

Case report

Chronic predominant interstitial nephritis in a patient with systemic lupus erythematosus: a follow up of three years and review of the literature

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SUMMARY Predominant interstitial nephritis is a rare manifestation of systemic lupus erythematosus. Only seven cases have been reported in the literature. Owing to the rarity of this entity, the natural history of predominant interstitial nephritis in lupus has not been adequately recorded and an appropriate therapeutic approach has yet to be defined. In this report we present the case of a 25 year old woman with active systemic lupus erythematosus complicated by kidney failure and renal tubular acidosis due to predominant interstitial nephritis. We describe the course of her disease over a three year period. Seven additional patients with systemic lupus erythematosus and predominant interstitial nephritis are reviewed.

Key words: renal failure.

Tubulointerstitial involvement of the kidneys is a well recognised feature of lupus nephritis, occurring in 66% of kidney biopsy specimens of patients with systemic lupus erythematosus.¹ This extraglomerular disease occurs mainly in patients with proliferative and membranous lupus nephritis.¹ Therefore, the clinical significance of the renal interstitial disease is invariably obscured by the concomitant glomerular damage. The occurrence in patients with systemic lupus erythematosus of predominant interstitial inflammation with minimal glomerular involvement is rare, and only seven cases have been reported. Most of these patients presented with acute renal failure,^{2–5} and two patients had chronic renal disease.^{6,7}

In this report we present the natural history over a three year period of predominant interstitial nephritis in a 25 year old woman with systemic lupus erythematosus and review the other reported cases.

Case report

A 25 year old woman was admitted to our hospital in

April 1982 because of pneumonia and measles. She had a past history of non-thrombocytopenic purpura in 1965, and over the last few years she had had recurrent episodes of polyarthritides, pericarditis, pleuritis, maculopapular rashes, and anaemia of 75–100 g/l haemoglobin, but was not referred for further medical evaluation. There was no history of any drug intake before admission (e.g., non-steroidal anti-inflammatory agents) or features of Sjögren's syndrome. Physical examination disclosed a pale, thin, tachypneic young woman. Her temperature was 40°C, blood pressure 100/80 mmHg, and pulse rate 104/min. A morbilliform rash was noted over the face and trunk, as well as enanthema and Koplik's spots. Bilateral crepitant rales were heard over the lungs and a 2/6 systolic ejection type murmur was noted. There was mild hepatosplenomegaly and no pedal oedema.

Initial laboratory tests showed a sedimentation rate of 90 mm/h (Westergren), a haemoglobin value of 91 g/l, a white blood cell count of $17.6 \times 10^9/l$ (polymorphonuclear neutrophils 92%), and a platelet count of $105 \times 10^9/l$. The urine analysis showed positive protein, few erythrocytes, and leucocytes without casts. The urea level was 16.9 mmol/l, creatinine 354 $\mu\text{mol/l}$, and the creatinine clearance was 11 ml/min. The sodium value was 142 mmol/l, potassium 3.1 mmol/l, chloride 125

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mmol/l, and bicarbonate 7 mmol/l. The plasma pH was 7.2 and the urine pH did not fall below 6.5. The 24 hour urinary protein was 1.2 g. The electrocardiogram showed sinus tachycardia with diffuse ST-T changes that reverted to normal during the hospitalisation. A chest radiogram demonstrated multiple lung infiltrations.

Measles complicated by bronchopneumonia was diagnosed on the basis of the clinical data and the epidemiological set up of a measles outbreak at that time. Fluids, bicarbonate, hydrocortisone, and erythromycin were administered, and the patient improved within a few days. The fever and the rash subsided, the lungs became clear, and a repeat chest radiogram showed complete resolution of the pneumonia. In view of her past history of recurrent arthritis, pericarditis, pleurisy rash, and anaemia, as well as the persistent azotaemia, hypokalaemia, and renal tubular acidosis, however, further diagnostic evaluation was pursued.

