Urinary monoclonal free light chains in primary Sjögren’s syndrome: an aid to the diagnosis of malignant lymphoma

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SUMMARY Three patients, two with typical primary Sjögren’s syndrome (SS) and the third with several features of SS, including abnormal sialography and reduced tear secretion, developed B cell non-Hodgkin’s lymphoma (NHL) of parotid or lung, or both. Isoelectric focusing of concentrated urine specimens in agarose, followed by immunofixation, demonstrated the presence in each patient’s urine of monoclonal free light chains of the same class as that shown on the tumour cells. In one patient the level of urinary free light chains was monitored and found to correlate with disease activity. Similar techniques showed no monoclonal light chains in the urine from a further 26 cases of SS with no clinical evidence of lymphoma. The detection of monoclonal urinary free light chains may provide an early diagnostic clue to the development of lymphoma in patients with SS and be a means of tumour monitoring.

Key words: salivary glands, lung.

SS is an autoimmune, lymphocyte-mediated disorder characterised in the uncomplicated form by the destruction of exocrine glands and symptoms of mucosal dryness. Thus the hallmarks of the condition are keratoconjunctivitis sicca (KCS) and xerostomia. When there is no other recognised connective tissue disease (CTD) present the condition is called primary SS. When another CTD is associated (most commonly rheumatoid arthritis) the term secondary SS is used. Primary SS may be limited to glandular tissue or it may involve extraglandular sites, resulting in pulmonary disease, arthritis or arthralgia, non-thrombocytopenic purpuric rashes, renal tubular acidosis, and other distinctive clinical and serological abnormalities.1

It is well recognised that NHL can develop in both primary and secondary SS, with many case reports to assert this point.2-6 In a prospective study Kassan et al.7 demonstrated an increased risk for the development of NHL of 43-8 times for SS patients compared with controls. An increased risk of Waldenström’s macroglobulinaemia3,7 and myeloproliferative disorder8 are also reported, and there is one recorded case of light chain myeloma development.9

B Cell NHL arises from a clonal proliferation of neoplastic B lymphocytes and may often reflect properties of normal B lymphocytes ‘frozen’ at a particular point in differentiation. Until recently it was thought that such cells synthesised immunoglobulin (Ig) only for insertion into the cell membrane and were incapable of secreting Ig. However, in-vitro studies on neoplastic B cells from patients with NHL and chronic lymphocytic leukaemia (CLL) have shown that these cells are capable of secreting small amounts of immunoglobulin for export, often with an excess of light chain production.10 If sufficient tumour load is present this light chain might be expected to be found in the urine.11

Previous work in this unit with the highly sensitive technique of isoelectric focusing of concentrated 24-hour urine specimens in agarose, followed by immunofixation, has shown small amounts of monoclonal light chain, of the same type as that displayed...
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at the tumour cell surface, in the urine of 44% and 74% of patients studied with NHL and B cell CLL respectively. No patient had a monoclonal immunoglobulin band detectable in either serum or concentrated urine when analysed by electrophoresis or immunoelectrophoresis. It was possible in two cases to show unequivocally that the urinary light chain was produced by the tumour cells.12

We present the findings of two patients with typical primary SS, one of whom developed malignant pulmonary lymphoma and the other malignant parotid lymphoma and a third patient with lymphocytic infiltration of the parotid gland and features of SS, who was subsequently shown to have malignant parotid and pulmonary lymphomata. In the urine from all three cases monoclonal light chains of one type were found by the method described12 and were associated with and aided the diagnosis of lymphoma. This non-invasive technique may be important in the early diagnosis of B cell neoplasia in SS.

Patients and methods

PATIENT 1
This patient presented in 1982 at the age of 69 with a 13-year history of a non-erosive, symmetrical polyarthritis. Her sicca symptoms consisted of severe xerostomia, KCS, and vaginal dryness. Oral prednisolone was commenced in 1973 but was changed to ACTH injections due to the development of Cushingoid features. Investigation of frequent urinary infections led to a diagnosis of renal tubular acidosis. Other relevant features included recurrent transient parotid swellings, non-thrombocytopenic purpuric rashes, and multiple antibiotic allergies. Serological abnormalities included a sheep cell agglutination titre (SCAT) of 1/512, antinuclear antibodies (ANA) by indirect immunofluorescence (DNA binding normal), SS-A (Ro) and SS-B (La) antibodies, but no organ-specific antibodies.

