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Original Article

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Distinguishing C1q nephropathy from lupus nephritis

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Abstract

Background. 'Seronegative lupus nephritis' describes patients with renal histology typical of lupus nephritis who have no clinical or serological evidence of systemic lupus erythematosus (SLE). We report our experience in nine patients identified as having 'seronegative lupus nephritis' who met the diagnostic criteria for C1q nephropathy.

Methods. A retrospective review of clinical case notes and renal histology was carried out.

Results. We describe nine patients with C1q nephropathy in whom the diagnosis of 'seronegative lupus nephritis' was initially considered. All had renal histological features typical of lupus nephritis with 'wire loop' appearances on light microscopy, 'full house' immunoglobulin and complement deposition by immunoperoxidase, and electron-dense deposits in at least two glomerular locations. None of these nine patients developed clinical or serological evidence of SLE over a median follow-up of 6 years (range 0.1–9). There was no consistent evidence of a response to immunosuppressive therapy. In all cases, C1q staining was dominant on immunoperoxidase, and no tubuloreticular inclusions were seen. These appearances accord with previous descriptions of C1q nephropathy.

Conclusions. The implications of a diagnosis of lupus are considerable, and we propose that the term 'seronegative lupus nephritis' is unhelpful, and should be avoided when there is diagnostic uncertainty. The term C1q nephropathy should be preferred when these histological features are seen in the absence of overt lupus, when C1q deposition is dominant and when tubuloreticular bodies are absent. The clinical course in the cases reported here does not support the use of immunosuppressive therapy in C1q nephropathy.

Keywords: C1q; glomerulonephritis; lupus nephritis

Introduction

The diagnosis of lupus nephritis is often straightforward. Patients typically have clinical evidence of extrarenal lupus with diagnostic serological changes. Although light microscopic appearances on renal histology may be very variable, the so-called 'full house' of glomerular immune reactants along with electron-dense deposits at two or more sites in the glomerulus are characteristic features.

However, a variant has been described, sometimes called 'seronegative lupus nephritis'. This term is usually used to describe patients in whom the renal histology is typical of lupus nephritis, yet at the time of presentation with renal disease there is no past or present evidence, either clinical or serological, of systemic lupus erythematosus (SLE). Such patients were recognized soon after the introduction of renal biopsy for the investigation of lupus nephritis, but little has been published on this topic in the last 20 years.

It has been proposed that if patients have renal histology entirely consistent with lupus nephritis, a significant proportion of them will in due course develop overt systemic lupus. As a consequence, many such patients are treated with immunosuppressive regimens which are used for typical lupus nephritis with equivalent histology—often including corticosteroids with cyclophosphamide and/or azathioprine. Published evidence to support these approaches is limited, and not all studies have shown that such patients will progress to overt lupus.

C1q nephropathy, first described by Jennette and Hipp in 1985, is a pattern of glomerulonephritis characterized by predominant mesangial C1q deposition but with other histological features resembling lupus nephritis, although no extrarenal disease [1–4].

In this report, we describe our experience of C1q nephropathy. We explain why this pattern of glomerulonephritis should not be regarded as 'seronegative lupus nephritis', which we propose is a clinically unhelpful term, since evidence is scant that such patients have a clinical course and response to treatment similar to those with overt lupus nephritis.

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We argue, furthermore, that our patients, who would have been described by some authorities as having 'seronegative lupus nephritis', all meet the diagnostic criteria for C1q nephropathy.

Subjects and methods

Case ascertainment

Renal biopsies coded on histopathological criteria as lupus nephritis were identified from the 3006 native renal biopsies undertaken in our Institution between 1990 and 2001. The medical records of the 81 cases thus identified were then reviewed to establish the clinical and serological evidence of SLE at the time of presentation.

