Nephrotic syndrome associated with hypocomplementaemic urticarial vasculitis syndrome: successful treatment with cyclosporin A

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Introduction

Hypocomplementaemic urticarial vasculitis syndrome (HUVS) is an uncommon disorder that resembles systemic lupus erythematosus (SLE), the basic diagnostic criteria of which are recurrent urticaria and hypocomplementaemia, plus at least two of the following: vasculitis of the dermis on biopsy, arthralgia or arthritis, glomerulonephritis, uveitis or episcleritis, recurrent abdominal pain, and a decrease in C1q and a positive C1q precipitin test [1]. This condition is also occasionally accompanied by anti-Ro (SS-A) and antinuclear antibodies (Ab) [2,3]. Renal involvement in this disease has been reported to show mild to heavy proteinuria [2–8]. Histologically, mesangio proliferative and membranoproliferative glomerulonephritis are predominant, and several cases have been associated with leucocytic infiltration in the interstitium [2–8]. In this report, we describe a patient with nephrotic syndrome associated with HUVS. Nephrotic syndrome was resistant to prednisolone therapy, but treatment with cyclosporin A (CyA) was effective against nephrotic syndrome and improved renal function.

Case

In October 1996, a 43-year-old man was admitted to our hospital because of proteinuria with hypocomplementaemia. Two months before admission, he consulted a doctor because of lid oedema and proteinuria. Hypocomplementaemia had been noted at that time. Family history and past medical history were unre markable, except for recurrent urticaria. He did not complain of joint pain, dry eyes, dry mouth or abdominal pain.

Physical examination showed slight facial oedema. Urinalysis showed 3+ protein and 1 red blood cell/high-powered field without casts. Creatinine clearance was 88 ml/min and proteinuria was 3 g/day. The urine β2-microglobulin concentration was 463 μg/l (normal, 5–253 μg/l). Total haemolytic activity (CH50) was markedly diminished at 11.8 U/ml (normal, 30–45 U/ml) as were serum complement 4 (C4) (4 mg/dl; normal, 14–37 mg/dl) and complement 3 (C3) levels (51 mg/dl; normal, 83–140 mg/dl). Cryoglobulinaemia was absent. Anti-Ro (SS-A) Ab was positive at 109 (normal, <7) and anti-nuclear Ab was positive at 1:160 exhibiting a speckled and cytoplasmic pattern. Anti-double-stranded DNA Ab, anti-sm Ab, anti-La (SS-B) Ab, anti-ribonucleoprotein (RNP) Ab, perinuclear anti-neutrophil cytoplasmic Ab (P-ANCA), cytoplasmic anti-neutrophil cytoplasmic Ab (C-ANCA) and rheumatoid factor were all negative. The results of other laboratory tests included blood urea nitrogen 23 mg/dl, serum creatinine 0.7 mg/dl, uric acid 6.4 mg/dl, total protein 6.7 g/dl, serum albumin 3.5 mg/dl, total cholesterol 260 mg/dl, triglycerides 228 mg/dl, white blood cells 9000/μl, red blood cells 427 × 106/μl, haemoglobin 13.4 g/dl, platelets 27.8 × 109/μl and normal values for electrolytes, glucose and liver enzymes. Hepatitis C virus serology and surface antigen of hepatitis B virus were negative. No abnormalities were found on ophthalmologic examination including the Schirmer and rose bengal tests. Parotidography revealed no abnormalities. A minor salivary gland biopsy showed mild and diffuse lymphocytic infiltrates, but no remarkable lymphocytic infiltrates were seen around the excretory ducts. A skin biopsy was not performed, since the patient did not experience a urticarial attack after admission. In November 1996, renal biopsy was performed.

