS. Of note, she developed a T cell lymphoma of the skin after 5 years. Although B cell non-Hodgkin's lymphoma (NHL) occurs at a significantly greater frequency in patients with primary SS[8], the development of NHL, most notably of T cell origin, in a patient with secondary SS needs to be emphasized.

PBC is an autoimmune disease of unknown etiology. Characteristic findings include antimitochondrial antibodies, especially of the AMA-M2 subclass[9]. There are many associ-

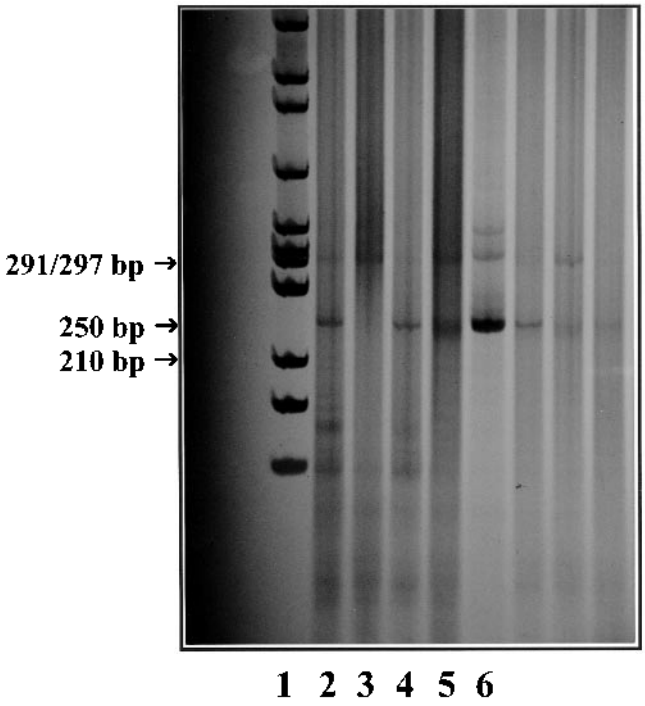

Figure 3. Gel separation of the TCR-γ polymerase chain reaction (PCR) products amplified from tissue infiltrating T cells by temperature gradient gel electrophoresis (TGGE). Lane 1: Molecular weight markers: HincII digest of X 174 DNA (USB Biochemicals, Cleveland, OH, USA). Lanes 2 and 4: skin samples. Lanes 3 and 5: Blood samples containing peripheral blood mononuclear cells (PBMC) from the patient. Lane 6: Jurkat T cell lymphoma line (control). For lanes 2 and 3, the samples were used after denaturation procedures at 95˚C for 10 min and 55˚C for 20 min (heteroduplex loading). Arrows mark bands of interest (~250 bp). A single sharp band is seen in skin samples 2 and 4, suggesting monoclonality, whereas patient's PBMC analysis showed polyclonal amplification products (appearing as a smear, lane 5, which disappeared after denaturation, lane 3). PCR of the rearranged TCR-γ chain genes was performed using consensus γV and J primer[27]. The TGGE technique[28] was applied to discriminate monoclonal and polyclonal amplification products.

ations of PBC with other autoimmune disorders, such as RA, systemic lupus erythematosus, and progressive systemic scleroderma or CREST syndrome[10]. One of the most frequent associations of PBC is secondary SS in about 69–81%[11]. Lymphocyte mediated focal infiltration mainly of the T helper type and damage of exocrine glands result in the typical clinical picture of impaired glandular function in SS[12]. Detection of anti-Ro (96%) and anti-La (87%) antibodies[13], RF, and hypergammaglobulinemia of the IgG class are typical serological findings in SS. An interesting serological finding was the detection of anticentromere antibodies that can be found in patients with PBC/CREST overlap, but also in a subgroup of patients with SS[14]. Further studies are needed to evaluate whether patients positive for anticentromere antibodies may represent a subgroup with a characteristic risk pattern.