From this group, nine cases were identified with no clinical or serological evidence of SLE at the time of presentation. The renal biopsies of these cases were reviewed to assess the confidence in the histological diagnosis. In every case, the biopsy had been examined by light microscopy (haematoxylin and eosin stain, and methenamine silver stain); immunoperoxidase for IgG, IgA, IgM, C3 and C1q; and electron microscopy. Cases were eliminated if: (i) the original report identified some other diagnosis as being more likely than SLE (thereby indicating a disease coding error); (ii) the biopsy failed to show positivity for all three immunoglobulins; or (iii) electron-dense deposits were not present in at least two locations (subepithelial, subendothelial and mesangial).

The clinical records of the remaining nine cases were reviewed to determine whether any clinical or serological evidence of SLE had become apparent on follow-up. The natural history and outcome were assessed, as was the use of corticosteroids or other immunosuppressive therapies and the response to treatment. The electron microscopy was also reviewed with the specific intention of detecting any tubuloreticular inclusions in endothelial cells.

Results

Patients

Eighty-one patients were identified who had a renal biopsy coded as lupus nephritis in the 11 year study period. All those with clinical and serological evidence of SLE at presentation of renal disease (or noted previously) were excluded. This left nine individuals with no evidence of SLE who were designated 'seronegative lupus nephritis' and are the subject of this report. There were seven females, median age 26 years (range 19–63), and two males, aged 39 and 65 years.

Clinical presentation (Table 1)

Five presented with asymptomatic proteinuria and haematuria, one with isolated asymptomatic proteinuria, and one with nephrotic syndrome.

Two patients had renal impairment at presentation, one with nephrotic syndrome, serum creatinine 266 μmol/l; and one with acute renal failure, serum creatinine 744 μmol/l. Only one patient was hypertensive at presentation.

Renal histology (Table 2)

In accordance with the selection criteria, all the cases had positive glomerular staining for all three main immunoglobulin heavy chains. In every case, immunostaining for C1q was strongly positive.

Electron-dense deposits were present in mesangial and subendothelial locations in all patients and also in the subepithelial location in three patients. A search failed to find tubuloreticular inclusions in any of the biopsies.

On light microscopy, all nine patients had glomerular capillary wall thickening recognizable as 'wire loops' (Figure 1). All patients had at least some mesangial hypercellularity, though with considerable variation in severity; it was global in seven and segmental in two. Hence, even in the cases with minimal hypercellularity, the 'membranous' pattern resembled lupus rather than idiopathic membranous glomerulonephritis. One patient with severe mesangial hypercellularity had cellular crescents in Bowman's space.

Table 1. Clinical characteristics at presentation of nine patients with 'seronegative lupus nephritis'

Case no.	Gender	Age (years)	Serum creatinine (μmol/l)	Urine protein (g/24 h)	Haematuria (dipstick)	Blood pressure (mm Hg)	Lupus serology
1	M	65	744	2+	2+	185/85	NAD
2	M	39	266	10	1+	230/130	NAD
3	F	16	76	1.9	1+	150/80	NAD
4	F	15	72	3.3	1+	140/80	C3 high[a]
5	F	26	72	1.1	1+	110/70	NAD
6	F	63	99	5.6	1+	180/90	NAD
7	F	30	60	0.9	–	118/54	NAD
8	F	19	59	0.8	1+	120/80	C4 low[b]
9	F	31	78	0.9	1+	110/70	NAD
	7F:2M	30 (15–65)	Median 70 (59–744)	Median 1.5 (0.7–10)	8/9 positive	145/80	

[a]C3 high at presentation; thereafter normal on repeated testing.
[b]C4 consistently low; presumed C4 null allele.

