Systemic lupus erythematosus, Sjögren's syndrome and glomerular nephritis

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Summary

The combination of systemic lupus erythematosus, Sjögren's disease and severe diffuse glomerular nephritis has only rarely been reported. A 14-year-old girl is described with lupus nephritis in whom co-existent clinical and histological features of Sjögren's syndrome were found. These include bilateral parotid enlargement, xerostomia, increased serum amylase, reduced salivary secretion and lymphocyte infiltration of both salivary glands and kidneys.

The co-existence of systemic lupus erythematosus with Sjögren's syndrome is discussed together with a consideration of pathogenesis.

Introduction

Systemic lupus erythematosus (SLE) occurs in less than 5% of patients with classical Sjögren's syndrome (SS) (Shearn, 1973; Mason, Gumpel and Golden, 1973). Although glomerular nephritis is common in SLE, the combination of SS, SLE and glomerular nephritis is rare; a search of the literature by Shearn (1971) revealed only three cases, but three further cases were described by Steinberg and Talal in 1971. A young girl is described who presented with lupus nephritis and was found to have associated xerostomia and Sjögren's syndrome.

Case report

A 14-year-old Arab girl was admitted with a history of progressive weakness and fatigue. She had lost 5 kg of weight during the 6 months before admission, complained of nausea, anorexia, arthralgia and had an erythematous rash on the sun-exposed areas of the face and hands. On direct questioning she admitted to xerostomia over the same period.

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Examination revealed a pale thin young girl with diffuse bilateral enlargement of the parotid salivary glands. There was a scaling erythematous rash with a butterfly distribution on her face. She had a functional systolic murmur, there was moderate hepatosplenomegaly and occipital and axillary lymphadenopathy. The blood pressure was normal and there was no oedema.

Laboratory investigations were as follows: haemoglobin 6.4 g/100 ml, with normocytic normochromic red cell morphology, reticulocytes 6.6%, direct and indirect Coombs negative. Leucocytes 4,300/mm³, platelet count normal and erythrocyte sedimentation rate 132 mm in the first hour.

Numerous LE cells were observed; the rheumatoid factor was negative as was the VDRL test. Haemoglobin electrophoresis and G 6-PD estimation was normal. Blood urea was 150 mg/100 ml, calcium 9.4 mg/100 ml and phosphorus 5.9 mg/100 ml. Total serum protein estimation was 8.6 g/100 ml, albumin 4 g/100 ml, globulin 4.6 g/100 ml. Other investigations included; serum iron 54 µg/100 ml, TIBC 268 µg/100 ml, fibrinogen 535 mg/100 ml, cholesterol 360 mg/100 ml, serum amylase 144 Street-Close units [=475 Somogyi units] (normal values 45 S-C units/100 ml of plasma), uric acid 9.5 mg/100 ml and creatinine 2.5 mg/100 ml. Urine examination revealed multiple erythrocytes, a few leucocytes and numerous granular casts with moderate proteinuria. There was marked hypertriglyceridaemia on nephelometry. Liver function and coagulation tests were normal, as were the ECG and radiograph of the chest.

Bone marrow aspiration revealed mild hypoplasia of erythrocyte precursors and intravenous pyelography showed slight enlargement of both kidneys with impaired excretion of contrast medium. Immunological investigations showed: IgG 3500

FIG. 1. Buccal salivary gland with infiltration by lymphocytes, plasma-cells and immunoblasts.

FIG. 2. A glomerulus with focal thickening of the Bowman capsule, 'wire loops' and proliferation.