Renal biopsy findings

The specimen contained nine glomeruli, none of which were globally sclerotic. They showed mild expansion...
Fig. 1. (a) The glomerulus shows mild thickening of the capillary walls, but no mesangial proliferation. The tubulointerstitial changes are severe and accompanied by marked lymphocytic infiltration. Elastica-Masson, ×110. (b) Immunofluorescence study shows granular IgG deposition on the capillary walls and in the mesangium. Anti-IgG, ×180. (c) Electron-micrograph of a glomerulus shows electron-dense deposits in both the subepithelial area (small arrowheads) and mesangium (large arrows). Foot processes are extensively fused. ×2700.

of the mesangium and thickening of the capillary walls. Endocapillary or mesangial proliferation, crescentic formation and adhesion of the glomerular tuft to Bowman’s capsule were not observed. Severe tubular atrophy was associated with interstitial fibrosis and lymphocytic infiltrates (Figure 1a). Mild arterio- and arteriolosclerosis were observed, but arteritis was not identified. Immunofluorescence showed coarse granular deposits of immunoglobulin G (IgG; 2+), C1q (1+) and C3 (1+) along the glomerular capillary walls and in the mesangium (Figure 1b). Staining for IgA, IgM and fibrinogen was negative. There was no positive staining for IgG, C1q or C3 on tubular basement membranes. Electron-microscopy revealed both epithelial and mesangial electron-dense deposits, presumably compatible with the immunofluorescence findings. Foot processes were extensively fused (Figure 1c).
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Leucocyte analysis in the interstitium

For leucocyte analysis in the interstitium, a three-layer immunoperoxidase staining was performed on ethanol-fixed and paraffin-embedded tissues as reported previously [9]. The following monoclonal antibodies were purchased from DAKO Japan Co. Ltd (Kyoto, Japan): T3, anti-human CD3 (Pan-T-cell marker); andUCHL1, anti-human CD45RO (activated/memory T-cell marker). Numerous T cells were observed in the interstitium (Figure 2a), and most of these were activated/memory T cells (Figure 2b). However, neither T cells nor activated/memory T cells were observed in glomeruli.

Clinical course after renal biopsy

Although the patient was treated with prednisolone 20 mg/day and dipyridamole 150 mg/day, urinary protein excretion remained at 3–4 g/day. However, urinary protein excretion decreased to 2 g/day about 1 month after the start of treatment with an angiotensin-converting enzyme inhibitor (temocapril 1 mg/day), and the patient was discharged at the end of December 1996. At the outpatient clinic, prednisolone was tapered to 15 mg/day from the beginning of February 1997, and the patient remained symptomless. From the beginning of April 1997, he became aware of pretibial oedema. At that time, laboratory examinations showed total protein 4.4 g/dl, serum albumin 2.1 g/dl, serum creatinine 0.7 mg/dl, blood urea nitrogen 22 mg/dl, CH50 11.0 U/ml, C3 54 mg/dl, C4 5 mg/dl, anti-Ro (SS-A) Ab 16.9, and anti-nuclear Ab 1:80. In May 1997, he was admitted to the hospital again, because general oedema was becoming marked. Urinalysis showed 3+ protein and 1–4 red blood cells/high-powered field without casts. Urinary protein excretion was 8 g/day. Total protein was 3.7 g/dl, serum albumin 1.7 g/dl, serum creatinine 0.8 mg/dl and creatinine clearance 88 ml/min. Just after the second admission, prednisolone was increased to 40 mg/day and followed by methylprednisolone pulse therapy (1 g/day × 3 days). Although the patient was treated with 40 mg/day prednisolone for a month, heavy proteinuria of >6 g/day continued. CyA 2.5 mg/kg/day, which is a relatively low dose, was started beginning at the end of June. The trough level of CyA was maintained at 40 to 60 ng/ml. At the beginning of August 1997, proteinuria was reduced to 1–2 g/day, at which time CH50 was 38.1 U/ml, C3 116 mg/dl, C4 25 mg/dl, anti-Ro (SS-A) Ab (−) and anti-nuclear Ab (−). At the end of August 1997, the patient was discharged. He is currently being treated with CyA 2.0 mg/kg/day and is symptomless with no oedema at our outpatient clinic, where urinalysis shows (2+) protein and 1 red blood cell/high-powered field without casts, and total protein is 6.3 g/dl, serum albumin 3.7 g/dl, serum creatinine 0.8 mg/dl, Ccr 98 ml/min and urine β2-microglobulin concentration 61 μg/l. All immunological parameters are within the normal range.

