A Young Lady with Full-house Nephropathy and Negative Anti-nuclear Antibody

Chi-Keung Sung and Emily Wai-Lin Kun

Abstract: We hereby report a young lady suffering from glomerular disease with a "full-house" immunofluorescence pattern. The test for anti-nuclear antibody is negative and she has no other features of systemic lupus erythematosus. Electron microscopy demonstrates the presence of tubuloreticular inclusions and her response to steroid is satisfactory, hence resembling a case of lupus nephritis. However, past case series show that only some but not all patients with negative anti-nuclear antibody and "full-house" nephropathy behave like lupus nephritis. C1q nephropathy mimics lupus nephritis histologically but the response to immunosuppressive therapy is not as good as lupus nephritis. The presence of tubuloreticular inclusions and C1q antibodies favors the diagnosis of lupus nephritis rather than C1q nephropathy.

Keywords: C1q nephropathy, Full-house immunofluorescence, Lupus nephritis, Negative anti-nuclear antibody

Introduction

The most common cause of glomerular diseases with a "full-house" immunofluorescence (IF) pattern is lupus nephritis. However, a small proportion of patients is anti-nuclear antibody (ANA) negative and has no extra-renal manifestations of systemic lupus erythematosus (SLE). There is controversy whether they are really cases of lupus nephritis.

Case History

A 20-year old lady had history of Type 1 diabetes mellitus on insulin therapy since the age of four. Her diabetic control was satisfactory. She presented with a sudden onset of bilateral ankle edema. Her serum albumin was 26 gram/L and urine total protein was 2.3 gram/day. Anti-nuclear antibody was negative. Complement levels were normal. Ultrasound kidney findings were essentially normal. Light microscopy of renal biopsy showed segmental increase in mesangial cellularity and matrix. There was no endocapillary proliferation or thickening of glomerular capillary wall. IF study demonstrated granular depositions of IgG (2+), IgA (2+), IgM (weak), C3 (1+), and C1q (2+). Electron microscopy (EM) showed frequent subepithelial electron deposits and few tubuloreticular aggregates (Figure 1). The overall histological picture was suggestive of lupus or lupus-like condition.

Detailed physical examination of the patient did not reveal extra-renal manifestations of SLE. She was put on prednisolone 30 mg/day. After two months of steroid therapy, her proteinuria resolved. She did not develop other features of SLE upon her last follow-up three months later.

Discussion

"Full-house" nephropathy and negative ANA is a poorly understood clinical entity. Some authors use the term "ANA-negative lupus nephritis" because they think that lupus nephritis is the underlying pathology even though the test for
ANA is negative. A more descriptive term is "non-systemic mesangiopathic glomerulonephritis with full-house immunofluorescence". Recently, some authors believe that C1q nephropathy may have to be distinguished from "ANA-negative lupus nephritis".

"Full-house" nephropathy can be found in many clinical entities like lupus nephritis, posthepatic cirrhosis, diabetic nephropathy, de novo membranous nephropathy, C1q nephropathy and membranoproliferative glomerulonephritis. Lupus nephritis, by far, is the most common association. Around 5% of patients fulfilling the American College of Rheumatology criteria for SLE are ANA negative. Heavy proteinuria can result in loss of immunoglobulin and negative ANA.

On reviewing past literatures, it is found that there are a few case series describing this condition. We can focus on the risk of progression to SLE and the response to immunosuppressive therapy to see if all of these patients behave like lupus nephritis.

### Progression to SLE

Table 1 shows the number of patients with initial idiopathic "full house" glomerular disease with or without progression to definite SLE. It is found that not all patient progress to SLE. Among the patients recruited by Gianviti et al in 1983, electron microscopy showed that two patients had tubuloreticular inclusions favoring the diagnosis of lupus nephritis and one of them progress to SLE. In the case series reported by Sherman et al in 2004, all patients were negative for tubuloreticular inclusions and none of them developed SLE. It appears that patients with tubuloreticular inclusions have a higher chance of developing SLE in the future.

### Response to Immunosuppressive Treatment

In the case series reported by Enriquez et al 1988, all three patients responded well to steroid and immunosuppressive agent. However, poor response was observed in the case series reported by Jones and Magil in 1982 and Sharman et al in 2004. All the patients recruited by Sharman et al were negative for tubuloreticular inclusions. These observations suggest that only some patient response to immunosuppressive therapy and absence of tubuloreticular inclusions may predict a lack of response.

### Distinguishing Lupus Nephritis from C1q Nephropathy

C1q nephropathy was first described by Jennette and Hipp in 1985. It is believed that it is an immune complexes mediated glomerular disease. The diagnostic criteria laid down were:

1. Dominant staining for C1q
2. Mesangial deposits by electron microscopy
3. Absence of clinical or serology of SLE

### Table 1. Number of patients progressed to definite SLE

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients progress to definite SLE</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones &amp; Magil 1982</td>
<td>0 / 5</td>
<td>10-58 months</td>
</tr>
<tr>
<td>Adu et al 1983</td>
<td>5 / 17</td>
<td>1-10 years</td>
</tr>
<tr>
<td>Enriquez et al 1988</td>
<td>0 / 3</td>
<td>2 years</td>
</tr>
<tr>
<td>Gianviti et al 1999</td>
<td>1 / 3</td>
<td>3-10 years</td>
</tr>
<tr>
<td>Sharman et al 2004</td>
<td>0 / 9</td>
<td>Median 6 years</td>
</tr>
</tbody>
</table>

Figure 1. Renal biopsy under electron microscopy showing a tubuloreticular inculsion (arrow).
C1q nephropathy resembles lupus nephritis histologically, but these patients show no evidence of SLE serologically and clinically. It has been observed that the spectrum of light microscopic findings in C1q nephropathy was similar to the range seen in lupus nephritis. "Full-house" IF pattern is also a common finding in C1q nephropathy. However, the clinical course of C1q nephropathy is very different from that of lupus nephritis. There was no reported patient with the diagnosis of C1q nephropathy progressing to SLE. The response of steroid was poor in C1q nephropathy.

Tubuloreticular inclusion is a common electron microscopy finding in lupus nephritis though it is not specific for SLE. It reflects the underlying immune process and is associated with high level of interferon-α. Case report also shows that the presence of tubuloreticular inclusion can precede the onset of SLE. On the contrary, tubuloreticular inclusions have never been observed in C1q nephropathy. As a result, the pattern of "full-house" immunofluorescence staining together with presence of tubuloreticular inclusions increases the likelihood of lupus nephritis.

C1q antibodies may also be useful in differentiating lupus nephritis from C1q nephropathy. C1q antibodies are commonly observed in SLE patients especially in those with nephritis. A high titer is associated with proliferative glomeronephritis. There is evidence that C1q antibodies are absent in patients with C1q nephropathy. C1q antibodies are associated with hypocomplementaemia. Complement level may also be used in the differentiation.

**Conclusion**

We describe a young lady with "full-house" glomerular disease, negative ANA and EM findings of tubuloreticular inclusions and a good response to steroid. The patient is likely a case of lupus nephritis and should be followed up closely for SLE features.

It is important to distinguish lupus nephritis from C1q nephropathy. C1q nephropathy mimics lupus nephritis histologically but the response to immunosuppressive therapy is not as good as lupus nephritis. The presence of tubuloreticular inclusions and C1q antibodies favors the diagnosis of lupus nephritis rather than C1q nephropathy.

**References**