In 1976 exertional dyspnoea developed. Chest x-ray (CXR) showed diffuse bilateral lower lobe shadowing and an 81mKr, 99mTc ventilation/perfusion scan showed matched patchy abnormalities. Pulmonary function tests showed a diminished transfer factor (TF), and a presumptive diagnosis of pulmonary fibrosis was made. In 1982 owing to progressive dyspnoea, transbronchial and then open lung biopsies were performed.

In 1983 death followed relentless progression of the pulmonary disease, despite four-months' treatment with chlorambucil and an increased dose of steroids. A post-mortem examination was not performed.

PATIENT 2
This patient developed polyarthritis in 1972 at the age of 22. One year later she had an unexplained episode of pulmonary consolidation. In 1976 an acute right parotitis occurred, and a 10-year history of intermittent swelling of the right parotid gland was noted. Treatment with penicillin was instituted, but the gland remained enlarged and subsequently a parotidectomy was performed. Light microscopy showed an intense lymphocytic infiltrate, interpreted at that time as the benign lymphoepithelial lesion of SS.

When seen in June 1982, aged 34, she described Raynaud's phenomenon and had trophic changes affecting several fingers of the left hand. A non-erosive synovitis involved the hands, knees, and ankles. Photosensitivity and intermittent, transient purpuric rashes affecting the arms and legs were noted. She suffered from severe xerostomia and xerophthalmia. Examination showed no evidence of salivary gland enlargement or lymphadenopathy. Serological abnormalities included a SCAT of 1/64, ANA by indirect immunofluorescence (DNA binding normal), SS-A, SS-B, and smooth muscle antibodies. The C4 component of complement was reduced at <0.05 g/l, and cryoprecipitate was present in the serum. Monoclonal kappa (κ) free light chains were present in the urine.

She was not dyspnoeic and the CXR was normal, but the pulmonary carbon monoxide TF was reduced at 4.59 mmol/min/kPa (predicted 8.3).

In March 1984 there was deterioration in her general clinical condition and staphylococcal pneumonia. She had previously suffered repeated episodes of lower respiratory infection. After resolution of the pneumonia plasmapheresis was initiated for worsening digital ischaemia (attributed to the cryoglobulinaemia), but little improvement followed. Cyclophosphamide was commenced in September, resulting in significant clinical improvement and a marked fall in urinary light chain excretion. It was not possible to obtain a lung biopsy.

PATIENT 3
In 1975 this 68-year-old male was found to have diffuse bilateral patchy pulmonary shadowing on a routine CXR taken during the course of radiotherapy for a basal cell carcinoma of the nose. Pulmonary function tests showed normal ventilatory capacity but a reduced TF at 6.4 mmol/min/kPa (predicted 8.75). A 10-year history of recurrent bilateral parotid swelling was noted, and several subsequent parotid sialograms confirmed main duct ectasia and sacculcation, with diminished parotid secretions. The results of Schirmer's tests were 3 mm and 7 mm at five minutes.
By 1979 TF had fallen to 5.54 mmol/min/kPa (predicted 7.9), but CXR appearances were unchanged.

In February 1982 a right parotid abscess occurred after acute parotitis. At surgery a calculus was removed from the main duct, and biopsy showed an intense mononuclear cell infiltrate, associated with loss of parenchyma and one epimyoepithelial island. Autoantibodies were absent from the serum. TF had fallen to 3.84 mmol/min/kPa, and the previous CXR changes had progressed, with extensive bilateral interstitial shadowing and focal consolidation and cavitation on the right. Transbronchial biopsy and bone marrow examination were performed, but no treatment was instituted at this stage.

In February 1983 there was rapid progression of the lung disease and clinical deterioration, with bilateral inguinal and axillary lymphadenopathy. Despite intensive treatment with steroids, he died.

