Primary Sjögren's syndrome with minimal change disease: case series and literature review

Sirs,

Primary Sjögren's syndrome (pSS) is a multi-organ involved autoimmune disease, of which glomerular involvement is always underestimated because tubulointerstitial nephritis (pSS-TIN) and renal tubular acidosis nearly account for 50-70% of renal involvement of pSS (1, 2). Glomerular injuries of pSS include membranous nephropathy (pSS-MN), membranoproliferative glomerulonephritis, mesangioproliferative glomerulonephritis, and minimal change disease (pSS-MCD) (1, 2), among which pSS-MCD cases remain rarely reported. Here we report eight cases of pSS-MCD in our hospital and three cases from literature review, forming the largest case series of pSS-MCD so far. We summarised the clinical manifestation and prognosis of pSS-MCD, and explored its pathogenesis.

These eight cases of pSS-MCD (3.28%) were screened out of 244 pSS patients with biopsy-proven renal involvement from 1993 to 2018. The diagnosis of pSS was based on consensus of rheumatologist and American European Consensus Group classification criteria, and the diagnosis of MCD was confirmed by renal biopsy (no glomerular lesions, immunofluorescence negative, and foot process effacement under electron microscope) after ruling out other secondary causes (3). The main clinical features of pSS-MCD patients were summarised in Supplementary Table S1. Seven patients were diagnosed with pSS after the onset of nephrotic syndrome, though all had sicca symptoms (dry mouth and dry eyes) before the onset of oedema. Other suggestive clinical manifestations include arthritis (25%), haemocytopenia (25%), high IgG level (25%), and positive autoantibody results (Antinuclear antibody 75%, anti-Ro antibody 100%, anti-La antibody 25%). EULAR Sjögren's Syndrome Disease Activity Index among these patients were relatively low, ranging from 4 to 8 score (47 in total). Clinical characteristics related to nephrotic syndrome (NS) included oedema (100%), proteinuria (11.51± 6.76 g/24h), hypoalbuminemia (15.29 ±2.56 g/L), microscopic haematuria (87.5%), as well as hyperlipidaemia (87.5%). Acute kidney injury (AKI) occurred in three patients who had severe proteinuria (19.19±1.60 g/24h), and their glomerular filtration rate (eGFR) ranged from 28 to 48ml/min/1.73m^2.

All patients with pSS-MCD were treated with 1mg/kg/d of glucocorticoids (GCs, equivalent to prednisone), and three of them received immunosuppressive agents including cyclophosphamide, hydroxylchloroquine and *tripterygium wilfordii*. After three months of GCs treatment, five patients achieved complete remission (urinary protein <0.3g/d, normal serum creatinine, and serum albumin >35g/L), and two patients attained partial remission (urinary protein 0.3~3.5g/d, and change in creatinine <25%), (Fig. 1, A-C). Three patients experienced relapses among seven patients still at follow-up (18~99 months). Two out of three patients who experienced AKI had restored eGFR levels after treatment, which agrees with previous study that demonstrated pSS with glomerulonephritis was responsive to treatment (4).

