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CASE REPORT

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Marked hypocomplementemia and tubulointerstitial nephritis in a male patient with Sjögren's syndrome

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Abstract We report a case of marked hypocomplementemia and tubulointerstitial nephritis associated with Sjögren's syndrome (SS) in a male patient. Renal biopsy revealed tubulointerstitial nephritis but did not identify specific immune deposits of the tubulointerstitium. After steroid therapy, the renal failure and hypocomplementemia diminished. Hypocomplementemia without cryoglobulinemia is not commonly observed in SS patients, and hypocomplementemic tubulointerstitial nephritis was strongly suspected. Hypocomplementemic tubulointerstitial nephritis is rare; only one case has been described in the literature. In our case and the previous case, the patients were elderly men, and they had some similar clinical characteristics. Idiopathic hypocomplementemic tubulointerstitial nephritis resembling our case has been reported. These facts suggest that hypocomplementemic tubulointerstitial nephritis may occur in patients with SS, and such cases may not be as rare as once thought because it might be appropriate to include them in the category of idiopathic cases. Such a syndrome should be included in the differential diagnosis of hypocomplementemia.

Key words Hypergammaglobulinemia · Hypocomplementemia · Male · Sjögren's syndrome (SS) · Tubulointerstitial nephritis (TIN)

Introduction

Sjögren's syndrome (SS) is a chronic inflammatory disorder characterized by lymphocytic infiltration of the lacrimal and salivary glands, resulting in dry eyes and a dry mouth.[1] SS is about 10 times more common in women than in men, with women of middle to old age at peak risk. Renal involvement is a well-recognized extraglandular manifestation of primary SS. The most common histopathological lesion is an interstitial lymphocytic infiltrate with tubular atrophy and fibrosis.[2–4] Lymphocytic infiltration is mainly found in the etiology of tubulointerstitial nephritis (TIN) associated with primary SS,[5,6] and hypocomplementemic TIN is rare. Furthermore, hypocomplementemia without cryoglobulinemia is not commonly observed in SS patients. We herein report a case of marked hypocomplementemia and TIN associated with SS in a man.

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Case report

A 68-year-old man was admitted to our hospital because of renal dysfunction, a positive antinuclear antibody (ANA), and marked hypocomplementemia on January 31, 2001; he had no other symptoms. He had been receiving medication for hypertension and a previous myocardial infarction at another hospital since 1989. Renal dysfunction was indicated by a serum creatinine level of 1.6 mg/dl in 1999, increasing to 2.6 mg/dl in October 2000. A detailed history did not reveal consumption of any potentially nephrotoxic medications.

On admission, physical examination revealed a blood pressure of 128/74 mmHg, pulse of 66 beats/min, temperature of 36.5°C, no peripheral lymph node swelling, and no abnormal findings on the chest and abdomen. His urinary volume was about 2000 ml/day. The laboratory data were as follows: erythrocyte count $355 \times 10^4/\mu l$, hemoglobin 10.7 g/dl, and erythrocyte sedimentation rate 77 mm/h. Urinalysis showed a specific gravity of less than 1.005, pH 6.0, trace protein, and ± blood. The urinary sediment had no specific findings. Urinary protein was 0.3 g/day, β_2-microglobulin was 9999 μg/ml, and *N*-acetyl-β-D-glucosaminidase (NAG) was 2.5 U/l. Creatinine clearance was greatly decreased to 6.3 ml/min. Serum sodium was 138 mEq/l, potassium was 3.8 mEq/l, and chloride was slightly increased to 111 mEq/l. Liver function tests were normal. Serum total protein was 7.8 g/dl, albumin was 3.3 g/dl, and blood urea nitrogen