**IMMUNOHISTOLOGY**

Sections of routine formalin fixed, paraffin embedded material were examined for immunoglobulin determinants by methods previously described.\(^{13,14}\)

**CELL MARKER ANALYSIS**

Fresh biopsy material was minced through sterile wire mesh, followed by washing in minimal essential medium containing heparin (MEM, Gibco Ltd). Cell suspensions were prepared from biopsy material, blood, and marrow by density gradient centrifugation over Lymphoprep (Nyegaard and Co. AS, Oslo, Norway) as previously described.\(^{15}\) Cells collected at the interface were washed three times in phosphate-buffered saline, and viability tested by trypan blue exclusion. After incubation at 37°C for 60 min (to remove extraneous Ig) the cells were washed in MEM containing 20% bovine serum albumin. T Lymphocytes were identified in suspension by immunofluorescence with the mouse monoclonal antibody OKT11,\(^{16}\) in an immunoperoxidase method with the pan T cell mouse monoclonal antibody UCHT1\(^{17}\) and on cytocentrifuge preparations by the spontaneous sheep erythrocyte rosette test (E).\(^{15}\) Surface and cytoplasmic Ig was identified in a direct immunofluorescence test with fluorescein-conjugated polyclonal rabbit anti-IgG (Dako Ltd) to Ig heavy and light chain determinants as previously described.\(^{14}\)

**URINE IMMUNOGLOBULIN**

Concentrated urine samples were analysed for monoclonal free light chain by the method of isoelectric focusing in agarose, followed by immunofixation, as described previously by two of the present authors (FKS and JLS).\(^{12}\) Levels of urinary light chain were measured in 24-hour urine collections by the enzyme linked immunosorbent assay as described previously.\(^{18}\)

**SERUM IMMUNOGLOBULIN**

Serum immunoglobulins G, A, and M and complement C3 and C4 were measured by laser nephelo-

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<th>B Cell</th>
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<tr>
<td></td>
<td>Marrow</td>
<td>58</td>
<td>NT</td>
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</table>

All figures are expressed as percentages.

- MAb=monoclonal antibody.
- Blood (1) examined in 1982; blood (2) examined with marrow in 1984.
- NT=not tested.
- Cells staining for G 7%, M 18%, D 20%.
- Cells cytoplasm positive for \(\kappa\) or \(\lambda\); no monoclonal population.
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Results

HISTOLOGY AND CELL MARKER ANALYSIS (Table 1)

Patient 1
Transbronchial biopsy showed a heavy lymphocytic infiltration of the bronchial wall and an interstitial infiltration consisting of lymphocytes and histiocytes. No interstitial fibrosis was present. The appearance was highly suggestive of malignant lymphoma. Open lung biopsy confirmed malignant lymphoma with a pattern of infiltration identical to that described as lymphocytic interstitial pneumonia (LIP). The histological classification was diffuse follicle centre cell lymphoma with plasmacytic differentiation arising in mucosa-associated lymphoid tissue (MALT) (Fig. 1). Immunohistochemical staining showed a predominant cytoplasmic (15%) IgMK lymphoplasmacytid and plasma cell population (Figs 2a and b).

Patient 2
Review of the right parotidectomy specimen (1976) showed a follicle centre cell lymphoma with plasmacytic differentiation and appearances typical of primary malignant lymphoma arising in MALT (Fig. 3). Immunohistochemistry showed a monotypic B cell population producing IgMK (Figs 4a and b).

Patient 3
Analysis of peripheral blood lymphocytes showed a monotypic B cell population with cytoplasmic IgM lambda (λ). An iliac crest marrow aspirate was normal, and a trephine biopsy specimen showed an occasional lymphoid follicle but no evidence of lymphoma. Immunohistochemistry of the bone marrow was not performed.

Transbronchial biopsy showed a dense lymphocytic infiltration (with some histiocytes and centrocytes) invading lung and bronchial epithelium, interpreted as malignant lymphoma. There was insufficient lung and parotid biopsy tissue for immunohistochemical assessment.
Postmortem examination showed extensive infiltration of both lungs by malignant lymphoma. Both parotids showed lymphoma, largely periductal, without evidence of sialadenitis in unaffected surrounding acini. Immunohistology of paraffin embedded tissue confirmed a monotypic IgMκ cell population. The malignant lymphoma showed a distribution within the lung and parotids typical of malignant lymphoma involving MALT. There was no involvement of lymph nodes, liver, or spleen.

**IMMUNOCHEMISTRY** (Table 2)

Patient 1 had 2.8 mg/24 h of monoclonal K free light chain present in her urine at the time of diagnosis of malignant lymphoma.

Patient 2 had a urinary excretion of monoclonal K free light chain of 143 mg/24 h in October 1983.