mg/100 ml (normal 770–1130 mg/100 ml), IgA 420 mg/100 ml (90–170 mg/100 ml), IgM 620 mg/100 ml (80–200 mg/100 ml) and serum C3 was 0.6 mg/ml. Anti-DNA antibodies were present in high titre of 27% (percentage bound DNA; normal values < 20%) and salivary duct antibodies were negative. Schirmer test was likewise negative; however salivary studies showed a saliva secretion of 0.11 ml/min (normal level 0.57 ml/min) and secretory IgA 7 mg/100 ml (normal 2–12 mg/100 ml). Biopsy of lower lip (Fig. 1) showed focal infiltration of salivary

glands by lymphocytes, plasma cells and immunoblasts. Four glomeruli were present in the kidney biopsy specimen, one of which was totally fibrotic, one showed proliferation of endothelial and mesangial cells, with thickening of the walls and two glomeruli showed focal thickening of Bowman's capsule and capillary wall (Fig. 2). There was focal fibrosis of the interstitium with prominent patchy infiltration of lymphocytes and plasma cells (Fig. 3). Electron microscopy (Figs 4 and 5) revealed thickening of basement membrane, collapse of capillary

FIG. 3. Lymphocytic and plasma cell infiltration of the renal interstitium.

FIG. 4.

Electron microscopic view ($\times 4900$ and $\times 7500$) with thickening of basement membrane and numerous subepithelial and intramembranous electron-dense deposits.

FIG. 5.

lumen in focal manner and numerous subepithelial and intramembranous electron-dense deposits.

The findings were consistent with diffuse glomerulonephritis whilst the lymphocyte infiltration was suggestive of Sjögren's disease of the kidney. Therapy was commenced with prednisone 1.5 mg/kg/day and azathioprine 2 mg/kg/day. Within a few days clinical improvement was observed, accompanied by a rise in haemoglobin to 11.3 g/100 ml. Serum C3

activity increased with a decrease in immunoglobulin titre, sedimentation rate, blood urea, plasma creatinine, and uric acid and urinary erythrocyte excretion. Prednisone was decreased and alternate day therapy regimen continued together with a reduction in the azathioprine dose to 50 mg/day.

At follow-up examination 4 months after discharge, the blood urea was 33 mg/100 ml, plasma creatinine 1.3 mg/100 ml and uric acid 5.9 mg/100 ml.

Urine was normal apart from a trace of protein. Parotid swelling decreased over this period and was absent at 6 months. Other investigations included: C3 0.8 mg/ml, IgG 2500 mg/100 ml, IgA 500 mg/100 ml, IgM 300 mg/100 ml.

Discussion

The renal manifestation of the sicca complex includes interstitial nephritis (Tu *et al.*, 1968), renal tubular acidosis (Shioji *et al.*, 1970; Shearn and Tu, 1965; Talal, Zisman and Schur, 1966) and, less commonly, glomerulonephritis, the latter being non-specific and usually mild (Shearn, 1973; Talal *et al.*, 1966). The principal lesion is undoubtedly the lymphocyte infiltration of the interstitial tissue. Other lesions include Fanconi's syndrome and nephrogenic diabetes insipidus (Shearn and Tu, 1965).

SLE occurs less frequently than rheumatoid arthritis in association with sicca complex and has been reported to coexist in less than 5% of patients with Sjögren's syndrome (Shearn, 1973; Mason *et al.*, 1973). Even more uncommon is the association between lupus nephritis and SS. The present case is only the seventh recorded in the English literature. Renal histology demonstrated the typical features of interstitial nephritis compatible with SS. The glomerular involvement, on the other hand, accompanied by reduced plasma C3-activity and a high titre of anti-DNA antibodies and LE cells was highly suggestive of lupus nephritis. The clinical response to immunosuppressive therapy was consistent with the immunopathogenesis of the nephritis.

The histological features of lupus nephritis include focal or diffuse proliferative glomerulonephritis as well as membranous nephropathy. The prognosis and response to therapy have been correlated with both the histological type and the localization of the electron-dense deposits. Poor response to therapy is usually seen with diffuse proliferative glomerulonephritis and subendothelial electron-dense deposits, although therapy may transform the diffuse type to the less damaging membranous form or to focal glomerulonephritis (Dillard, Tillman and Sampson, 1975; Cheatum *et al.*, 1973). In the patient described the morphological features were those of diffuse proliferative glomerulonephritis with sub-epithelial and intra-membranous electron-dense deposits. A good response to immunosuppressive therapy was achieved.

