
Clinical manifestations and outcome of ANCA-related pauci-immune glomerulonephritis in patients with Sjögren's syndrome

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ABSTRACT

Objectives. Pauci-immune ANCA-related glomerulonephritis (GN) is extremely uncommon in patients with underlying Sjögren's syndrome (SS) and its clinical and laboratory characteristics have not been previously explored.

Methods. We carried out a thorough literature review in order to establish predisposing factors, clinical and laboratory manifestations, kidney biopsy features, treatment modalities and response to treatment of biopsy proven ANCA-related pauci-immune GN in patients with SS.

Results. From 1967 to 2011, seven patients with a mean age of 63 ± 14.7 years were identified. The average duration of SS prior to development of pauci-immune GN was 50 ± 62 months. A high incidence of extraglandular manifestations was identified: 50% had interstitial lung disease and/or peripheral neuropathy. All patients suffered from proteinuria (average 1397 ± 905 mg per 24 hours) and haematuria at presentation. Almost 70% of patients suffered from severe anaemia (average haemoglobin 6.6 ± 1.9 gr%). ANCA MPO was positive in all six patients, while ANCA PR3 was negative in all. All patients received corticosteroids and 70% received cyclophosphamide. One patient died and one patient developed end stage kidney disease. The rest of the study patients had improved renal function over time.

Conclusions. Our study emphasises that patients with SS can present with atypical kidney pathology as ANCA-related GN. Thus, high clinical awareness is warranted to establish correct diagnoses. Given the powerful impact of kidney pathology on management of these patients and responsiveness to treatment demonstrated in our case series, the significance of timely diagnosis can not be overestimated.

Introduction

Sjögren's syndrome (SS) is an autoimmune disease characterised by lymphocytic infiltration of salivary, parotid, and lacrimal glands (1, 2). In addition to the exocrine glands, many other organs can be involved including skin, lungs, heart, gastrointestinal tract, kidneys, peripheral nervous system and others. The most commonly reported renal diseases in SS are an acute or chronic tubulointerstitial nephritis, defect in distal acidification (distal RTA) and nephrogenic diabetes insipidus (3, 4).

Glomerular involvement is uncommon in SS and when it occurs it is often associated with mixed cryoglobulinaemia and proliferative glomerulonephritis on kidney biopsy (5, 6). In addition, membranoproliferative glomerulonephritis and membranous nephropathy may appear late in the course of Sjögren's syndrome (7, 8). The pathogenesis of glomerular disease, including the possible etiologic relationship to SS, is unclear (7, 8).

Pauci-immune necrotising and crescentic ANCA-related glomerulonephritis (GN) is extremely uncommon in patients with underlying SS and the incidence, predisposing factors, clinical and laboratory characteristics of this disorder in patients with SS have not been previously explored. Therefore, this condition is difficult to recognise and can be overlooked or mistaken for more common renal manifestations in SS. The prognosis and therapeutic approach to ANCA-related GN in chronic SS is largely unknown, but currently available data support the possibilities of a favourable outcome in cases of timely and correct diagnosis.

We report a patient who developed progressive kidney injury due to biopsy proven pauci-immune necrotising crescentic ANCA-related GN in the setting of SS. This patient was initially thought

Competing interests: none declared.

to have kidney disease related to her underlying SS. We performed a thorough literature review in order to establish predisposing factors, clinical and laboratory manifestations, treatment modalities and response to treatment of ANCA-related pauci-immune GN in patients with underlying Sjögren's syndrome.

Case presentation

A 66-year-old woman was referred to our hospital by her family physician because of general weakness, normocytic anaemia and recently diagnosed renal insufficiency. Six years earlier she had developed Raynaud's phenomenon and prominent eye and oral dryness. At that time serology screening revealed rheumatoid factor of 111 U (normal <22 U) and an antinuclear antibody (ANA) titer of >1:400 with negative Anti.dsDNA Ab, Anti SS-A Ab, Anti SS-B Ab, ANCA MPO and PR3. A labial minor salivary gland biopsy revealed infiltration by lymphocytes and destruction of epithelial tissue. In addition, an objective evidence of ocular and salivary gland involvement was demonstrated by thorough ophthalmologic and oral cavity examination: both positive Schirmer's test and decreased unstimulated whole salivary flow have confirmed the diagnosis of primary SS. She was managed by artificial tears, adequate oral hygiene and topical moisturisers. Her medical history was remarkable for chronic hypertension and dyslipidaemia and she was on an oral angiotensin receptor blocker and a statin.