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**Table 2** Immunohemistry

<table>
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<tr>
<th>Patient</th>
<th>Serum immunoglobulins*</th>
<th>Electrophoresis</th>
<th>Complement*</th>
<th>Immune complexes*</th>
<th>Urinary light chain (mg/24 h)</th>
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<tr>
<td></td>
<td>G</td>
<td>A</td>
<td>M</td>
<td>C3</td>
<td>C4</td>
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<td>3 (1982)</td>
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<td>1-2</td>
<td>28-7</td>
<td>1-27</td>
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</table>

*Normal ranges (g/l): IgG=7-5-16-7; IgA=0-9-4-5; IgM=0-4-3-7; C3=0-89-2-09; C4=0-12-0-53.

*Undetectable in normal serum.
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<th>Schirmer's test (mm/5 min)</th>
<th>Tear break-up time (s)</th>
<th>Simulated parotid rate (ml/min)</th>
<th>Parotid sialogram</th>
<th>^99m^Tc pertechnetate salivary imaging</th>
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<td>6</td>
<td>2.4</td>
<td>Dilated main duct and intraglandular ducts with diminished branching</td>
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NA = not available.
ranging to 946 mg/24 h by March 1984, associated with clinical deterioration. A reduction in urinary light chain excretion and clinical improvement followed cyclophosphamide treatment (Fig. 5).

Patient 3 had an IgMλ paraprotein band on serum electrophoresis (EP), and his urine contained 32.2 mg/24 h of monoclonal λ free light chain.

**CONTROLs (Table 3)**

Eight patients with definite or probable primary SS and 18 patients with secondary SS and no clinical evidence of lymphoma were examined for the presence of urinary monoclonal free light chains. Diagnostic criteria for primary SS were the presence of KCS (two of the following abnormalities: Schirmer’s test <10 mm at 5 min, van Bijsterveld score ≥4, tear break-up time <10 s) and xerostomia (two of the following abnormalities: parotid saliva flow rate <1 ml/min under maximal stimulation with lemon juice, 19 abnormal sialography, abnormal salivary radionuclide imaging). Several patients also had other characteristic clinical features and serological abnormalities, which included anti-Ro and anti-La antibodies. Lip biopsy was not performed routinely but was abnormal in control patients 2 and 3. Secondary SS was present when either KCS or xerostomia, or both, were present with another connective tissue disease. Monoclonal free light chains were not detected in any patient’s urine.

**Discussion**

The malignant lymphomas associated with SS are usually B cell neoplasms producing monoclonal IgMκ and occasionally IgMλ.4 21 25 These lymphomas often run an indolent course, involve a wide variety of tissues, and may be compatible with many years free of symptoms. Diagnosis is often difficult, because as with other malignant lymphomas of MALT the histological appearance is often deceptively benign, and they tend to remain localised for a long time.23 24

The term ‘benign lymphoepithelial lesion’ introduced by Godwin in 195225 is no longer tenable to describe the histological appearance of the salivary gland in SS, as Schmid26 has shown that the cellular infiltrates frequently contain monotypic populations of B cells.

Lymphocytic infiltration of the lungs in SS is well recognised. Strimlan et al.27 reviewed 343 SS patients and found pulmonary involvement in 9%. The term ‘lymphocytic interstitial pneumonia’ was introduced by Carrington and Liebow28 to imply diffuse pulmonary infiltration by lymphocytes and plasma cells but without histological characteristics generally accepted as malignant, though progression to malignant lymphoma has been recognised.29-33 The present authors believe that the histopathology of LIP is typical of malignant lymphomas of MALT and that differences between this type of lymphoma and nodal lymphomas account for the difficulties in diagnosis.24 34

The precise diagnosis of malignant B cell lymphoma requires immunohistochemical methods to demonstrate monoclonal immunoglobulin production by lymphocytes.26 29 Peripheral blood lymphocytes may show a normal distribution of immunoglobulin surface markers on B lymphocytes and serum and urine EP can be normal. Biopsy material
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may be readily accessible from superficially affected tissues, e.g., lymph nodes, but is more difficult to obtain when deeper structures are involved, particularly the lungs. Furthermore, the indolent progression of pulmonary lymphoma, as illustrated by these three cases, leads to irreversible lung damage, which might have been arrested by early recognition and treatment.

Thus a dilemma may arise when lymphoma is suspected but all conventional non-invasive tests are normal. The finding of a tumour-related product in the urine should lead to the institution of a more diligent search for NHL.

