Mod Rheumatol (2004) 14:236–240
DOI 10.1007/s10165-004-0298-1

CASE REPORT

Hiro Kuroda · Keita Ishii · Yuji Negoro
Hiroko Sugiyama · Junko Inoue · Chiga Ogurusu
Takeshi Kikuchi · Keisei Shimoe · Katsutoshi Sunami

A case of mixed connective tissue disease presenting with nephrotic syndrome

Received: April 23, 2003 / Accepted: February 3, 2004

Abstract A 70-year-old woman was admitted to our hospital for the treatment of diffuse scleroderma and marked edema in the lower extremities. Renal biopsy revealed membranous change, interstitial nephritis, and intimal hyperplasia of the small arteries. The patient was diagnosed as having mixed connective tissue disease (MCTD) presenting with nephrotic syndrome (NS). She responded well to a combination treatment consisting of methylprednisolone (m-PSL) pulse therapy, oral PSL, and cyclosporine A (CsA). We speculated on the actual pathogenesis of NS in this case of MCTD.

Key words Corticosterioid · Cyclosporine A (CsA) · Mixed connective tissue disease (MCTD) · Nephrotic syndrome (NS)

Introduction

Mixed connective tissue disease (MCTD) is often complicated with various organ involvements. Membranous nephropathy (MN) is the commonest cause of nephrotic syndrome (NS), and has a well-defined histological image. Few cases of MCTD presenting with NS have been reported, and the etiology of NS has not been confirmed except for drug-induced NS. A rare case of MCTD with NS was admitted to our hospital. Renal biopsy revealed histopathological findings of membranous change, interstitial nephritis, and intimal hyperplasia of the small arteries. We treated this case successfully with a combination of methylprednisolone (m-PSL) pulse therapy, oral PSL, and cyclosporine A (CsA).

H. Kuroda (✉) · K. Ishii · Y. Negoro · H. Sugiyama · J. Inoue · C. Ogurusu · T. Kikuchi
Department of Internal Medicine, Chugoku Central Hospital of the Mutual Aid Association of Public School Teachers, 6-3-1 Nishifukatsu-cho, Fukuyama 721-8581, Japan
Tel. +81-84-923-5585; Fax +81-84-925-8738
e-mail: h-kuroda@fukuyama.hiroshima.med.or.jp

K. Shimoe
Department of Dermatology, Chugoku Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuyama, Japan

K. Sunami
Department of Orthopedic Surgery, Chugoku Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuyama, Japan

Case report

A 70-year-old woman developed Raynaud's phenomenon and sclerodactyly in 1995 and received treatment for the diagnosis of systemic sclerosis (SSc) for 2 years. Knee joint pain and hypertension appeared in January 2002, and pretibial edema in mid-May. She was admitted to our hospital on June 21. Physical findings on admission were as follows: height 149 cm, body weight 43 kg, and body temperature 36.8°C. Her blood pressure was 156/76 mmHg and her pulse was 76/min. Marked edema of the lower extremities and systemic sclerosis (upper and lower extremities, face, chest, and abdomen) were observed. A chest examination showed bilateral fine crackle and systolic heart murmur; an abdominal examination showed slight ascites and no hepatosplenomegaly. Laboratory data on admission were as follows (Table 1): C-reactive protein (CRP) 0.3 mg/dl; elevated erythrocyte sedimentation rate (ESR) (150 mm/h); high titer for ferritin (915 ng/ml); hypoalbuminemia (1.4 g/dl); hypergammaglobulinemia (1.68 g/dl). Blood urea nitrogen (BUN) (34 mg/dl) and creatinin (1.6 mg/dl) were slightly increased, and creatinine clearance (Ccr) was decreased to 17.5 ml/min. The patient tested positive for antinuclear antibody (ANA) (×1280, speckled), anti-ribonucleoprotein (RNP) Ab (171), anti-Sm Ab (16), and RF (113 IU/ml), and negative for anti-Scl-70 Ab, anti-centromere Ab, anti-Jo-1 Ab, anti-dsDNA-IgG Ab, anti-SSA Ab, anti-SSB Ab, PR-3 antineutrophil cytoplasmic antiboby (ANCA), and MPO-ANCA. Serological markers for hepatitis viruses such as antihepatitis A IgM antibodies, hepatitis B surface antigen (HBs Ag), and antihepatitis C virus antibodies (anti-HCV Ab) were all negative. The