On admission the patient's temperature was normal, pulse regular and blood pressure 180/100 mmHg. The physical examination was normal except of a dry oral mucosa. The haematocrit was 21%, and haemoglobin was 7.5 g/dl (normocytic normochromic). The white cell and platelet count were normal. Erythrocyte sedimentation rate was 136 mm/h. Blood urea was 37 mg/dl, plasma creatinine 2.8 mg/dl (2 months earlier her creatinine had been 0.8 mg/dl). Liver enzymes and thyroxin levels were normal. The urinary sediment showed 5–6 white and 20–30 dysmorphic red blood cells per high-power field without casts. The 24-h protein excretion was 2400 mg. Immunoelectrophoresis of plasma

and urinary proteins was performed in order to exclude multiple myeloma and was normal as well as cranial and whole body x-ray studies. Rheumatoid factor was 125 U and ANA was positive with a titer of >1:400. Additional serological tests revealed ASTO-74 IU/ml, CRP-2.56 mg/dl, negative HBV and HCV Abs, C3-108 mg/dl (normal 86–186 mg/dl), C4-26 mg/dl (normal 16–47 mg/dl), negative Anti.dsDNA Ab, Anti SS-A Ab, Anti SS-B Ab, Anti Sm Ab, Anti RNP Ab, Anti Jo-1 Ab and anti-cardiolipin antibody. However, ANCA test showed perinuclear staining (p-ANCA), and antimyeloperoxidase (MPO) antibodies were detected at titer of >180 U (normal, <20U). Renal biopsy contained 12 glomeruli, 3 sclerosed and 4 containing cellular crescents. Mild interstitial fibrosis was seen. No immune deposits were detected by electron microscopy. A diagnosis of pauci-immune crescentic GN in a patient with a high titer of ANCA MPO and primary SS was made. The patient received three boluses of methylprednisolone (0.5 g daily), followed by oral prednisone (1 mg/kg per day) and oral cyclophosphamide 75 mg/d. Four weeks later her profound weakness and haemoglobin levels dramatically improved and plasma creatinine was 1.6 mg/dl. Eight weeks later her ANCA MPO was 40 U and plasma creatinine 1.3 mg/dl. During the following 2 years the patient has had stable kidney function (creatinine ranged between 1.1–1.3 mg/dl), minimal proteinuria (130–140 mg/24 hours), but continues to have positive ANCA MPO.

Materials and methods

Patient selection

A comprehensive search of the MEDLINE, EMBASE, PubMed and Google scholar from 1967 to 2011 was performed in order to identify patients with the diagnosis of SS associated with ANCA-related pauci-immune GN. Over this 34-year time frame, seven patients, including our case, were identified (9–14).

Clinical diagnosis of SS and ANCA-related pauci-immune GN

All patients were classified as having SS based on ocular and oral symptoms (keratoconjunctivitis sicca and xeros-

tomia), and at least 2 of the following criteria: positive Schirmer test, histopathology of a minor salivary gland biopsy and the presence of autoantibodies to SS-associated antigen A [SSA (Ro)] and B [SSB (La)]. Thus, the primary inclusion criterion for this case series was a consensus diagnosis based on 2002 American-European consensus (AECG) or European classification criteria, or both (15). All patients had primary SS except one patient with an evidence of MCTD and long standing secondary SS. Diagnosis of ANCA-related pauci-immune GN was made on the bases of clinical and histological criteria: acute kidney injury (AKI) with proteinuria and haematuria, biopsy proven pauci-immune crescentic glomerulonephritis and positive serology for ANCA MPO.

After this rigorous review process, 7 patients (including our case) fulfilled the inclusion criteria. One recently reported case of a 71-year-old Japanese woman with SS complicated with pulmonary amyloidosis, mononeuropathy multiplex and leucocytoclastic vasculitis revealed urinary abnormalities including proteinuria and haematuria without casts. Renal biopsy was not performed because the urinary findings were mild, and immediately improved following the initiation of therapy. Therefore, this case was excluded from this analysis (16).