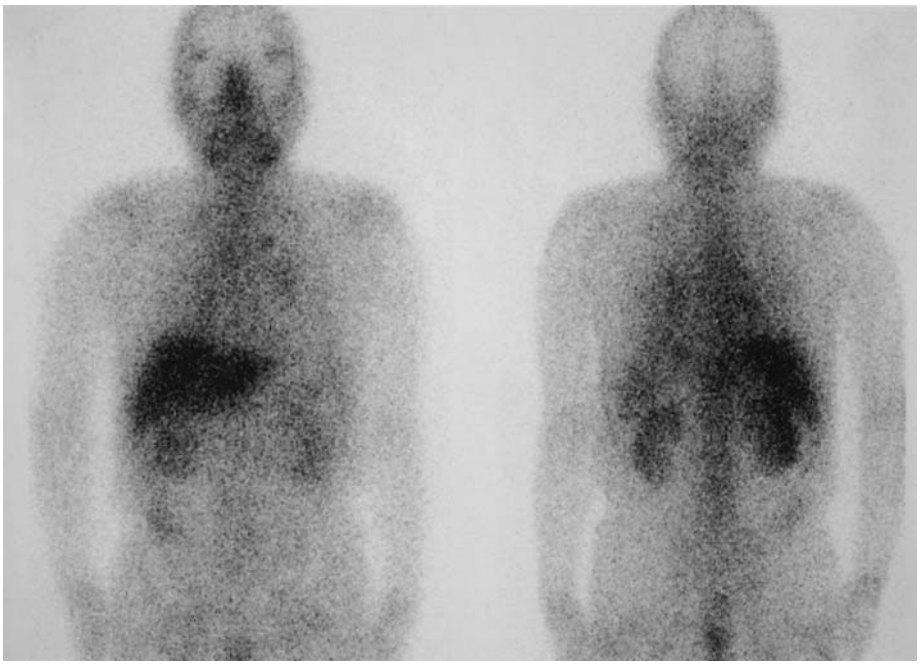

Fig. 1. Gallium scintigram revealed abnormal isotope accumulation in both the kidneys and the salivary glands

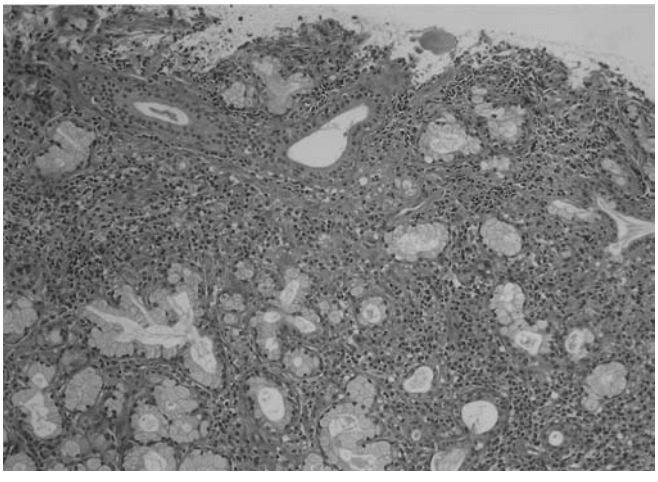

Fig. 2. Biopsy specimen of his lower lip revealed the presence of sialoadenitis with infiltration of numerous inflammatory cells in the periductal area and interstitium of the minor salivary gland, fibrosis of the interstitium, and atrophic changes of the acinar glands. H&E, ×100

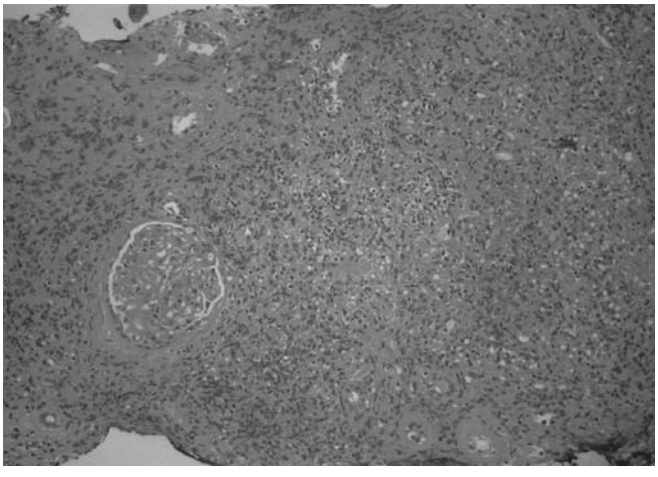

Fig. 3. Renal biopsy revealed intense inflammatory infiltration in the tubulointerstitium. The tubular pattern was distorted by marked tubular loss and atrophy. The glomeruli did not show any changes. H&E, ×100

(BUN) and creatinine were increased to 52.5 mg/dl and 5.62 mg/dl, respectively. Serum β_2-microglobulin was 19.5 mg/dl. Arterial blood gas studies showed obvious metabolic acidosis with a normal anion gap at an oxygen tension of 89.4 mmHg, carbon dioxide tension of 28.1 mmHg, bicarbonate level of 12.6 mmol/l, pH of 7.271, and a base excess of −12.6 mmol/l. Serum C-reactive protein was 0.5 mg/dl, and rheumatoid factor was negative.