The fluorescent antinuclear antibody (FANA) was highly positive on a qualitative scale (+3/+3) and in a titre of 1/320. The anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibody was 3.4 µg bound DNA/ml serum (normal values in our laboratory 1.0–1.4 µg DNA/ml), and the anti-SM antibody test was positive. The level of the third component (C3) was 330 mg/l (normal range (NR) 600–1200 mg/l). The albumin level was 29 g/l (NR 35–50), globulin 54 g/l (NR 25–30), IgG 36.54 g/l (NR 8–17 g/l), IgM 1.01 g/l (NR 0.65–2.8), and IgA 1.64 g/l (NR 0.9–4.5). The lupus erythematosus cell preparation (LE cell), the Rose-Waaler, latex, Venereal Disease Research Laboratory (VDRL), and the Coombs' tests were all negative.

A plain film of the abdomen did not show nephrocalcinosis. Ultrasound examination of both kidneys showed them to be of normal size and configuration without deformations, cysts, or calculi. A diagnosis of systemic lupus erythematosus was established and a percutaneous renal biopsy was performed, which showed predominant interstitial nephritis (to be detailed below).

The patient was later discharged without any treatment.

Results

RENAL HISTOPATHOLOGY

Light microscopy

The kidney biopsy specimen contained seven glomeruli. Of these, one had periglomerular fibrosis and one was sclerotic. The other glomeruli showed a minimal increase of mesangial cells without thickening of the capillary walls (Fig. 1). The main abnormality was in the interstitium, which showed

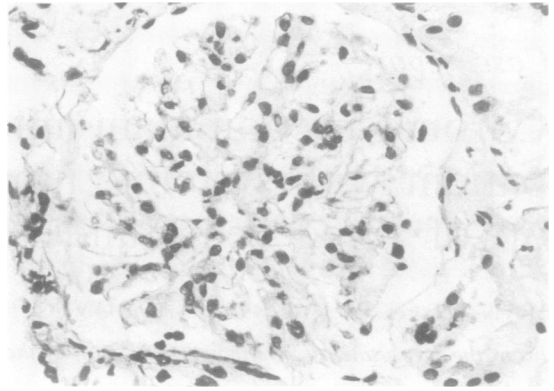


Fig. 1 Glomerulus with minimal mesangial hypercellularity. (Haematoxylin and eosin.)

focal mononuclear cell infiltration and groups of atrophic tubuli containing hyaline casts (Fig. 2).

Immunopathological examination

Five glomeruli were examined. IgG deposits were demonstrated along Bowman's capsule but not in the glomeruli. Speckled antinuclear antibodies of IgG were seen in the tubular epithelial cells. Granular C3 deposits were shown along the tubular basement membrane. Mild mesangial deposits of C3 were also seen.

Electron microscopy

No increase of mesangial cells or mesangial matrix was observed and no epithelial foot process fusion was seen. There were no electron dense deposits in the mesangium or along the capillary basement

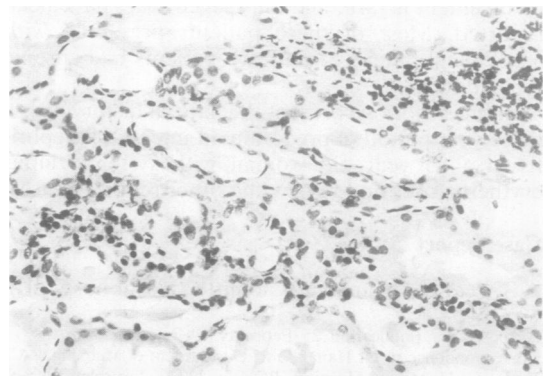


Fig. 2 Mononuclear cell interstitial infiltration and tubular atrophy. (Haematoxylin and eosin.)



Fig. 3 Electronmicrograph showing mesangial area and basement membrane. No electron dense deposits are seen.

membranes (Fig. 3). Tubular basement membranes were focally thickened and slightly irregular. No deposits were found.