Clinical and laboratory data

The extraglandular manifestations of SS were extensively reviewed. This included all reported data on skin, lung, peripheral neural system, heart and other organ or system involvement and Raynauds phenomenon. Duration of SS prior to development of ANCA-related GN was recorded. The clinical presentation of renal disease was reviewed, including symptomatology, initial presentation, urinalysis and laboratory evidence of renal dysfunction, serology test results including titers of ANCA MPO and PR3 tests. Treatment modalities and response to treatment through follow-up was included, when available.

Kidney biopsy

All patients had biopsy proven pauci-immune crescentic GN. Specific fea-

Table I. Baseline clinical characteristics of the patients with ANCA-related pauci-immune glomerulonephritis and underlying Sjögren's syndrome.

Case, n	1	2	3	4	5	6	7
	Kamachi M <i>et al.</i> , 1999	Hernandez <i>et al.</i> , 1996	Kitaura K <i>et al.</i> , 2006*	Guillot X <i>et al.</i> , 2009	Bottinger EP <i>et al.</i> , 1992	Wang <i>et al.</i> , 2011	Presented case
Age	67	74	42	49	63	86	66
Sex	f	f	f	f	f	m	f
Cause of referral	Epistaxis, increased creatinine	Dyspnea, progressive lung infiltrates	Haemoptysis, dyspnea	Polyarthralgia, xerostomia, xerophthalmia	Severe xerostomia, fever, night sweats, weight loss	Fever, weight loss, kidney injury	Weakness, anaemia and kidney injury
Known duration of Sjögren's disease, months	7	36	168	12	7	Diagnosis at presentation	72
Sicca syndrome (xerophthalmia+xerostomia)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Initial presentation of kidney disease	Proteinuria, AKI	Proteinuria, haematuria, AKI	Proteinuria, haematuria	Mild elevation of creatinine Biopsy proven interstitial nephritis	AKI	Proteinuria, haematuria, AKI	Proteinuria, haematuria, AKI
Raynauds phenomenon	No	Yes	Not reported	No	Not reported	Not reported	Yes
Skin involvement	Livedo Reticularis	Livedo Reticularis	No	Cutaneous vasculitis	No	No	No
Interstitial lung disease	Yes	Yes	Yes	No	No	Not reported	No
Schirmer's test	5 mm at 5 minutes	Positive	Not reported	Positive	Strongly positive	Positive	Not reported
Salivary gland biopsy	Yes	Yes	Not reported	Yes	Yes	Not reported	Yes
Salivary biopsy findings	Lymphocytic infiltration, acinal atrophy	Two foci of more than 50 lymphocytes		Grade 3 sialoadenitis	Irregular lymphocytic infiltration, small artery necrosis		Lymphocytic infiltration, destruction of epithelial tissue
Peripheral neuropathy	Yes	Yes	Not reported	Yes	No	No	No
Systolic blood pressure	160	150	142	130	Not reported	Not reported	180
Diastolic blood pressure	90	100	72	70	Not reported	Not reported	100

Kitaura K *et al.*, 2006* This patient suffered from MCTD and Sjögren's syndrome.

tures of kidney biopsy were recorded: total number of glomeruli and a number of sclerosed glomeruli in specimen, presence and number of crescents or necrosis, presence and severity of interstitial infiltrate or fibrosis, findings on immunofluorescence and electron microscopy, when available.

Results

Clinical features

The baseline characteristics, clinical symptoms of SS, renal presenting features and causes of referral are summarised in Table I. Seven patients at average age of 63±14.7 years were identified, all but one of them were female. The diagnosis of SS was based on keratoconjunctivitis sicca and xerostomia in all patients in addition to strongly positive Schirmer test in four and lymphocytic infiltration on salivary gland

biopsy in five patients. Patient n. 3 had MCTD and secondary SS, all others were diagnosed as primary SS. The average duration of SS prior to development of pauci-immune GN was 50±62 months (range 7–168 months). In patient 6, the diagnoses of both SS and ANCA-related pauci-immune GN was made at the same time. Two patients suffered from Raynaud phenomenon and in another three livedo reticularis or cutaneous vasculitis were reported. A high incidence of extraglandular manifestations was identified: 50% had interstitial lung disease and 50% suffered from peripheral neuropathy (two patients had a combination of both). Variable causes of referral were reported: two patients had dyspnea, two were referred due to kidney failure, two had fever and weight loss and one suffered from polyarthralgia. Patient n. 3 pre-

sented with severe dyspnea, life threatening pulmonary haemorrhage and AKI requiring renal replacement therapy.