The rationale for measuring urinary light chains to detect malignant lymphoma, and in established disease as an indicator of tumour load, has been discussed by Stevenson,35 Stevenson, Spellerberg, and Smith12 have developed a highly sensitive technique of isoelectric focusing in agarose, followed by immunofixation, that enables minute quantities (0-03 mg of light chain per 24-hour urine specimen) of monoclonal light chain to be detected against the normal polyclonal excretion of light chain. By this method they have shown that in the B lymphocyte diseases of CLL and NHL the majority of patients tested had monoclonal K or λ light chains present in their urine, which could be shown to be products of the malignant cells.12

In a study with sensitive electrophoresis combined with immunofixation on sera from 21 patients with primary SS Moutsopoulos et al. found free monoclonal λ light chains in 14 (67%); no urine analyses were reported.36 This suggests that very large amounts of λ light chain were being synthesised, since investigations on CLL showed that secreted free light chain was cleared rapidly from the circulation and could be detected only in the urine.18 Our three patients similarly showed good clearance, with only a trace of monoclonal K light chain found in the serum of patient 2. Also our small study would not suggest a special role for λ light chains in SS as suggested by Moutsopoulos et al., since two out of three produced K chains.

In a more recent paper Moutsopoulos et al.37 have investigated serum and urine of patients with primary SS. The incidence of homogeneous protein bands in serum (47%) and urine (76%) of such patients seems very high. In fact they report that 100% of patients with extraglandular SS showed such bands in the urine, sometimes with multiple bands. In our examination of 26 patients with SS (some of whom had extraglandular symptoms) (Table 3) and no evidence of a transition to lymphoma, by a technique which distinguishes monoclonal from polyclonal light chain, we found no evidence for monoclonal light chains in the urine.

Our experience with NHL suggests that such light chains can only be found in urine when there is sufficient tumour load.

The striking and common clinical feature of all three patients we have reported is pulmonary disease with slow clinical progression. Patient 1 had respiratory symptoms for 11 years before her eventual rapid demise from malignant pulmonary lymphoma and had been mistakenly diagnosed as having pulmonary fibrosis. There were no changes in her serum immunoglobulins, serum EP, or peripheral blood and bone marrow lymphocyte markers. It was the finding of K free light chains in her urine, in conjunction with lymphocytic infiltration of the bronchial mucosa, that prompted an open lung biopsy, enabling diagnosis of a follicle centre cell lymphoma.

Patient 2 had a malignant clone of B cells within the parotidectomy specimen taken in 1976, despite the apparently benign appearance on light microscopy. Although only a faint IgMK serum paraprotein band was present, monoclonal K free light chains were present in her urine. Peripheral blood lymphocyte analysis also showed predominant staining for IgMK. However, a bone marrow examination was normal. This patient suffered several unexplained episodes of pneumonia, with a progressive fall in TF despite a normal CXR. These observations raised the possibility of lymphomatous infiltration of the lungs, which has still not been proved histologically. The curious increase in urinary light chain excretion associated with the staphylococcal pneumonia is not easily explained. It was not due to renal protein leakage, as no other serum proteins were present in the urine. It is possible that the pneumonia was a result of compromised immune function as a result of relapse in her lymphoma. Urinary light chain levels fell as the pneumonia resolved but then rose again with further deterioration in her clinical condition. The levels did not fall with plasmapheresis but fell during treatment with cyclophosphamide, and her general condition improved.

Patient 3 was known to have pulmonary infiltrates for at least eight years and was relatively asymptomatic until the final stages of his disease when there was rapid progression of pulmonary lymphoma associated with depression of serum IgG, increase of serum IgM, an IgMλ paraprotein band, a monotypic B cell population in the peripheral blood, and monoclonal λ free light chains in the urine. The salivary gland lesion was subsequently shown to be malignant lymphoma.

In these three cases no single serological or haematological test was able to predict the presence of the eventually proved malignant lymphoma.
However, monoclonal urinary free light chain excretion was a constant finding. The finding of light chains in the urine of patients with leukemia and lymphoma has been recognised for several years, but the methods of detection were insensitive and clinical disease already apparent. We suggest that the detection of monoclonal free light chains in the urine of SS patients by the sensitive, non-invasive method described should lead to a careful search for malignant lymphoma, especially if there is evidence of pulmonary disease. This is further supported by our own failure to detect urinary free light chains in eight further patients with definite or probable primary SS (some with extraglandular features) and 18 others with secondary SS, all without clinical evidence of lymphoma. These preliminary observations indicate the need for a more extensive prospective study of urinary free light chains in SS.

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Urinary monoclonal free light chains in primary Sjögren’s syndrome


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