FOLLOW UP

The patient has been followed up for three years. Pertinent laboratory data are summarised in Table 1. She had recurrent episodes of fever, pleurisy symmetric arthritis of the small joints, Raynaud's phenomenon, maculopapular rashes, and occasional headaches. Blood pressure has remained normal and oedema has not developed. Laboratory data have shown active disease (low C3, low CH₅₀, and high antinuclear, anti-dsDNA and anti-SM antibodies), but the urine analysis has remained benign, without significant proteinuria, haematuria, or casts and only traces of protein. The creatinine clearance was stable, but an increase from 24 to 33 ml/min has been noted over the last year.

During the past three years the patient's treatment has consisted of potassium and bicarbonate supplements for the renal tubular acidosis and hypokalaemia and occasional treatment with non-steroidal anti-inflammatory agents for joint pain and pleurisy. Her functional capacity has remained satisfactory with a reasonably good quality of life.

Discussion

We have presented a patient who had clinical and laboratory features of active SLE,⁸ but the association of renal failure with predominant tubulointerstitial damage warrants explanation. There was no history of renal dysfunction before admission, nor was there evidence of hypercalcaemia, hyperuricaemia, Sjögren's syndrome, or use of nephrotoxic

Table 1 Laboratory findings during a follow up of three years in a patient with systemic lupus erythematosus and predominant interstitial nephritis

Date	Haemoglobin (g/l)	WBC × 10 ⁹ /l	Platelets × 10 ⁹ /l	Urine analysis	Serum urea (mmol/l)	Serum creatinine (μmol/l)	Cratinine clearance (ml/min)	FANA*	Anti-dsDNA (μg/ml serum)	Anti-SM test	C3† (mg/l)	C4† (mg/l)	CH ₅₀ † (U/ml)
Apr 1982 discharge	90	7.1	105	+ Protein, few RBC	12.0	212	11	+ 3			330		
Aug 1982	106	4.0	97	+ Protein	12.9	248	17	+ 3			380	100	
Jan 1983	84	3.7	126	+ Protein	12.6	256	18	+ 3	7.7	+	330	140	
Apr 1983	120	4.5	58	Traces of protein	12.0	265	16	1/320					
Sept 1983	103	4.6	248	+ Protein, few WBC	11.1	256	27	+ 3	4.23	+	340	100	
Sept 1984	106	5.6	200	Traces of protein	10.0	239	24	+ 3	1.83	+	330	80	11
May 1985	114	5.7	148	Traces of protein	9.3	115	33	≥ 1/320			300	50	

*Out of four grades or titres. WBC = white blood cells; RBC = red blood cells; FANA = fluorescent antinuclear antibodies; C3 = third component of complement; C4 = fourth component of complement; CH₅₀ = 50% activity of total haemolytic complement.

†Normal ranges: C3 600–1200 mg/l; C4 200–400 mg/l; CH₅₀ 20–40 U/ml.

Table 2 Clinical and laboratory features of seven patients with systemic lupus erythematosus and predominant tubulointerstitial nephritis