The main initial clinical features of renal disease were proteinuria: (average 1397±905 mg per 24 hours, range 430–2400), AKI (average creatinine 3.12±1.5 mg/dl, range 1.2–6 mg/dl) and haematuria. Patient n. 4 had a long standing history of mild chronic kidney disease and kidney biopsy proven chronic interstitial nephritis. Blood pressure was elevated in 60% of patients at presentation (average 152±18 for systolic and 86±14 for diastolic BP).

Laboratory characteristics

Laboratory characteristics of the study patients are summarised in Table II. Almost 70% of patients suffered from severe anaemia with average haemoglo-

Table II. Laboratory characteristics of the patients with ANCA-related pauci-immune glomerulonephritis and underlying Sjögren's syndrome.

Case, n	1	2	3	4	5	6	7
	Kamachi M <i>et al.</i> , 1999	Hernandez <i>et al.</i> , 1996	Kitaura K <i>et al.</i> , 2006	Guillot X <i>et al.</i> , 2009	Bottinger EP <i>et al.</i> , 1992	Wang <i>et al.</i> , 2011	Presented case
Laboratory findings							
Haemoglobin	5.2	8.8	4.9	Reported as Normal	Not reported	Not reported	7.5
BUN mg/dl	33	81	94	8.9 nmol/l	Not reported	Not reported	37
Creatinine mg/dl	2.8	2.6	6	1.2	2.3	4.2	2.8
ANA	1:320, speckled pattern	1:1280, speckled pattern	1:2560, homogeneous pattern	1:800, speckled pattern	Negative	Positive	1:400
RF	Positive	Positive, 50	Not reported	Negative	Negative	Positive	Positive
ANCA MPO, U/ml	Positive, 603	Positive, 59	Positive, 132	Positive, 21	Positive	Positive	Positive, >180
ANCA PR3, U/ml	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Anti SS-A, U/ml	32.5	Positive	500	Negative	Negative	Positive	Negative
Anti SS-B, U/ml		Positive	9.01	Negative	Negative	Positive	Negative
Cryoglobulins	Positive	Positive trace	Not reported	Negative	Not reported	Not reported	Not reported
Immunoelectrophoresis of plasma proteins bands	No monoclonal bands	Not reported	Not reported	No monoclonal bands	Not reported	Not reported	No monoclonal
Proteinuria, mg per24 h	430	1600	Yes	480	2075	Yes	2400
Microhaematuria	Yes	Yes	Yes	Yes	Yes	Yes	Yes
RBC casts	No	No	No	No	Yes	No	No

bin of 6.6±1.9 gr %. Serum creatinine was elevated in all patients (average 3.12±1.5 mg/dl, range 1.2–6 mg/dl). All patients suffered from microhaematuria and proteinuria (average 1397±905 mg per 24 hours, range 430–2400), while RBC casts were detected in one.

Positive serology to ANA was detected in 84% of patients, 55% were positive for SSA, and rheumatoid factor, SSB was positive in 40% of patients. Two of three patients tested for cryoglobulins were positive. Immunoelectrophoresis of plasma proteins did not detect monoclonal bands in all three patients in whom this test was performed. ANCA MPO was reported as positive in all six patients, while ANCA PR3 was negative in all.

Kidney biopsy findings

All reported patients underwent kidney biopsy and had crescentic necrotising glomerulonephritis with negative immunofluorescence (pauci-immune). In four patients, glomerular sclerosis was reported. Mild interstitial nephritis was noted in three patients. Three patients had interstitial fibrosis. Acute interstitial nephritis with active tubulitis was not detected in these patients.