Table 2. Renal histology at presentation in nine patients with 'seronegative lupus nephritis'

Case no.	Gender	Age years	Serum creatinine (μmol/l)	Light microscopy	Immunofluorescence microscopy[a]	Electron microscopy (sites of electron-dense deposits)
1	M	65	744	Crescentic	G, A, C3, C1q	Three sites
2	M	39	266	Membranous + mesangial proliferative	G, A, M, C3, C1q	Mesangial and subendothelial
3	F	16	76	Focal segmental proliferative	G, A, M, C1q	Three sites
4	F	15	72	Diffuse mesangial proliferative	G, A, M, C3, C1q	Mesangial and subendothelial
5	F	26	72	Membranous + mild mesangial proliferation	G, M, C3, C1q	Three sites
6	F	63	99	Diffuse mesangial proliferative	G, A, M, C3, C1q	Mesangial and subendothelial
7	F	30	60	Membranous + mild mesangial proliferation	G, A, M, C3, C1q	Three sites
8	F	19	59	Diffuse mesangial proliferative	G, A, M, C3, C1q	Mesangial and subendothelial
9	F	31	78	Focal segmental proliferative	G, A, M, C3, C1q	Mesangial and subendothelial

[a]Significant staining for immunoglobulin classes IgG, IgA, IgM, C1q was the predominant finding on immunoperoxidase in all cases. Three sites = electron-dense deposits in mesangial, subendothelial and subepithelial locations.

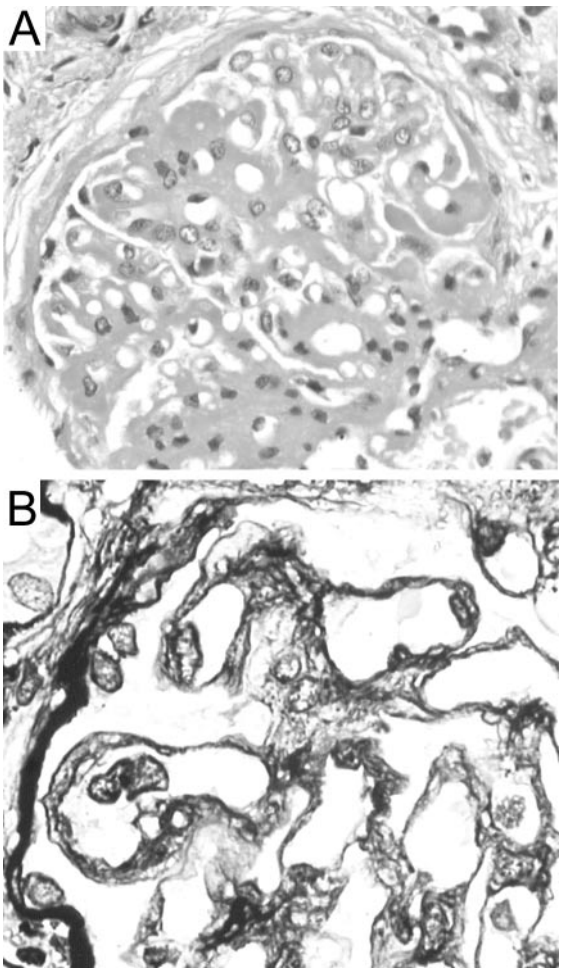

Fig. 1. Light microscopic appearances of a glomerulus showing glomerular capillary wall thickening: the 'wire loop' lesion. (**A**) Haematoxylin and eosin; (**B**) methenamine silver. Such lesions were seen in the glomeruli of all nine cases in this report.

Treatment (Table 3)

Four of the nine patients received immunosuppression. Their treatment and outcome are summarized in Table 3.

Patient 1. A 65-year-old man with acute renal failure and crescentic glomerulonephritis was treated with prednisolone and cyclophosphamide but died of a cardiovascular event within 1 month of presentation.

Patient 2. A 39-year-old man with renal impairment and nephrotic syndrome received prednisolone in reducing doses for 6 years. He has residual renal impairment (creatinine 160 μmol/l) but proteinuria <1 g/24 h.

Patient 3. A 16-year-old girl with preserved renal function was treated with immunosuppression on the basis that the renal histological appearances were thought to indicate a very high risk of progressive renal damage. There was indeed relentless progression despite treatment with prednisolone and cyclophosphamide followed by azathioprine. Within 4 years, she had reached end-stage renal disease and subsequently has been transplanted without recurrence of glomerular disease.