Table 1. Laboratory findings on admission

RBC	364 × 10^4/μl	Ferritin	915 ng/ml
Hb	10.6 g/dl	IgG	1517 mg/dl
Ht	31%	IgA	478 mg/dl
PLT	34.6 × 10^4/μl	IgM	125 mg/dl
WBC	3400/μl	CH_{50}	43.6 U/ml
TP 5.0 g/dl, Alb 1.4 g/dl		Anti-dsDNA-IgG Ab	1.7 IU/ml
Alb 25.5, α1-gl 3.5, α2-gl 26.1,		RF	113 IU/ml
β-gl 11.3, γ-gl 33.6 (%)		ANA	×1280 (speckled)
T-chol	365 mg/dl	Anti-RNP Ab	171
BUN	34.0 mg/dl	Anti-Sm Ab	16
Cr	1.6 mg/dl	Anti-Scl-70 Ab	(−)
Ccr	17.5 ml/min	Anti-centromere Ab	(−)
Na	130 mEq/l	Anti-Jo-1 Ab	(−)
K	5.2 mEq/l	Anti-SSA Ab	(−)
Cl	104 mEq/l	Anti-SSB Ab	(−)
ESR	150 mm/h	PR3-ANCA	(−)
CRP	0.3 mg/dl	MPO-ANCA	(−)

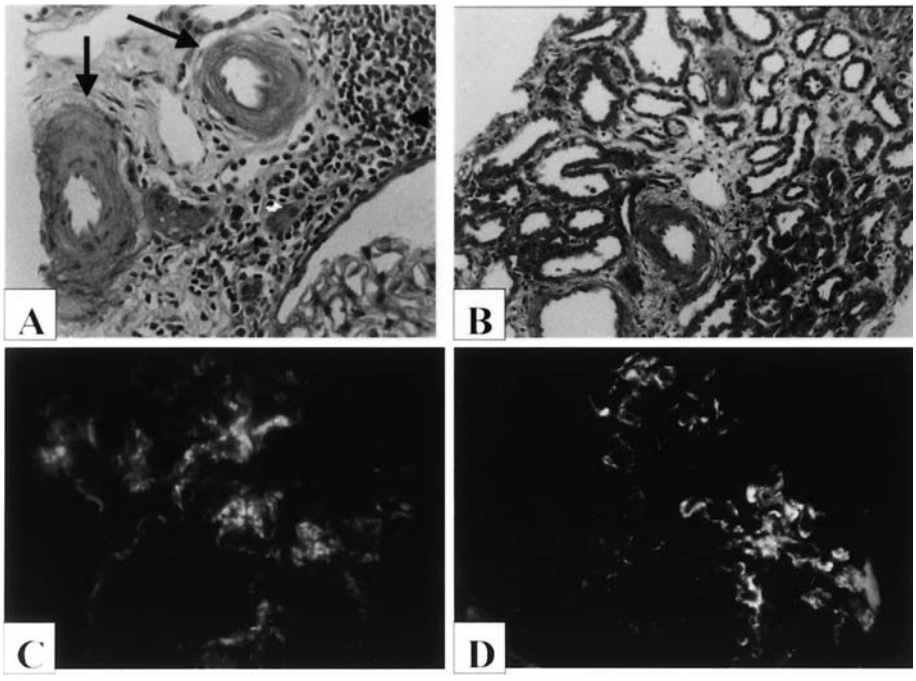


Fig. 1. Renal biopsy findings in the patient with MCTD. **A** Intimal thickening of small arteries (*arrows*) and severe interstitial mononuclear cell infiltration (*arrowhead*). (PAS, ×200). **B** Diffuse tubular atrophy was seen. (Masson, ×100). **C**,**D** Immunofluorescent studies of the glomerulus showing granular deposits of IgG (**C**) and C3 (**D**). ×400

plasma level of renin activity was normal (4.1 ng/ml/h). Urine protein was positive (3+) and sediment showed epithelial (10–19/wf) and granular (5–9/wf) casts. Arterial blood gas analysis in room air was normal (PH 7.37, PCO_2 33 mmHg, PO_2 86 mmHg). Chest radiographs showed cardiac enlargement and slight pleural effusion. Pulmonary function tests detected a decrease of 43% in %VC, while FEV 1.0% was a normal of 79%. Computed tomography (CT) of the chest and abdomen showed mild dorsal lower interstitial pneumonia (IP), mild upper lobe emphysema, slight pleural effusion, and mild ascites. An echocardiogram revealed mild hypertrophic heart disease (HHD) and mild pulmonary hypertension (PHT). A chest examination, abdominal CT, and tumor markers ruled out malignancies.