Treatment and follow-up

All patients were initially treated with intravenous methylprednisolone at dose of 125 to 1000 mg/day during three days. This regimen was followed by oral prednisone in five patients at an initial dose of 1 mg/kg per day with a median duration of 2 weeks to 3 months. In the remaining two patients, the detailed data on the oral prednisone regimen were not reported. Two patients (patient n. 1 and n. 3). received plasma exchange, patient n. 1 because of cryoglobulins and patient n. 3 due to severe life threatening disease with pulmonary hemorrhage. Five patients received cyclophosphamide in addition to corticosteroids (patients n. 1, 3, 5, 6, 7) and one patient was treated by mycophenolate mofetil (MMF, 2000mg/d, during 18 months, patient n. 4). The dose of cyclophosphamide was 25mg/d in patient n. 1, 2mg/kg/d in patient n. 5, 75mg/d in patient n. 6. Patient n. 3 had severe disease and received one dose of IV Cyclophosphamide. Cyclophosphamide was discontinued in patient n. 1 due to immunosuppression, but was well tolerated in the others.

The general prognosis of reported patients was favourable. Only one patient (n. 3), who suffered from secondary

SS and MCTD, died during the hospitalisation due to severe pulmonary haemorrhage and AKI requiring renal replacement therapy. Patient n. 6 developed end stage kidney disease despite immunosuppressive therapy. The remaining five patients were followed for 0.5–24 months after biopsy and sustained significant improvement of serum creatinine. ANCA was followed in four of six survivors, in whom the titer decreased in one patient and became negative in the remaining four patients. Other serological and inflammatory markers were followed inconsistently, therefore it is unknown to what degree these markers improved over time. Renal function has not deteriorated in the other patients. Patient n. 2 was treated with steroids alone and had improvement of kidney function (creatinine decreased from 2.6 to 1.6 mg/dl), but the follow-up was short. The remaining four patients received additional immunosuppression along with steroids. MMF therapy was given to a patient n. 4 who had mild renal injury at presentation (creatinine 1.2 mg/dl, proteinuria 480 mg/24 hours) and induces stabilisation of kidney function on follow-up of 18 months. There were no documented

severe adverse reactions (opportunistic infections, lymphoproliferative disorders) attributed to immunosuppressive therapy except patient n. 1 who required discontinuation of cyclophosphamide due to immunosuppression.

Discussion

Our study summarises currently available data related to pauci-immune necrotising crescentic ANCA-related glomerulonephritis in patients with SS. A comprehensive search revealed only six patients over the 34-year time frame (from 1967 to 2011), therefore this condition is extremely rare. Consistent with this observation, a recent study based on a review of kidney biopsy records of twenty-four of 7276 patients with primary SS confirmed that chronic tubulointerstitial nephritis is the predominant finding in patients with renal involvement (17). None of these patients had pauci-immune crescentic glomerulonephritis. Only seven patients illustrated glomerular lesions, with membranoproliferative glomerulonephritis, global glomerulosclerosis, minimal change disease and membranous nephropathy being the major findings.

In our study, the clinical diagnosis of SS was confirmed by either AECG or European classification criteria, or both. In our patient, minor salivary gland biopsy detected significant infiltration by lymphocytes and destruction of epithelial tissue, but the exact Chisholm and Mason scoring was not performed. Although a minor salivary gland biopsy is widely considered as a key tool for the diagnosis of pSS, its reproducibility depends on many factors such as size of the samples, glandular atrophy, number and depths of sections examined, and Chisholm and Mason grading, that allows to stratify the biopsies with absent, slight or moderate infiltration (18, 19). The diagnostic power of minor salivary gland biopsy could be improved significantly by standardised methods of scoring resulting in further improvement in international scientific communication (18, 19).