Patient 4. A 15-year-old girl with preserved renal function was treated on the basis that the renal biopsy confirmed a diagnosis of lupus. She received prednisolone and azathioprine for 6 years and had no change in renal function or low grade proteinuria.

Patients 5–9. The other five patients received no immunosuppressive treatment but had renal histological injury of severity equivalent to patient 4.

Outcome

There was a median follow-up of 6 years (range 0.1–9). As described above, one patient died at 1 month, and one developed end-stage renal disease at 4 years.

At latest follow-up, the remaining seven patients all had proteinuria <1 g/24 h. Five had serum creatinine <85 μmol/l. Two had chronic renal impairment (creatinine 160 and 176 μmol/l, respectively). Importantly, at the time of the most recent follow-up, none had developed any clinical or serological evidence of SLE despite repeated evaluation.

Table 3. Treatment and outcome in nine patients with 'seronegative lupus nephritis'

Case no.	Gender	Age (years)	Treatment	Treatment rationale	Follow-up (years)	Serum creatinine (μmol/l)		Urine protein (g/24 h)	
						Presentation	Latest	Presentation	Latest
1	M	65	Prednisolone (1 month) Cyclophosphamide (1 month)	Crescentic GN, ARF	0.1 (died)	744	–	2+	–
2	M	39	Prednisolone (1 year)	Nephrotic syndrome, renal impairment	3	266	160	10	0.4
3	F	16	Prednisolone (1 year) Cyclophosphamide (2 months); then azathioprine (1 year)	Crescentic GN	9	76	ESRD (4 years)	1.9	–
4	F	15	Prednisolone (6 years) Azathioprine (6 years)	'Lupus' nephritis	6	72	65	3.3	1.5
5	F	26	Nil		2	72	81	1.1	2+
6	F	63	BP control only		5	99	176	5.6	<0.3
7	F	30	Nil		6	60	76	0.9	0.5
8	F	19	Nil		7	59	64	0.8	0.4
9	F	31	Nil		8	78	80	0.9	1+

Discussion

Previous studies of 'seronegative lupus nephritis' have suggested that progression to overt lupus is not infrequent. The initial presentation and renal histology were heterogeneous in other reports, and direct comparisons with our own series are not straightforward. Nevertheless, Cairns *et al*. in 1979 [5] reported 11 patients of whom four developed overt lupus over 1–7 years of follow-up. Adu *et al*. in 1983 [6] reported 17 patients of whom they felt five developed definite evidence of lupus and four probable lupus over 1–10 years follow-up. In contrast, however, Jones and Maggil in 1982 [7] describe five patients, none of whom developed overt lupus over 5 years; the renal lesion in these patients was described as 'non-systemic mesangiopathic glomerulonephritis with full house immunofluorescence' [7]. Enriquez *et al*. in 1988 [8] described three children who did not develop overt lupus over a short follow-up period of no more than 2 years, although all three received substantial immunosuppressive therapy during that time.

From the 36 patients in these four reports, it is possible to identify with some confidence 17 patients who appear to meet the criteria we used to identify the cases in this study: glomerular injury with 'full house' immunoperoxidase or immunofluorescence staining and electron-dense deposits in at least two sites in the glomerulus (Table 4). Of the 17 patients who met those criteria, five developed positive lupus serology during follow-up, and three developed clinically overt lupus (Table 4). However, our own experience in the cases reported here is that these patients did not develop lupus; none showed any clinical features of SLE, nor any positivity of serological tests for lupus over a prolonged follow-up. At the time of presentation with renal disease in SLE, the extent and range of extrarenal involvement, and the serological evidence of lupus are very variable [9]. However, we emphasize that the patients we describe here are a very specific group: although they had characteristic histology consistent with lupus nephritis, by our inclusion criteria they had absolutely no other clinical and serological features of lupus, past or present, at the time of diagnosis of renal disease.