Whilst numerous studies have commented upon the incidence of SLE in Sjögren's syndrome (Shearn, 1973; Mason *et al.*, 1973; Steinberg and Talal, 1971; Bloch and Bunim, 1963), it was only recently that the prevalence of sicca features were studied in SLE. Shearn (1971) noticed the presence of parotid swelling in 7% of eighty-three patients with SLE, but

histological confirmation was obtained in only one case, suggesting again that SLE and SS are uncommonly associated. This is contrary to the findings of two recent studies (Katz and Ehrlich, 1972; Alarcon-Segovia *et al.*, 1974). Alarcon-Segovia *et al.*, while agreeing that fully established sicca complex was uncommon, were nevertheless able to show that salivary gland and ophthalmic manifestations compatible with the diagnosis of SS were present in forty-nine of fifty unselected consecutive cases of SLE. Heaton (1959) considered SS to be a variant of SLE because of the identical sex incidence, multiple organ involvement and presence of both organ and non-organ specific autoantibodies.

It would appear that SLE and SS may co-exist with a varying spectrum of presentation. Thus, typical sicca complex may occur with no overt SLE but with serological evidence, including LE cells, anti-DNA antibodies and reduced plasma complement. The opposite end of the spectrum, as described by Alarcon-Segovia *et al.* (1974), is clinical SLE and subclinical Sjögren's disease (Steinberg and Talal, 1971). New Zealand black mice who develop a lupus-like syndrome also have lymphoid infiltrates of salivary glands remarkably similar to those of Sjögren's syndrome (Kessler, 1968; Howie and Helyer, 1968).

In conclusion, Sjögren's syndrome and systemic lupus erythematosus may not only be associated, but there may be a considerable immunopathological overlap caused by the interreaction of related genetic, viral and immune mechanisms.

References

- ALARCON-SEGOVIA, D., IBANEZ, G., VELAZQUEZ-FORERO, F., HERNANDEZ ORTIZ, J. & GONZALEZ-JIMENEZ, Y. (1974) Sjögren's syndrome in systemic lupus erythematosus clinical and subclinical manifestations. *Annals of Internal Medicine*, **81**, 577.
- BLOCK, K.J. & BUNIM, J.J. (1963) Sjögren's syndrome and its relationship to connective tissue diseases. *Journal of Chronic Diseases*, **16**, 915.
- CHEATUM, D.E., HURD, E.R., STRUNK, S.W. & ZIFF, M. (1973) Renal histology and clinical course of systemic lupus erythematosus. *Arthritis and Rheumatism*, **16**, 670.
- DILLARD, M.G., TILLMAN, R.L. & SAMPSON, C.C. (1973) Lupus nephritis—correlations between the clinical course and presence of electron-dense deposits. *Laboratory Investigations*, **32**, 261.
- HEATON, J.M. (1959) Sjögren's syndrome and systemic lupus erythematosus. *British Medical Journal*, **1**, 466.
- HOWIE, J.B. & HELYER, B.J. (1968) The immunology and pathology of NZB mice. *Advances in Immunology*, **9**, 215.
- KATZ, W.A. & EHRLICH, G.E. (1972) Acute salivary gland inflammation associated with systemic lupus erythematosus. *Annals of Rheumatic Disease*, **31**, 384.
- KESSLER, H.S. (1968) A laboratory model for Sjögren's syndrome. *American Journal of Pathology*, **52**, 671.
- MASON, A.M.S., GUMPEL, J.M. & GOLDEN, P.L. (1973) Sjögren's syndrome. *Seminars in Arthritis and Rheumatism*, **2** (4), 301.
- SHEARN, M.A. (1971) Sjögren's syndrome. In: *Major*

- Problems in Internal Medicine*. W. B. Saunders Co., Philadelphia.
- SHEARN, M.A. (1973) Sjögren's syndrome. *Seminars in Arthritis and Rheumatism*, **2** (4), 165.
- SHEARN, M.A. & TU, W.H. (1965) Nephrogenic diabetes insipidus and other defects of tubular function in Sjögren's syndrome. *American Journal of Medicine*, **39**, 312.
- SHIOJI, R., FURUYAMA, T., ONODERA, S., SAITO, H., ITO, H. & SASAKI, Y. (1970) Sjögren's syndrome and renal tubular acidosis. *American Journal of Medicine*, **48**, 456.