Patient No	Age (years)	Sex	Presentation of the tubulointerstitial disease	Associated clinical features	Urine analysis	Serum urea (mmol/l)	Serum creatinine (μmol/l)	Creatinine clearance (ml/min)	FANA	C3 (mg/l)	CH ₅₀ (U/ml)	Remarks
1 (2)*	52	F	Acute renal failure	Active SLE polyarthritis, pleuropericarditis, rashes, history of convulsions	+ 2 Protein, no cells or casts	20.9	557	—	+	820	200 (normal)	The first reported case of isolated lupus interstitial nephritis. Treated with corticosteroids. Improved slightly, no follow up
2 (6)*	23	F	Renal tubular acidosis. Completely asymptomatic	A past history of encephalitis, malar rash, arthritis	Clear sediment, urine pH 6.4 in the presence of arterial pH 7.27	—	—	110	—	—	—	Asymptomatic, unaffected by corticosteroid therapy, unassociated with glomerular disease or renal failure
3 (4)*	30	F	Acute oliguric renal failure	Fever, polyarthritis, pleuropericarditis, minimal lupus nephritis (previous biopsy)	No proteinuria, 5-8 RBC, 10-20 WBC	17.6	239	18	1/640	—	34 (normal)	High dose corticosteroid treatment. Renal function improved
4 (5)*	42	F	Acute anuria	Fever, polyarthritis, pleuropericarditis, facial erythema, pneumonia	Mild proteinuria	—	—	—	+	240	—	Haemodialysis and prednisone 80 mg/day 3 weeks after anuria diuresis resumed
5 (5)*	24	F	Acute anuria with high blood pressure	Fever, pleuritis, arthralgia	Proteinuria	39.0	937	—	+	1040	—	Peritoneal dialysis. Diuresis resumed after 3 months. Hypertensive and vascular lesions as well as interstitial nephritis
6 (3)*	72	M	Acute renal failure superimposed on nephrotic syndrome to minimal change disease	Fever, pleuropericarditis, Coombs' positive haemolytic anaemia	Proteinuria of 6 g/day, 10 RBC, 10 WBC	—	513	7	1/2560	530	33 (low)	The acute renal failure was due to interstitial lupus nephritis. Prednisone 100 mg daily and cyclophosphamide. Creatinine clearance increased to 30 ml/min. Patient died 1 month later from sepsis
7 (7)*	3	M	Mild proteinuria without deterioration of renal failure	Fever epistaxis, rashes, Coombs' positive haemolytic anaemia	+ Protein, few granular casts	3.7	44	86	1/160	460	—	Combination of immune complex glomerular disease and anti-TBM antibody. Prednisone. Two years' follow up. Renal function and urine analysis unchanged

*No of reference.

FANA = fluorescent antinuclear antibody; C3 = third component of complement; CH₅₀ = 50% activity of total haemolytic complement; TBM = tubular basement membrane.

Table 3 Histopathological findings of predominant tubulointerstitial nephritis in seven patients with systemic lupus erythematosus

Patient No	Light microscopy	Immunofluorescence examination	Electron microscopy
1	Three of 25 glomeruli were sclerotic. All others appeared normal. Severe interstitial fibrosis, tubular atrophy, thickening, and reduplication of TBM and interstitial mononuclear cell infiltration	Granular deposits of IgG, IgM, and C3 along the basement membranes of most of the proximal tubules. Some deposits in the interstitium as well. The glomeruli were stained only partially for C3 in the mesangium	Numerous interstitial lymphocytes and mast cells. Irregular dense deposits in some of the thickened TBM
2	Normal glomeruli. Focal patchy areas of interstitial fibrosis and tubular atrophy	Negative immunofluorescence studies of the glomeruli. Deposits of C3 were found on the tubular basement membrane	—
3	Increase in the interstitial inflammation with mononuclear cell infiltration and tubular damage. Mild increase in mesangial cells, which had not changed from previous biopsy	Granular deposits of IgG and C3 in the mesangium, interstitium, along TBM, and Bowman's capsule	—
4	Mild and focal mesangial cell proliferation. Most of the tubular cells appear sclerotic. Diffuse oedematous fibrosis in the interstitium with mononuclear cell infiltration	Diffuse granular deposits of IgG and Clq along the TBM. Small mesangial deposits of IgG, Clq, and C3	—
5	Ischaemic changes with shrinkage of the tufts in almost all of the glomeruli. Mild segmental mesangial cell proliferation. Diffuse interstitial fibrosis with mononuclear cell infiltration	Diffuse granular deposits of IgG, Clq, and to a lesser degree of C3 and IgM along the TBM. No deposits on the glomeruli. Immune deposition vessels	—
6	Focal chronic interstitial inflammation and fibrosis. Minimal glomerular cellular abnormalities	Interstitial deposits of IgG, IgM, and C3	Fusion of glomerular basement membrane foot processes
7	Mild increase in mesangial cells and matrix. Oedema, fibrosis, and monocytic infiltration of the interstitium. Atrophic tubules with thickened and tortuous TBM	Granular staining in the mesangium of glomeruli for IgG, C3, Clq, and fibrin. Diffuse +3 linear staining for IgG along the TBM and Bowman's capsule	Increase in mesangial cells. Electron dense deposits in the mesangium. The glomerular and TBM appear normal