The AECG criteria currently requires demonstration of focal lymphocytic sialoadenitis with a focus score >1, defined as a number of lymphocytic foci

(which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue (20). This criteria is essential for the diagnosis in patients with absent anti-Ro/SSA and anti-La/SSB, as in our patient. However, European classification criteria does not require minor salivary gland biopsy. Despite the fact that the exact minor salivary gland grading was not available in our patient, and thus the AECG criteria set was not fulfilled, she did fulfilled European classification criteria (20). Recent studies conducted in daily practice confirmed that the Preliminary European classification criteria are less specific but more sensitive than the AECG-criteria. The higher stringency of the AECG-criteria only apparently selected more severe pSS patients while on the other hand, they potentially lead to the exclusion from the diagnosis of pSS of those patients with negative salivary gland biopsy and negative autoantibodies, who have demonstrated nonetheless to have a similar outcome over the follow-up as the AECG patients (21, 22). In addition, it seems that the AECG-criteria did not imply any clear prognostic significance for the patients over the follow-up and did not influence the outcome of patients with primary SS, irrespective of the autoantibody pattern or the labial biopsy positivity. Therefore, currently available data consistently demonstrated the global validity, usefulness and feasibility of both the Preliminary European classification criteria and the AECG-criteria sets.

In our study, the clinical diagnosis of ANCA-related pauci-immune GN was considerably confirmed based on typical clinical, laboratory and kidney biopsy features. The remarkable clinical feature of SS was a high incidence of extraglandular disease: interstitial lung disease (ILD), peripheral neuropathy, cutaneous vasculitis or the combination of these pathologies. However, in primary SS the proportion of patients who develop extraglandular manifestations is substantially lower than in our series. The incidence of ILD varies from 12 to 25%, (23-26) and peripheral neuropathy occurs in approximately 10% of patients (27, 28). Raynaud phenomenon, livedo

reticularis and cutaneous vasculitis were reported in more than 30% of patients in our series, whereas the prevalence is usually lower in primary SS (10% for cutaneous vasculitis, 13-30% for Raynaud's phenomenon) (29, 30).

Two out of three our patients tested positive for cryoglobulins. Interestingly, both cryoglobulinaemia and cutaneous vasculitis in primary SS have been associated with a higher prevalence of extraglandular disease, development of non-Hodgkin lymphoma and life-threatening vasculitic involvement (31-33).

Thus, clinically significant and widespread extraglandular symptoms in our patients is biologically plausible and can serve as a clinical feature that indicates the subgroup of SS patients in which atypical renal involvement may appear. Although the pathogenesis of this phenomenon and the possible etiologic relationship between ANCA-related pauci-immune GN and SS has not yet been elucidated, our finding is of interest and able to have a considerable clinical impact.

Our patients presented with renal disease characterised by significant proteinuria, AKI, prominent anaemia, haematuria and elevated blood pressure. RBS casts were detected only in single patient. These entire features are not typical for chronic tubulointerstitial nephritis. In addition, positive serology for ANCA MPO pointed toward the correct diagnosis. This serological marker, however, can appear in a wide variety of patients with connective tissue disease, including SS, and its influence on clinical patterns of disease expression or specific predilection for renal vasculitis is uncertain.

Immunologically, ANCA is one of the most frequent atypical autoantibodies found in primary SS, with a prevalence ranging between 10 and 20%, whereas only few of these patients develop vasculitis at any body site (34). ANCA positivity in SS led to more extraglandular manifestations in one series (articular involvement in 66% patients, peripheral neuropathy in 55%, Raynaud's phenomenon in 44% and cutaneous vasculitis in 44%), but other study have not found statistical differences in the prevalence of extraglandular manifes-

tations except for Raynaud's phenomenon (28% vs. 7%, $p=0.001$). However, patients with SS and ANCA positivity tend to develop additional systemic autoimmune diseases later in the clinical course of their disease (systemic lupus erythematosus, antiphospholipid syndrome, limited scleroderma, and microscopic polyangiitis) (34-36).

Despite some controversy in terms of clinical significance of ANCA positivity in SS, our study emphasises the importance of high clinical awareness for possible miscellaneous kidney pathology in SS and warrants a more aggressive diagnostic approach to these patients. We believe that patients with widespread extraglandular symptoms, proteinuria, haematuria, impaired renal function and ANCA seropositivity undergo nephrology consultation and kidney biopsy to allow timely diagnosis and appropriate therapy.