- STEINBERG, A.D. & TALAL, N. (1971) Coexistence of Sjögren's syndrome and systemic lupus erythematosus. *Annals of Internal Medicine*, **74**, 55.
- TALAL, N., ZISMAN, E. & SCHUR, P.H. (1966) Renal tubular acidosis, glomerular nephritis and immunological factors in Sjögren's syndrome. *Arthritis and Rheumatism*, **11** (6), 774.
- TU, W.H., SHEARN, M.A., LEE, J.C. & HOPPER, J. (1968) Interstitial nephritis in Sjögren's syndrome. *Annals of Internal Medicine*, **69**, 1163.

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Transient hypercalcaemia following acute renal failure

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Summary

Two patients with transient hypercalcaemia during recovery from acute renal failure are described. The literature is reviewed and possible pathophysiological mechanisms discussed. Patients with renal failure following muscle damage should have regular measurement of plasma calcium.

Introduction

Hypercalcaemia is well recognized in untreated chronic renal failure and following haemodialysis and renal transplantation. The subject has been reviewed by Goldsmith, Johnson and Arnaud (1974) but hypercalcaemia in acute renal failure was not mentioned. Transient hypercalcaemia following acute renal failure was first described by Tavill *et al.* (1964) and since then there have been further reports (Butikofer and Molleyres, 1968; De Morgan and Waterhouse, 1968; Gossman and Lange, 1968; Segal, Miller and Moses, 1968; Turkington *et al.*, 1968; Leonard and Eichner, 1970; Leonard and Nelms, 1970; Grunfeld *et al.*, 1972; Wu *et al.*, 1972; Wilson *et al.*, 1973; Grossman *et al.*, 1974; Lynn, 1975). The highest plasma calcium recorded is 17.2 mg% (4.3 mmol/l) by Gossman and Lange (1968) and the longest period of hypercalcaemia was 25 days (Turkington *et al.*, 1968). There is a striking association with muscle damage, seventeen of the nineteen patients previously described having skeletal muscle damage of some type before renal failure. In the two remaining cases (Turkington, *et al.*, 1968) no cause for renal failure was identified.

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In fourteen cases, hypercalcaemia occurred during the diuretic phase.

Case 1

A 23-year-old male chronic schizophrenic took an overdose of trifluoperazine and had two grand-mal seizures before admission to another hospital. The following day he had apparently recovered and the blood urea was 8.3 mmol/l. Twelve days later he presented with abdominal pain and vomiting, and was found to have generalized oedema. The urine contained a trace of protein and numerous red cells. The haemoglobin was 14.0 g/dl; plasma urea 94.6 mmol/l; creatinine 2334 mmol/l; sodium 121 mmol/l; potassium 7.4 mmol/l; bicarbonate 13 mmol/l; calcium 1.67 mmol/l; phosphate 3.38 mmol/l; alkaline phosphatase 5 KAU; total proteins 66 g/l; albumin 31 g/l. Peritoneal dialysis was undertaken for 3 days. Renal function rapidly improved, the lowest daily urine output being 0.8 l. An intravenous urogram on the fifth day was normal. On the seventh day, the plasma calcium was 2.95 mmol/l and phosphate 1.90 mmol/l. By the ninth day the calcium was 3.85 mmol/l and phosphate 1.92 mmol/l. Sodium cellulose phosphate (20 g daily) was given orally for 3 days to reduce calcium absorption. The plasma calcium fell steadily to 2.62 mmol/l, phosphate 0.68 mmol/l and alkaline phosphatase 11 KAU, on the fifteenth day. On the sixteenth day, plasma parathyroid hormone (PTH) was <0.1 µg/l [normal range, up to 0.73 µg/l. The assay is insensitive for low and normal levels]. He had no corneal calcification. At 6 weeks all biochemistry was normal.