Histopathological findings of a renal biopsy that was performed soon after admission are described below (Fig. 1). Light microscopy revealed that ten glomeruli were available for analysis, while two had collapsed due to ischemia. Mesangial cell proliferation was low, with no thickening of the glomerular basement membrane (GBM). A PAM stain did not reveal any thickening of the GBM and clear spike formation. Tubulointerstitium showed diffuse cell infiltration, which was especially prominent around the small arteries, diffuse tubular atrophy, and intimal thickening of the small arteries with severe mononuclear cell infiltration. Diffuse tubular change was the most outstanding with these renal changes in the chronic active phase. Moderate staining for IgG and C3 showed a mild granular pattern, but no staining for C1q by immunofluorescence microscopy. Electron microscopy revealed irregular dense deposits in the subepithelium of the GBM, a slightly swollen endothelium, but no dense deposits in either the subendothelium or the mesangium (Fig. 2). These data suggested that NS was

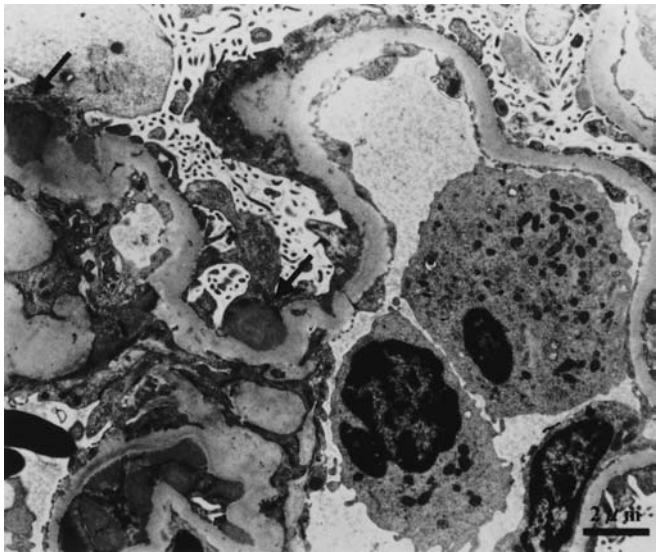
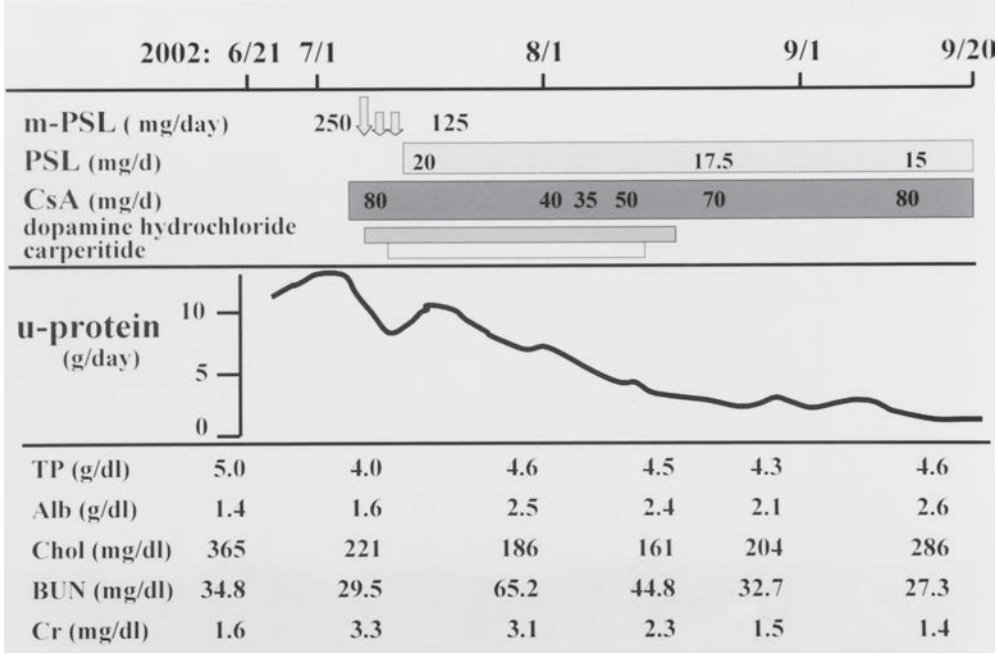


Fig. 2. Electron microscopic finding. Subepithelial electron-dense depositions can be seen (*arrows*), but no electron-dense deposit in either the subendothelium or the mesangium

caused by membranous change mainly due to the systemic lupus erythematosus (SLE) component, and the changes in the small arteries were due to the SSc component, which had not induced scleroderma renal crisis in this case. In general, tubulointerstitial changes seemed to be much more severe than those of the glomeruli.