TBM = tubular basement membrane.

drugs (e.g., non-steroidal anti-inflammatory agents). The finding of a sclerotic glomerulus in the renal biopsy specimen, however, indicated previous renal damage, and although acute interstitial nephritis related to the viral infection with which she presented cannot be excluded, it seems unlikely. Furthermore, the mononuclear cell interstitial infiltration and the positive immunofluorescent findings along the tubular basement membrane and Bowman's capsule are in accordance with interstitial lupus nephritis.⁹ IgG was not found together with C3 along the tubular basement membrane in our case, but deposits of C3 alone have been demonstrated in kidney biopsy specimens of lupus nephritis with tubulointerstitial involvement.⁹ Moreover, the association of renal tubular acidosis with lupus nephritis, as in our patient, is a frequent finding,¹⁰ which suggests lupus renal involvement in our case. It is possible that the tubular damage was not caused by deposits of immune complexes, but rather by cell mediated injury. Although the mononuclear cell infiltrates have not been functionally characterised in SLE, morphologically similar cell populations in other types of interstitial nephritis have been identified as activated T cells.¹¹ We therefore assume that this young woman had a rare manifestation of lupus renal disease—predominant interstitial nephritis.

Tubulointerstitial involvement is now a well known feature of lupus nephritis.^{1,9} Interstitial inflammation is found in 66% of lupus nephritis biopsy specimens.¹ A higher degree of interstitial inflammation is associated with more severe renal insufficiency¹² and with advanced forms of lupus nephritis, mainly diffuse proliferative glomerulonephritis.¹ It is assumed that the tubulointerstitial damage is a sequel to the deposition of immune complexes.¹² Extraglomerular immune deposits and electron dense deposits are present in more than half of the biopsy specimens of patients with systemic lupus erythematosus.^{1,9} IgG and C3 are most commonly present in the deposits¹² and they are found along the basement membranes of peritubular capillaries, within the interstitium and along the tubular basement membrane.¹³ Clinically, the tubulointerstitial involvement may contribute to the development of renal failure⁹ and to tubular dysfunction, marked by impaired maximal concentrating ability, reduced fractional urinary excretion of β_2 microglobulin,¹⁰ and a renal tubular acidifying defect.¹⁴

Despite the frequency of interstitial involvement in lupus nephritis, only a few cases of isolated or predominant tubulointerstitial nephritis have been reported in patients with systemic lupus erythematosus. Tables 2 and 3 summarise the seven well recorded cases. Most of the patients with pre-

dominant interstitial nephritis are distinguished by clinically active lupus, positive tests for antinuclear antibodies and DNA binding, benign urine analysis, and a predominant interstitial inflammation with only mild glomerular damage.^{2-5,7} The interstitial inflammation is associated with immune deposits along the tubular basement membrane, Bowman's capsule, and within the interstitium.²⁻⁶ In one case, however, Makker reported a child who presented with autoantibody induced interstitial nephritis. The autoantibodies reacted with the tubular basement membrane of the proximal renal tubules and the Bowman's capsules of the glomeruli.⁷