IgG was 4090 mg/dl, IgA was 251 mg/dl, and IgM was 44.2 mg/dl. M-protein and cryoglobulin were negative. C3 was 20 mg/dl (normal 60–115 mg/dl), C4 was less than 4 mg/dl (normal 15–50 mg/dl), and CH50 was less than 5 U/ml (normal 25–50 U/ml). Circulating immune complex (CIC) was greatly increased to 33.7 μg/ml (determined by C1q solid-phase radioimmunoassay; normal <3.0 μg/ml). ANA was positive in a titer of 1:1280 with a homogeneous, speckled pattern. Anti-double-stranded (ds)-DNA antibody was slightly increased to 17 IU/ml (normal <10 IU/ml). Other autoantibodies, including anti-SS-A, anti-SS-B, anti-RNP, anti-Sm, and anti-cardiolipin-β2 glycoprotein-1 antibody as well as anti-cardiolipin IgG antibody, lupus anticoagulant, myeloperoxidase anti-neutrophil cytoplasmic antibody, and proteinase-3 anti-neutrophil cytoplasmic antibody, were all negative. Soluble interleukin-2 receptor was increased to 5940 U/ml (normal 145–519 U/ml). Gallium scintigraphy revealed abnormal isotope accumulation in both kidneys and the salivary glands (Fig. 1).

Although he had hypocomplementemia, renal dysfunc-

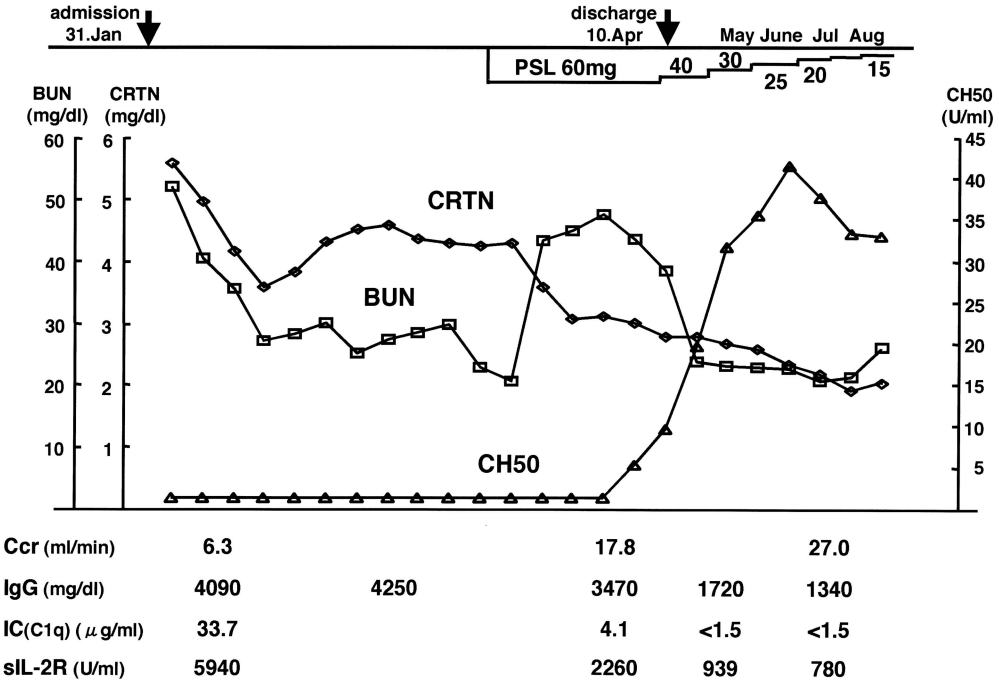

Fig. 4. Clinical course of the patient. *BUN*, blood urea nitrogen; *CCr*, creatinine clearance; *CRTN*, creatinine; *IC(C1q)*, circulating immune complex determined by C1q solid-phase radioimmunoassay; *PSL*, prednisolone; *sIL-2R*, soluble interleukin-2 receptor

tion, a strongly positive ANA, and positivity for anti-ds-DNA antibody, the clinical profile did not meet the criteria of systemic lupus erythematosus (SLE), as classified by the American College of Rheumatology.