Information on the treatment of our group of patients inevitably is anecdotal. However, there is little convincing evidence of a response to treatment in these patients, with the single exception of the nephrotic patient who appeared to respond well to corticosteroids. Immunosuppressive treatment did not convincingly alter the natural history in patients 3 and 4, and the remaining five untreated patients (patients 5–9) with histological injury of severity equivalent to patient 4 do not seem to have been compromised by our chosen conservative approach to treatment with no use of immunosuppressive agents.

There have been no coherent studies defining the appropriate treatment for 'seronegative lupus nephritis', and standard texts do not offer recommendations for such patients. However, many physicians have noted the risk of progression to overt lupus and recommend immunosuppressive treatment regimens similar to those proposed for overt lupus nephritis with equivalent histological severity. Such patients may therefore receive not only corticosteroid therapy but

Table 4. Published cases of 'seronegative lupus nephritis'

	Number (total cases in report)	Initial histological features	Development of positive serology; time after presentation	Development of clinically overt lupus; time after presentation	Immunosuppressive treatment and response
Cairns 1979 [5]	1 (11)	Membranous Full house IF (including C1q) Deposits at two sites	Yes (1) at 3 months	None	Not treated
Jones 1982 [7]	5	Mesangial hypercellularity Full house IF (C1q predominant) Deposits at two or three sites	None Follow-up 10–58 months	None	Prednisolone (2) ± azathioprine (3) Response uncertain
Adu 1983 [6]	8 (17)	Mesangial hypercellularity (3) *or* Membranoproliferative (3) *or* Membranous (2) Multiple IF (5) *or* 'Full house' IF (3) Deposits at two or three sites	Yes (4)	Yes (3) at 24–120 months	Prednisolone + azathioprine (3) one definite, one probable response; one death
Enriquez 1988 [8]	3 children	Mesangial hypercellularity 'Full house' IF (including C1q) Mesangial deposits (2) or deposits at two sites (1)	None Follow-up 16–24 months	None Response uncertain	Prednisolone + cyclophosphamide/azathioprine (3)

Cases have been selected from larger series if there was typical lupus nephritis at initial renal biopsy with no clinical or serological evidence of extrarenal lupus.
Full house IF (immunofluorescence) = glomerular staining for IgG, IgA, IgM and complement component(s); multiple IF = staining for at least two immunoglobulin classes and complement.
Deposits at two or three sites = glomerular electron-dense deposits in at least two of subepithelial, subendothelial, and mesangial sites.

also cytotoxic agents including cyclophosphamide and azathioprine. The potential morbidity of these regimens, including adverse effects on fertility, requires that their use be restricted to proven indications. There is at present no published evidence to support their use in 'seronegative lupus nephritis'.

From our experience, we conclude that the term 'seronegative lupus nephritis' is unhelpful. The true and perceived implications of a diagnosis of lupus are considerable, particularly in the contemporary era when many patients have access to extensive information on the Internet. Even the tentative suggestion that a diagnosis of lupus is being considered requires considerable care, and may provoke uncertainty and anxiety for the individual concerned. The term lupus should therefore be avoided unless clinical or serological features of lupus are identified unequivocally.

If the term 'seronegative lupus nephritis' is to be deprecated, what alternative should be used? The renal histological features of all our nine patients are consistent with C1q nephropathy as defined by Jennette and Hipp [1]. The predominance of mesangial C1q usually with multiple other immune reactants combined with mesangial hypercellularity and electron-dense deposits in two or more sites are characteristic [1,3]. Jennette himself described the lesion as 'resembling lupus nephritis', but noted that unlike lupus nephritis, none of his cases showed tubuloreticular inclusions in glomerular endothelial cells on electron microscopy [1]; our cases all follow this description precisely. Jennette's series include 79 patients with C1q nephropathy who were typically proteinuric and often nephrotic [3]. In his experience, they were young adults and mainly black males (perhaps reflecting the catchment population of his institution in North Carolina). A poor response to corticosteroid therapy was typical and overall renal survival was good (84% at 3 years). Other substantial reports on C1q nephropathy are a study of 15 nephrotic children who were uniformally steroid resistant [4], and a report on four nephrotic adults [3], one of whom received immunosuppressive treatment but the other three went into spontaneous remission. Most recently, Markowitz *et al*. report a cohort of 19 patients with C1q nephropathy in whom light microscopic appearances of minimal change disease/focal segmental glomerulosclerosis (FSGS) were prominent [10]. Fourteen of the 19 patients in their report were African Americans, and all of them had FSGS on light microscopy, perhaps reflecting the known susceptibility of this racial group to FSGS.