Kidney biopsy is rarely performed in patients with Sjögren's syndrome. In a retrospective study assessed 471 patients over a 10-year follow-up, 20 patients (4.2%) were found to have overt renal disease, of which 18 underwent renal biopsy (37). In an additional large series only 0.3% patients with confirmed SS were evaluated by kidney biopsy (17). However, it is unknown how many patients had clinical findings of renal dysfunction and did not undergo kidney biopsy. Thus, at least some patients with renal involvement can go undiagnosed and therefore the true incidence of ANCA-related pauci-immune GN in the setting of primary SS is unknown. In our study, a large variety of pathological findings were detected by kidney biopsy: crescentic necrotising glomerulonephritis was demonstrated along with glomerular sclerosis, interstitial nephritis and interstitial fibrosis. The patients in our series demonstrated responsiveness to treatment and most maintained or improved renal function during follow-up. Only one of the six patients died from severe reno-pulmonary disease despite appropriate therapy with IV cyclophosphamide, plasmapheresis and steroids (11). All patients in this study received therapy with corticosteroids, 70% were treated with cyclophosphamide, MMF was used in

one patient and one patient received corticosteroid monotherapy. Therefore, the therapeutic approach in the setting of SS was similar to that used for ANCA-related GN without underlying SS. We demonstrated a significant improvement in renal function with treatment of any kind, but proteinuria was not consistently followed. We suggest that the therapeutic strategy in the such cases should be guided not only by the kidney biopsy pathology, but clinical evaluation including quantitative and qualitative assessment of proteinuria, kidney function, and urine sediment. These clinical features are particularly useful in the initial diagnosis and follow-up of the disease activity and relapse.

Our patients present a unique clinical situation in which SS is associated with pauci-immune necrotising crescentic ANCA-related glomerulonephritis.

One of the most intriguing and unclear questions is whether this association is co-incidental or is based on the common etiology and pathogenetic mechanisms. Also the precise pathogenesis of both disorders remains unclear, several aspects including genetic, environmental (infection) and immune cellular and humoral factors are involved in both disorders (38). Moreover, potential role of B cells in the pathogenesis of both diseases was revisited recently due to the efficacy of B-cell depletion therapy in both disorders (39-43). In ANCA-associated vasculitis, the number of activated B cells in circulation correlates with disease activity scores and the ability to deplete B cells precisely with anti-CD20 therapies represents new therapeutic insight. Two randomised controlled trials have been published recently and evaluated whether the routine use of cyclophosphamid should remain the induction therapy of choice for most patients with this life threatening disease. Both trials (RAVE and RITUXVAS) showed that rituximab is not inferior to cyclophosphamid for remission induction (39, 40). The rationale for why B cell depletion may be effective in ANCA-associated vasculitis is not clear, but possibilities include the complete removal or substantial reduction of ANCA production; diminution of the contribution of B cells to antigen

presentation and cytokine production; and the inhibition of B cell/T cell cross-talk (38).

In SS, treatments directed against B cells are an active area of study in patients with extraglandular manifestations. In this disorder, excessive of the B cell-activating factor (BAFF) causes B-cell quantitative and qualitative anomalies, making SS a quintessential model of B cell-induced autoimmunity (44). Several case series and a small randomised trial have already illustrated encouraging effect of rituximab as a therapeutic agent in SS (41-44) and in the future, inhibitors of BAFF, such as belimumab, an anti-BAFF antibody may be applied to SS (45-47).

Thus, both SS and ANCA-related vasculitis share common pathogenetic mechanism and therefore, it is logical to speculate that patients who suffer from both disorders may potentially benefit from rituximab as a first line therapy. Until now, based on our study, this therapeutic option had not been used by the treating physicians, including in our case. Although the beneficial effect of B cells depleting agents in such patients sounds reasonable and biologically plausible, more data are needed to determine the optimal management in these intriguing clinical situation.

In summary, our study emphasises that patients with SS can present with atypical kidney pathology as pauci-immune necrotising crescentic ANCA-related GN and high clinical awareness is warranted to establish correct diagnosis. We believe that patients with prominent extraglandular disease should undergo thorough evaluation for possible renal involvement including urinalysis, quantitative proteinuria assessment, serum creatinine, and kidney biopsy if indicated. Despite some controversy in terms of clinical significance of ANCA positivity in SS, it might be associated with more extraglandular manifestations, and possible tendency to develop pauci immune glomerulonephritis. Given the powerful impact of kidney pathology on the management of these patients and responsiveness to treatment demonstrated in our case series, the significance of timely diagnosis can not be overestimated.

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