The Schirmer test revealed 8/8 mm in 5 min (right/left eye) of wetting; and the salivary secretion test using the chewing gum test revealed 5 ml in 10 min (normal >10 ml). Salivary gland scintigraphy revealed decreased salivary function. A biopsy of his lower lip revealed the presence of sialoadenitis with infiltration of numerous inflammatory cells in the periductal area and interstitium of the minor salivary gland, fibrosis of the interstitium, and atrophic changes of the acinar glands (Fig. 2).

A renal biopsy was performed, and 14 glomeruli were obtained with one sclerotic glomerulus. The interstitium was diffusely infiltrated with numerous inflammatory cells, comprising predominantly lymphocytes and plasma cells. The tubular pattern was distorted by marked tubular loss and atrophy, but the glomeruli did not show any changes (Fig. 3). An immunofluorescence examination showed non-specific depositions of IgG and C3 along the tubular, interstitial, and glomerular areas. There was no monoclonality of the infiltrating cells, and there were no gene rearrangements of the immunoglobulin heavy chain and T-cell receptor of the β chain by a polymerase chain reaction (PCR) method. The histological findings from the renal and minor salivary gland biopsies supported the diagnosis of SS with TIN.

The patient was treated with 60 mg of prednisolone. After starting the treatment, the serum complement and CIC were restored gradually, the serum creatinine level decreased to about 2 mg/dl, and creatinine clearance increased. Since then the patient has been followed, and the prednisolone dose has been gradually reduced without relapse (Fig. 4).

Discussion

Sjögren's syndrome is about 10 times more common in women than in men, with women of middle to old age at peak risk. The clinical characteristics are not well recognized in men. Significant serologic and immunogenetic differences between men and women have been reported.[7] In sharp contrast to women with SS, men with SS were seronegative with respect to the presence of serum rheumatoid factor and anti-SS-A antibody, although men were at the same risk of developing extraglandular complications.

Clinical and, more often, subclinical renal involvement is a well documented extraglandular manifestation of primary SS and often results in TIN. The most common histopathological lesion is interstitial lymphocyte infiltration with tubular atrophy and fibrosis.

TIN has been described in about 30% of primary SS patients.[2,3] In a cohort study of 471 patients with primary SS, Goules et al. reported that 20 patients (4.2%) developed overt renal disease, and TIN was observed in 10 patients (2.0%).[4] These authors stated that the inclusion of subclinical TIN cases in previous studies has certainly been overestimated. They concluded that TIN associated with SS has proved to be a rather benign condition, as none of the patients presented with end-stage renal failure. On the other hand, cases of TIN with renal failure have been reported;[8–11] and although there have been no controlled stud-

Table 1. Characteristics of hypocomplementemic TIN without any significant glomerular involvement in idiopathic or associated primary SS cases

Case	Clinical diagnosis	Age, sex	Renal presentation	Creatinine (mg/dl)	Urine protein (g/day)	Complement (mg/dl, U/dl*)	Immune complex (μg/ml)	IgG (mg/dl)	ANA
Kambham[12]	Idiopathic TIN	82 M	RI	4.0	0.34	C3 47, C4 < 10, CH50 10*	NA	NA	–
		42 M	RI	2.3	0.40	C3 34, C4 < 1	NA	NA	×640 spe
		80 M	RI	5.3	1.05	NA	NA	NA	–
		72 M	RI	5.0	1.35	NA	NA	NA	–
		68 M	RI	2.5	1.90	C3 103, C4 5, CH50 < 10*	(Raji cell assay++)	NA	–
		68 F	NS	1.7	4.78	CH50 11*	NA	NA	–
		62 M	RI	3.2	0.50	C3 33, C4 < 8	NA	NA	×80 homo
		52 M	RI	1.7	–	C3 60,C4 7	NA	NA	×160 spe
Tokumoto[13]	Idiopathic TIN	66 M	RI	3.6	0.90	C3 24, C4 3, CH50 < 4*	C1q 28.2, C3D 14.8	3271	×40 spe
Winer[11]	SS	49 M	RI	4.6	1.40	C3 84 (normal 123–147)	NA	7500	–
Present case (suspicious case)	SS	68 M	RI	5.6	0.30	C3 20, C4 < 4, CH50 < 5*	C1q 33.7, C3D 26.4	4090	×1280 homo, spe