Description of a new clinico-pathological entity within the classification of glomerular disease is often contentious, and the term C1q nephropathy has been slow to be adopted. Categorization of glomerular disease remains dominated by morphology. An ideal classification would not only define glomerular diseases by tight histological and clinical criteria, but it would relate histological findings to pathogenic mechanisms. This is often not the case. IgA nephropathy, for example, is now accepted as a discrete type of glomerular disease, yet the mesangial deposition of IgA is associated with a very wide range of morphological injury and clinical course, and direct evidence that IgA has a pathogenic role in glomerular injury is sparse. Acceptance of IgA nephropathy as a distinct glomerular disease evolved over some years as increasing numbers of patients were described. We support the notion that C1q nephropathy is a distinct histological entity, but recognize that its characterization remains incomplete. There is as yet little evidence that the defining feature of C1q deposition is directly pathogenic, and our knowledge of the full range of its histological and clinical expression will require the expansion of available published reports.

In retrospect, we believe C1q nephropathy was the correct diagnosis in our nine patients. It is an entity which is probably under-recognized, since many institutions do not include C1q staining as a routine part of renal biopsy analysis. An informal survey of renal pathologists in the UK in 1998 showed that only 50% undertook routine C1q staining (I. Roberts, personal communication). Many pathologists regard tubuloreticular inclusions as an ultrastructural curiosity of no great diagnostic value, a non-specific finding probably attributable to high levels of interferon-α [11], although others have emphasized their value in favouring a diagnosis of lupus nephritis in equivocal cases [12,13]. Our results suggest that when 'seronegative lupus nephritis' is contemplated, the absence of tubuloreticular inclusions is a relevant pointer towards a diagnosis of C1q nephropathy. Such inclusions are found in a high proportion of cases of active, untreated lupus nephritis [14]. Indeed, the presence or absence of such inclusions has been proposed previously as a method to distinguish between idiopathic membranous glomerulonephritis and lupus class V nephropathy [15].

Our own series had more patients with asymptomatic proteinuria and fewer with nephrotic syndrome compared with some other reports [1–4], but such clinico-pathological correlations in glomerular disease are often imprecise. The histological resemblance to lupus nephritis without any past or present evidence of SLE is the feature of our series and of most previously published series of C1q nephropathy. Another characteristic feature of lupus nephritis which has been emphasized recently is the presence of circulating anti-C1q antibodies [16]. We did not have the opportunity to test for anti-C1q antibodies in the patients we report here, but there is evidence that anti-C1q antibodies are absent in patients with C1q nephropathy [J. C. Jennette, personal communication], providing an additional approach to assist in the distinction between C1q nephropathy and lupus nephritis.

Although we set out to review our experience of patients whom we previously had regarded as having seronegative lupus nephritis, we concluded that those who fitted our selection criteria all fully satisfy the published clinico-pathological criteria for C1q nephropathy. We propose that C1q nephropathy may be an under-recognized entity, and further reports are needed to define the range of its histological and clinical

features. We encourage routine use of C1q staining of renal biopsy analysis, and a search for tubuloreticular inclusions whenever 'lupus nephritis' is an unexpected finding on renal biopsy; as well as measurement of circulating anti-C1q antibodies. We suggest that 'seronegative lupus nephritis' is an unhelpful term which should no longer be used.

Conflict of interest statement. None declared.

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