Some studies report clinical, serological, and genetic differences of secondary SS associated with RA or progressive systemic sclerosis. Secondary SS associated with progressive systemic scleroderma exhibits a higher frequency of anti-Ro and anti-La antibodies, and of the HLA-A1, B8, DR3, and DRw52 genotype, whereas these frequencies are significantly lower in secondary SS associated with RA[10]. Moreover, the clinical course of SS appears to be more severe and complicated in patients with progressive systemic sclerosis associated with secondary SS. In 38 patients with PBC and secondary SS, Tsianos, *et al* observed the same features of SS as seen in patients with RA accompanied by secondary SS[1]. In a study of 40 patients with PBC we demonstrated that all patients positive for anti-52 kDa Ro antibodies (7 of 40) developed a secondary SS. In addition, 3 of these 7 patients also developed interstitial pneumonitis[15].

Interestingly, other studies have shown the aforementioned 44-fold enhanced relative risk for the development of NHL in patients with SS[2,8]. In the majority, patients with NHL had primary SS[16]. A recent literature review of malignant lymphoma in SS determined that the lymphomas were mainly of B cell origin, representing extranodal low grade B cell NHL[17,18]. There are only a few case reports of cutaneous T cell lymphoma occurring in patients with SS[3-6]. In 2 cases, primary SS was the underlying disease[3,4]. Another patient had lymphocytic interstitial pneumonia and SS[5]. In another case, SS was observed 18 years after the first manifestations of the cutaneous lymphoma[6]. All cases were consistent with the histologic findings of cutaneous T cell lymphoma[19].

Nijhawan and colleagues focused on the incidence of cancer in PBC[20]. Among a total of 1692 patients with PBC, the number of malignancies was 49% greater than anticipated by chance alone. The vast majority of these patients had hepatobiliary malignancies.

To our knowledge, there has been no description of mycosis fungoides as a T cell lymphoma in PBC associated with secondary SS by the European Community criteria for classification of SS[21]. Based on observation of 4 cases and a review of the literature, Fransway and Winkelmann proposed chronic antigenic immunostimulation as a major cause of clonal lymphocytic malignancy[22].

The exact underlying mechanisms causing the lymphoma in our patient as well as in SS in general remain unclear. Moreover, SS is also known for remarkable changes in T cell regulation[23], and there seems to be a Vß chain restriction in the salivary gland[24]. A recent molecular analysis of the complement determining region 3 from liver specimens of patients with PBC/CREST overlap syndrome provided evidence that persistent stimulation of clonal populations of CD8+ T cells leads to clonal expansion of T cells in this syndrome[25]. The identification of a T cell clone employing genes of the Vγ family is unexpected, since the vast majority of studies identified Vß gene rearrangements of the T cell receptor in inflamed tissues. One fundamental difference between T and B cells is that B cells use somatic hypermutation to increase the variability of the B cell receptor. It remains to be elucidated if this functional difference may account for the high frequency of B

cell versus T cell lymphoma. Whether the lymphoma is due to SS (usually B cell lymphoma) or to the PBC that is accompanied with a variety of T cell abnormalities[26] cannot be determined in the current case.

Our findings indicate that lymphoma might occur in secondary SS associated with PBC. The observation of a T cell lymphoma in this case was unexpected, because SS is usually associated with B cell lymphoma. However, T cells play a significant role in autoimmunity and appear to be involved in potential loss of cell regulation.

Another aspect of this case is the association of interstitial pneumonitis/lung fibrosis and the development of T cell lymphoma in PBC, as reported[5]. Further studies are needed to evaluate whether the pulmonary manifestations together with Sjögren's disease might indicate development of T cell lymphoma.

Based on recent improvements of molecular techniques, the detection of lymphoma has become more certain. It remains to be elucidated whether secondary Sjögren's syndrome in primary biliary cirrhosis is more commonly associated with non-Hodgkin's lymphoma, especially of T cell origin. Studies are needed to address the risk of developing lymphoma in secondary SS in patients with PBC as well as in other autoimmune diseases.

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