TIN, tubulointerstitial nephritis; SS, Sjögren's syndrome; RI, renal insufficiency; NS, nephrotic syndrome; NA, not available; C1q, C1q solid phase radioimmunoassay; C3D, anti C3D antibody assay; homo, homogeneous pattern; spe, speckled pattern; ANA, antinuclear antibody

ies on renal failure, corticosteroids and cytotoxic drugs are empirically used with frequently favorable outcomes. Moreover, no patients with TIN who presented with renal failure requiring continuous hemodialysis have been reported. Most forms of TIN associated with SS are cell-mediated and lack hypocomplementemia, tubulointerstitial immune deposits, and CIC.[2–4] In fact, hypocomplementemic TIN with tubulointerstitial immune deposits is rare: Only one case has been described in the literature.[11]

In our case, a 68-year-old man presented with renal dysfunction, a positive ANA, hypergammaglobulinemia, and marked hypocomplementemia with no other symptoms. TIN associated with SS was diagnosed. Although we could not make a definite diagnosis of hypocomplementemic TIN because the immunofluorescence examination showed nonspecific immune deposits, the fact that marked hypocomplementemia and high levels of CIC were restored in parallel with renal function by steroid therapy is compatible with the clinical course of hypocomplementemic TIN. Furthermore, hypocomplementemia without cryogulobulinemia in SS is not commonly observed, and only one other case of clinically significant hypocomplementemia has been reported.[11] These facts strongly suggest that the most likely diagnosis in our case is hypocomplementemic TIN associated with SS.

Interestingly, the previously reported case of hypocomplementemic TIN associated with primary SS was an elderly man (Table 1).[11] Our case was also an elderly male patient diagnosed with SS complicated by marked hypocomplementemia and TIN. As in the previous case, he had renal failure, hypergammaglobulinemia, and marked hypocomplementemia. Thus, there are some similar clinical characteristics, although the situation is rare in SS. However, we believe that no disease other than SS involves both the salivary gland and renal tubular interstitium.

On the other hand, Kambham et al. described eight cases of idiopathic hypocomplementemic TIN occurring primarily in elderly men in the absence of SLE or SS.[12] This was a retrospective study in which 5320 native kidney biopsy specimens were reviewed for the presence of predominantly tubulointerstitial immune deposition with minimal or no glomerular involvement; all eight patients studied were hypocomplementemic (Table 1). An elderly male patient similar to these idiopathic cases has also been reported.[13] Our case and the previous case of SS with hypocomplementemic TIN are similar to those idiopathic cases in terms of the renal presentation, laboratory findings, and renal histopathological findings. However, three of the above eight idiopathic TIN cases had ANAs, and information on the anti-SS-A antibody, anti-SS-B antibody, salivary secretion test, Schirmer test, and salivary gland biopsies was not available in the literature. Therefore, SS cases such as ours might be included with the idiopathic hypocomplementemic TIN cases.

The previous findings suggest that hypocomplementemic TIN associated with SS resembles idiopathic TIN in terms of the following clinical characteristics: (1) it occurs primarily in elderly men; (2) it presents with renal failure; (3) the patient is negative for anti-SS-A and anti-SS-B antibodies; (4) hypergammaglobulinemia is present.

The pathogenesis of such cases may differ from that of typical SS. Latent cases may exist because it was clinically asymptomatic in many of these TIN patients. Therefore, it seems important to pay attention to hypocomplementemia and to survey patients for SS aggressively, including a salivary gland biopsy when interstitial nephritis of unknown origin is encountered. These cases of TIN associated with SS might be reversible if properly treated. We expect that such cases will accumulate and enable us eventually to establish a separate disease entity.

Conclusions

Hypocomplementemia is commonly observed in patients with rheumatic diseases, including SLE, rheumatoid arthritis, some types of systemic vasculitis, and cryoglobulinemia, but not ordinary SS.[14] Nevertheless, hypocomplementemic TIN associated with SS should be included in the differential diagnosis of hypocomplementemia.

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