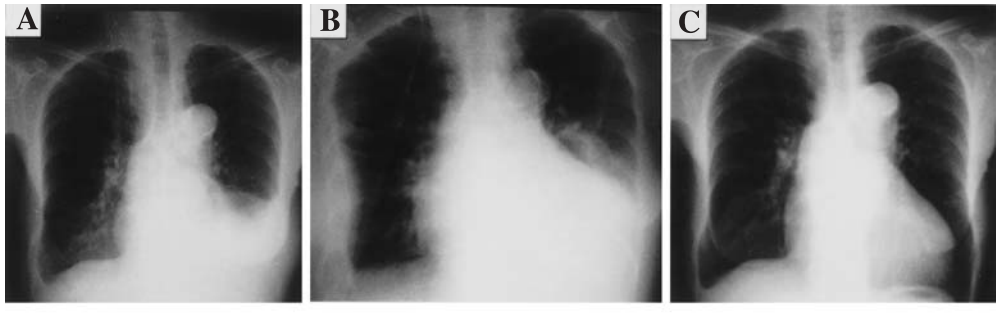
Following a definite diagnosis of NS, a combination treatment was initiated consisting of m-PSL pulse therapy 250 mg/day for a day and 125 mg /day for 2 days followed by 20 mg/day of oral PSL, and 80 mg/day of oral CsA (Fig. 3). The patient responded well to the treatment, and her daily total proteinuria decreased gradually. During the clinical course, her heart and renal failure deteriorated and pleural effusion increased markedly (Fig. 4). However, continuous intravenous infusion of dopamine hydrochloride and carperitide was effective in improving her clinical condition. The patient was discharged after 3 months of hospitalization.

Fig. 3. The clinical course of the patient with MCTD presenting with NS. The combination treatment of m-PSL pulse therapy, oral PSL, and CsA was effective for this patient



TP (g/dl)	5.0	4.0	4.6	4.5	4.3	4.6
Alb (g/dl)	1.4	1.6	2.5	2.4	2.1	2.6
Chol (mg/dl)	365	221	186	161	204	286
BUN (mg/dl)	34.8	29.5	65.2	44.8	32.7	27.3
Cr (mg/dl)	1.6	3.3	3.1	2.3	1.5	1.4

Fig. 4. Changes in chest radiographs in the clinical course. **A** Pleural effusion increased on July 1, 2002. **B** Cardiac failure was worst on July 19, 2002. **C** Cardiac failure almost recovered on September 17, 2002



Discussion

MCTD was described in 1972 by Sharp et al.[1] as a syndrome of overlapping features of systemic lupus erythematosus (SLE), SSc, and polymyositis. MCTD is usually not associated with major organ involvement and has a good prognosis. In the early stage, MCTD appears to be highly responsive to corticosteroids. When severe pulmonary or renal complications occur, high doses of corticosteroid or a combination of corticosteroid and immunosuppressant are usually required.[2] Renal involvement in MCTD has been reported to be rare by some authors. However, recently the ratio of renal involvement in patients with MCTD has been reported to be between 10% and 50%.[3–5] The renal changes usually take the form of membranous glomerulonephritis. In a series in which 40% of the patients with MCTD showed renal involvement, NS occurred in 75% of patients with renal involvement, mainly in association with membranous nephropathy.[4]

In this study, we investigated the actual cause of NS based on renal biopsy specimens, and speculated on the extension of histological changes due to several components in MCTD. The patient had already been diagnosed with SSc in 1995. She had not received any drug treatment, such as D-penicillamine or antihypertensive drugs, that could have resulted in this syndrome. On admission, she presented with a manifestation of diffuse scleroderma. At first, we also diagnosed SSc. On the other hand, the possibility of a MCTD overlap in cases reported to be complicated with NS, which are very rare,[6,7] could have been more likely because of the high anti-RNP Ab titer, Raynaud's phenomenon, arthritis, leukopenia, scleroderma, and pulmonary fibrosis. Finally, we diagnosed this patient as having MCTD rather than SSc. A definite diagnosis of NS was reached based on the clinical features and laboratory data. Immunofluorescence and electron microscopic examination revealed that the pathogenesis of NS was due to membranous change which was believed to be in the early stages and showed unusually small amounts of irregular dense deposits in the subepithelium of the GBM in electron microscopy, rather than diffuse dense deposits that are usually observed in membranous nephropathy. This finding was outstanding in one case of MCTD and was assumed to be mainly due to the SLE component.[5,6] The most characteristic lesions of SSc involve the interlobular arteries and consist of concentric internal thickening with hyperplastic intimal cells in a loose mucoid ground substance.[8–10] The lesions in interlobular arteries in this case were not as severe as those of typical SSc. Renal immunofluorescence findings of SSc are not uniform; fibrinogen and IgM have been demonstrated in the vascular lesions[11] and complement has been noted less frequently.[12] Electron microscopic examination has revealed subendothelial granular deposits and mild thickening of the GBM in SSc.[13,14]