Discussion

In this case, hypocomplementaemia with anti-nuclear Ab and renal histology showing both epimembranous and mesangial electron-dense deposits accompanied by coarse granular staining of IgG and C1q on glomerular capillary walls and in the mesangium were suggestive of lupus nephritis. However, this case did not satisfy the American Rheumatism Association (ARA) criteria for SLE despite being positive for anti-nuclear Ab and showing renal disorders. Sjögren’s syndrome was also considered as a diagnosis, since the present case had anti-Ro (SS-A) Ab, which occurs in 30–90% of patients with Sjögren’s syndrome [10,11], and showed severe tubulointerstitial injuries with interstitial infiltration of lymphocytes [12–14]. However, clinical examination did not reveal dry eyes, dry mouth or parotid gland enlargement, and was inconsistent with that in Sjögren’s syndrome. Moreover, the results of the Schirmer and rose bengal tests, parotidography and minor salivary gland biopsy, which are diagnostic clues for Sjögren’s syndrome were all negative.

Another possible diagnosis was hypocomplementaemic urticarial vasculitis syndrome. HUVS is an...
uncommon disorder that resembles SLE. The basic diagnostic criteria of HUVS established by Schwartz are recurrent urticaria and hypocomplementaemia. In addition, at least two of the following criteria should be present: vasculitis of the dermis on biopsy, arthralgia or arthritis, uveitis or episcleritis, recurrent abdominal pain, glomerulonephritis, and a depletion of C1q and a positive C1q precipitin test [1]. Other diseases must be excluded. HUVS has been reported to be occasionally accompanied by anti-Ro (SS-A) and anti-nuclear Ab [2,3]. According to Schwartz’s criteria, the patient has two basic criteria plus glomerulonephritis as a minor criterion. Unfortunately, neither a skin biopsy nor an anti-C1q precipitin test were performed. However, when we examined the C1q level after CyA treatment, it was still low (7.9 mg/dl; normal, 8.8–13.5 mg/dl), even though CH50, C3 and C4 had already normalized. In addition, the morphological features of this case were similar to those described by others; mesangiproliferative or membranoproliferative glomerulonephritis, immunohistologically demonstrated granular deposits of IgG and complements, and electron-dense deposits in the mesangium and subepithelial regions [2–8]. Leucocytic infiltration in the interstitium has also been found in several cases [5,6,8], similar to the present case. Taken together, we diagnosed the present case as HUVS.

HUVS is defined as a syndrome which shows the clinical manifestations mentioned above. However, it has been reported that HUVS does not appear to be a distinct clinical entity but rather a syndrome that can occur in a spectrum of diseases ranging from SLE to HUVS [6], since HUVS is similar to SLE with regard to its immunological features and histological findings of the kidney, as in the present case. Clinical examination of the present case did not show arthralgia or arthritis, which is commonly observed in HUVS [2]. Also other clinical manifestations such as uveitis or episcleritis and recurrent abdominal pain, which are suggestive of vasculitis, were not observed. Accordingly, the present case may be atypical as HUVS and may be considered a disorder within a spectrum of diseases ranging from SLE to HUVS. In addition, Simmons-O’Brien et al. [15] reported, in a follow-up study of anti-Ro (SS-A)-positive patients, that 65% had a chronic progressive disease process and that at least 25% demonstrated a dynamic change in clinical presentation with the development of Sjögren’s syndrome and/or a progressive rheumatoid-like arthritis. Clinically, this case showed steroid-resistant nephrotic syndrome, which improved with CyA. CyA has been used to treat several glomerular diseases that are associated with nephrotic syndrome [16]. Although its primary action is to suppress the activation of T cells [17], it contributes haemodynamically to the contraction of afferent arterioles, resulting in a decrease in the glomerular filtration rate [18]. These immunological and haemodynamical actions are considered to lead to a decrease in proteinuria [19]. Interestingly, in this case, most of the infiltrating lymphocytes in the interstitium were positive for CD45RO, which is a marker of activated/memory T cells [20]. Therefore, the severity of tubulointerstitial injuries may be decreased by treatment with CyA, since the urine β2-microglobulin concentration was normalized after CyA therapy. It is possible that the decrease in proteinuria in this patient reflects not only a decrease in glomerular filtration, but also an improvement of tubular reabsorption of protein. Tubulointerstitial lesions were reported as side-effects of CyA treatment [21], and to our knowledge, there has been no report of CyA treatment for tubulointerstitial nephritis. Nevertheless CyA is known to be effective against interstitial pneumonitis associated with rheumatoid arthritis or dermatomyositis [22,23]. Therefore, CyA therapy could be useful for treating tubulointerstitial nephritis showing a marked infiltration of activated T cells.

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