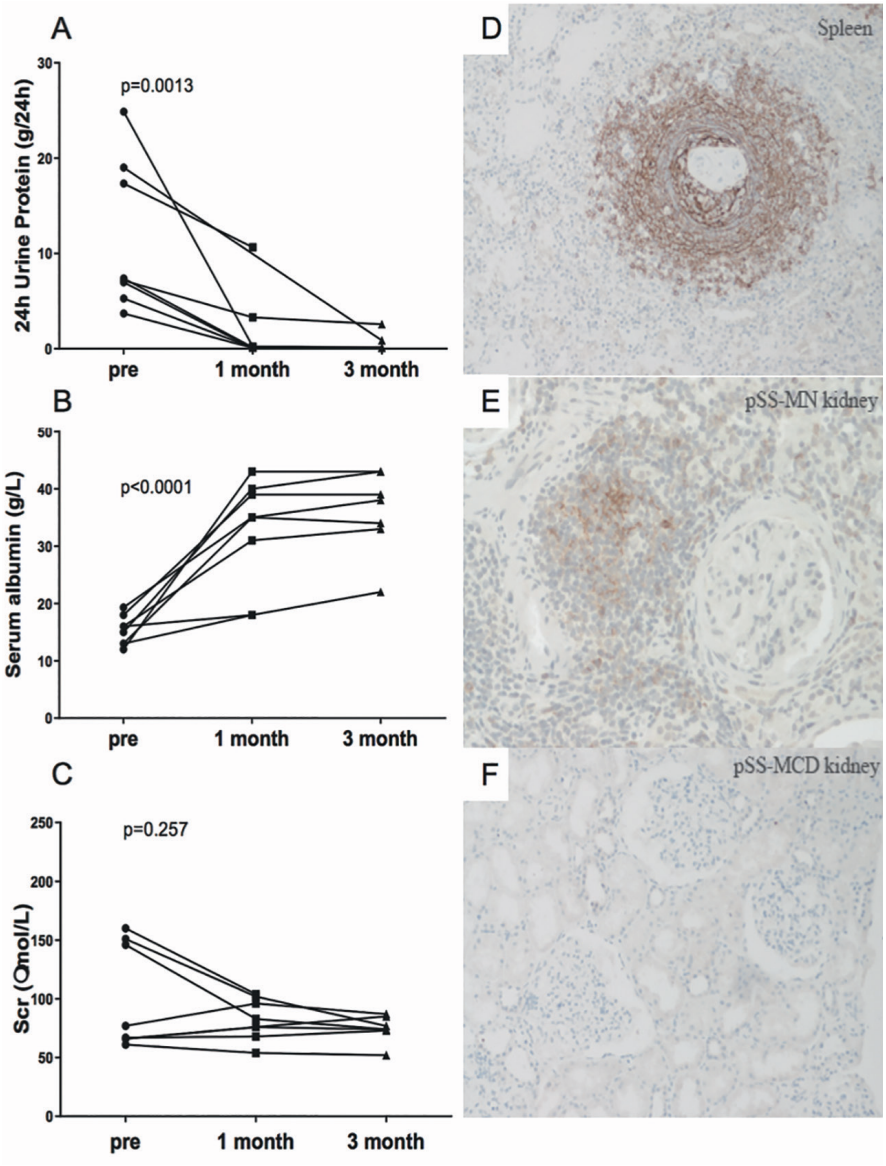

Fig. 1. The corticosteroids treatment response (**A**-**C**) and immunohistochemisty stain of CD21(D-F) in pSS-MCD patients. Treatment response was indicated by the change of 24h urine protein (**A**), serum albumin (**B**) and serum creatine (**C**). Immunohistochemisty stain of CD21 in spleen (**D**. positive control), pSS-MN (**E**) and pSS-MCD (**F**), showed no ectopic germinal centre observed in pSS-MCD patient.
Scr: serum creatine; pSS-MCD: primary Sjögren's syndrome with minimal change disease; pSS-MN: primary Sjögren's syndrome with membranous nephropathy.

Ectopic germinal centre (EGC)-like structure was reported to be associated with multi-organ involvement in pSS (5) and the pathogenesis of kidney involvement in pSS-MN (6) and pSS-TIN (7). We performed immunohistochemical stain of CD21 (a typical marker of EGC) for all eight cases to explore the possible pathogenesis of pSS-MCD. Surprisingly, EGC was not observed in any of cases, although it was positive in pSS-MN cases (Fig. 1, D-F) (6). This result suggested an alternative mechanism might be involved in the pathogenesis of pSS-MCD, different from pSS-MN. Although it remained arguable that MCD in these cases might have been a co-existing condition with pSS, fact that all eight cases showed the same lacking of EGC remains intriguing.

In conclusion, pSS-MCD patients presented with typical sicca symptoms and nephrotic symptoms with good steroid response. The diagnosis of pSS is often absent at the onset of NS, even when sicca symptoms are

evident, which could be attributed to a relatively low pSS activity. However rare, glomerular involvement of pSS should not be underestimated by clinical practitioners, as earlier diagnoses and better care for patients is what we all strive for.

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