The pathogenesis of membranous change in this case could be assumed to be either an incidental development of membranous change during the course of MCTD, or alternatively a manifestation of membranous change due to the SLE component. Glomerular ischemia itself may produce podocyte changes and increase the permeability of the GBM to protein, which eventually produces massive proteinuria. Clinically, there was a possibility of SLE overlapping because of the presence of four indications of proteinuria (over 0.5 g/day), leukopenia, and positive ANA and anti-Sm Ab (low titer) according to the revised criteria for the clinical diagnosis of SLE. Nevertheless, there was a very mild overlap of lupus nephritis because of low mesangial cell proliferation, negative immunofluorescence staining of C1q, and no electron-dense deposits in either the subendothelium of the GBM or the mesangium. Recent studies have suggested a direct participation of antiribosomal P antibody in the pathogenesis of lupus nephritis.[15,16] Hirohata et al.[17] reported a case of SSc presenting with NS who tested positive for antiribosomal P antibody, which might have been involved in the development of NS. In this case, no such antibody was detected. Malignancies, hepatitis virus infections, and drugs associated with membranous nephropathy were all ruled out based on the clinical history and examination results.

In summary, this case could be diagnosed as MCTD from clinical features and histopathological findings consisting both of SSc and SLE components. Furthermore, the pathogenesis of NS was attributed to the membranous change mainly due to the SLE component.

References

1. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease: an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med 1972;52:148–59.
2. Prakash MD, Luthra HS, Divertie MB. Intrathoracic manifestations in MCTD. Mayo Clin Proc 1985;60:813–21.
3. Bennett RM, Spargo BH. Immune complex nephropathy in mixed connective tissue disease. Am J Med 1977;63:534–41.
4. Kitridou RC, Akmal M, Turkel SB, Ehresmann GR, Quismorio FP, Massry SG. Renal involvement in MCTD: a longitudinal clinicopathologic study. Semin Arthritis Rheum 1986;16:135–45.
5. Kobayashi S, Nagase M, Kimura M, Ohyama K, Ikeya M, Honda N. Renal involvement in mixed connective tissue disease. Am J Nephrol 1985;5:282–9.
6. Horita Y, Tsunoda S, Inenaga T, Kawano Y, Ishibashi-Ueda H, Chiba Y, et al. Pregnancy outcome in nephrotic syndrome with mixed connective tissue disease. Nephron 2001;89:354–6.
7. Kessler E, Halpern M, Chagnac A, Zevin D, Hammel I, Ben Bassat M. Unusual renal deposit in mixed connective tissue diseases. Arch Pathol Lab Med 1992;116:261–4.
8. Fisher ER, Rodman GP. Pathologic observations concerning the kidney in progressive systemic sclerosis. Arch Pathol 1958;65:29–39.
9. Dichosa CC. The kidney in progressive systemic sclerosis. In: Eknoyan S, editor. The kidney in systemic disease. New York: Wiley; 1976. p. 62.
10. Jenis EH, Lowenthal DT. Kidney biopsy interpretation. Philadelphia: Davis; 1977. p. 206.
11. Fennell RH, Reddy CRRM, Vasquen JJ. Progressive systemic sclerosis and malignant hypertension: immunohistochemical study of renal lesions. Arch Pathol 1961;72:209–15.
12. McGiven AR, Deboer WGRM, Barnett AJ. Renal immune deposits in scleroderma. Pathology 1971;3:145–50.
13. Pardo V, Fisher ER, Perez SE, Rodnan GP. Ultrastructural studies in hypertension: . Renal vascular changes in progressive systemic sclerosis. Lab Invest 1976;15:1434–41.

14. Vidt DG, Robertson AL, Deohar SD. Renal changes in progressive systemic sclerosis: report of five cases. Cleve Clin Q 1971;38: 141–52.
15. Chindalore V, Neas B, Reichlin M. The association between anti-ribosomal P antibodies and active nephritis in systemic lupus erythematosus. Clin Immunol Immunopathol 1998;87:292–6.
16. Reichlin M, Wolfson-Reichlin M. Evidence for the participation of anti-ribosomal P antibodies in lupus nephritis. Arthritis Rheum 1999;42:2728–9.
17. Hirohata, S, Ohse T, Takeuchi A, Hashimoto T. Systemic sclerosis complicated with nephrotic syndrome: relevance with antiribosomal P antibody. Rheumatol Int 2001;21:40–3.