Clinically, these patients had variable presentations, courses, and treatments. Acute renal failure occurred in five of the seven cases (Nos 1, 3-6 in Tables 2 and 3). High dose corticosteroids were administered in four patients, with improvement of their renal function. In contrast, in case No 5 diuresis resumed after three months of peritoneal dialysis without specific treatment.⁵ The long term course of the patients who partially improved after the corticosteroid therapy is not mentioned. The patient (No 2) reported by Disler *et al* presented with asymptomatic renal tubular acidosis as the sole manifestation of lupus nephritis and, in contrast with our case, did not have active lupus or impairment of renal function.⁶

The patient we have presented here was distinguished by a chronic course of interstitial lupus nephritis, renal tubular acidosis, and chronic renal failure. Considering the limited information on this rare manifestation of lupus nephritis, we decided not to treat her with corticosteroids, and thus were able to follow the natural history of predominant tubulointerstitial lupus nephritis in this patient for more than three years. In spite of her active lupus, manifested by exacerbations of arthritis, rash, pleuritis, and fever, and by high dsDNA binding and low C3 and CH₅₀ levels, her renal function has remained stable and may in fact be improving, and thus she presents a relatively benign course, being spared the complications of corticosteroids and immunosuppressive therapy. It is probably prudent to observe such cases and only in the event of renal function deterioration consider immunosuppressive therapy.

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References

- 1 Brentjens J R, Sepulveda M, Baliah T, *et al*. Interstitial immune complex nephritis in patients with systemic lupus erythematosus. *Kidney Int* 1975; 7: 342-50.
- 2 Epstein W H, McCluskey R T. Weekly clinicopathological

- exercises of the Massachusetts General Hospital. Case 2-1976. *N Engl J Med* 1976; **294**: 100-5.
- 3 Klahr S, Lynch R. Clinicopathological conference: interstitial nephritis in a patient with systemic lupus erythematosus. *Am J Med* 1980; **69**: 775-81.
 - 4 Cunningham E, Provost T, Brentjens J, Reichlin M, Venuto R C. Acute renal failure secondary to interstitial lupus nephritis. *Arch Intern Med* 1978; **138**: 1560-4.
 - 5 Tron F, Gineval D, Droz D. Immunological mediated acute renal failure of nonglomerular origin in the course of systemic lupus erythematosus (SLE). *Am J Med* 1979; **67**: 529-32.
 - 6 Disler P B, Lewin J R, Laidley L, Meyers A M. Systemic lupus erythematosus with pure interstitial disease: a case report [Abstract]. *Kidney Int* 1978; **13**: 428.
 - 7 Makker S P. Tubular basement membrane antibody induced interstitial nephritis in systemic lupus erythematosus. *Am J Med* 1980; **69**: 949-52.
 - 8 Tan E M, Cohen A S, Fries J F, *et al*. The 1982 revised criteria for the classification of SLE. *Arthritis Rheum* 1982; **25**: 1271-7.
 - 9 Schwartz M M, Fennell J S, Lewis E J. Pathologic changes in the renal tubule in systemic lupus erythematosus. *Hum Pathol* 1982; **13**: 534-47.
 - 10 Yeung C K, Wong K L, Ng R P, Ng W L. Tubular dysfunction in systemic lupus erythematosus. *Nephron* 1984; **36**: 84-8.
 - 11 Husby G, Tung K S K, Williams R C Jr. Characterization of renal tissue lymphocytes in patients with interstitial nephritis. *Am J Med* 1981; **70**: 31-8.
 - 12 Park M H, Appel E B, Piran C L. Significance of tubulointerstitial changes in lupus nephritis [Abstract]. *Kidney Int* 1983; **23**: 196.
 - 13 Ferluga D, Vizjak A, Kvala A, *et al*. Tubulointerstitial immune deposits (ID) in patients with lupus nephritis (LN) [Abstract]. *Pathol Res Pract* 1982; **176**: 19.
 - 14 Fennell J S, Schwartz M M, Bidani A K, *et al*. Renal tubular acidifying defect in tubulointerstitial diseases of lupus nephritis [Abstract]. *Kidney Int* 1981; **19**: 125.