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*Case Report*

# Non-Randall proliferative glomerulonephritis with humps and monotypic IgG deposits in primary Sjögren's syndrome: a first case report

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**Abstract**

Renal involvement is frequent in patients suffering from primary Sjögren's syndrome (pSS). Tubulointerstitial infiltration is the most common renal lesion, while glomerular involvement is rare. We report the case of a 50-year-old woman with pSS who developed renal failure due to an unusual proliferative glomerulonephritis with humps and monotypic IgG1-kappa deposits. Searches for cryoglobulinaemia, anti-double-stranded DNA and anti-neutrophil cytoplasmic antibodies were negative. Serum protein electrophoresis and immunofixation revealed no monoclonal immunoglobulin. Extensive work-up excluded associated infectious, collagen or lymphoproliferative disease. This case adds to the spectrum of pSS-related glomerular disease which is reviewed in depth.

**Keywords:** crescentic glomerulonephritis; renal involvement; Sjögren's syndrome

## Case report

A 50-year-old woman was referred to our nephrology unit in August 2002 for evaluation of polyarthralgia, fever and glomerular syndrome.

The patient had been suffering from Raynaud's phenomenon for 10 years. Since February 2001, she has experienced asymmetric joint pain and swelling associated with relapsing episodes of fever. She had mild proteinuria (1 g per day, proteinuria over creatinine ratio 885 mg/g), intermittent microscopic haematuria and normal renal function (creatinine 75 μmol/L, normal range ≤120 μmol/L; MDRD 75 mL/min/1.73 $m^2$, normal range ≥90 mL/min/1.73 $m^2$) associated with inflammatory syndrome (C-reactive protein 50 mg/L, normal range ≤10 mg/L). Immunological investigation showed antinuclear antibodies (ANA, 1/640; normal range ≤1/1280), antibodies against SSA (117 U, normal range <20) and SSB (104 U, normal range <40), and positive rheumatoid factor (RF), but searches for cryoglobulinaemia, anti-double-stranded DNA antibodies and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Complement profile was unaltered. No monoclonal component could be detected in blood or urine by immunoelectrophoresis and immunofixation. Renal ultrasonography showed normal kidneys. In December 2001, a first renal biopsy was performed. Light microscopy examination revealed segmental proliferative crescentic glomerulonephritis with mild mesangial proliferation and voluminous hump-like deposits, without double contours or circulating cells in capillary lumens. Segmental crescents were present in 3 of 15 glomeruli with a mixed cellular and fibrous aspect. Tubules, interstitium and vessels were preserved (Figure 1A–C). Immunofluorescence showed IgG and C3 deposits in the humps. Given the normal, stable renal function and the absence of established diagnosis, no treatment was undertaken.

In August 2002, the patient was referred to our nephrology unit to perform a more detailed renal work-up including a second kidney biopsy. Her physical examination was unremarkable. Blood chemistry showed elevated total serum protein (91 g/L, normal range 65–75 g/L) with hypergammaglobulinaemia (31.6 g/L) (consisting mainly of polyclonal IgG1 20.2 g/L, normal range 4–12 g/L). Plasma creatinine had increased to 120 μmol/L (normal range ≤120 μmol/L; MDRD 44 mL/min/1.73 $m^2$, normal range ≥90 mL/min/1.73 $m^2$). Urinalysis showed proteinuria (1.1 g/day, normal range ≤0.3 g/day; proteinuria over creatinine ratio 914 mg/g, normal range ≤300 mg/g) containing 68% of albumin, and there was no glucosuria. The urinary sediment was normal. The immunological tests previously performed were unchanged. In addition, antiphospholipid antibodies were positive (IgG 19 U, normal range <15; IgM 20 U, normal range <15) with presence of lupus anticoagulant, anticardiolipin (IgG 41 U, normal range <15; IgM 32 U, normal range <20) and anti β2-glycoprotein antibodies (27 U, normal range <10) but

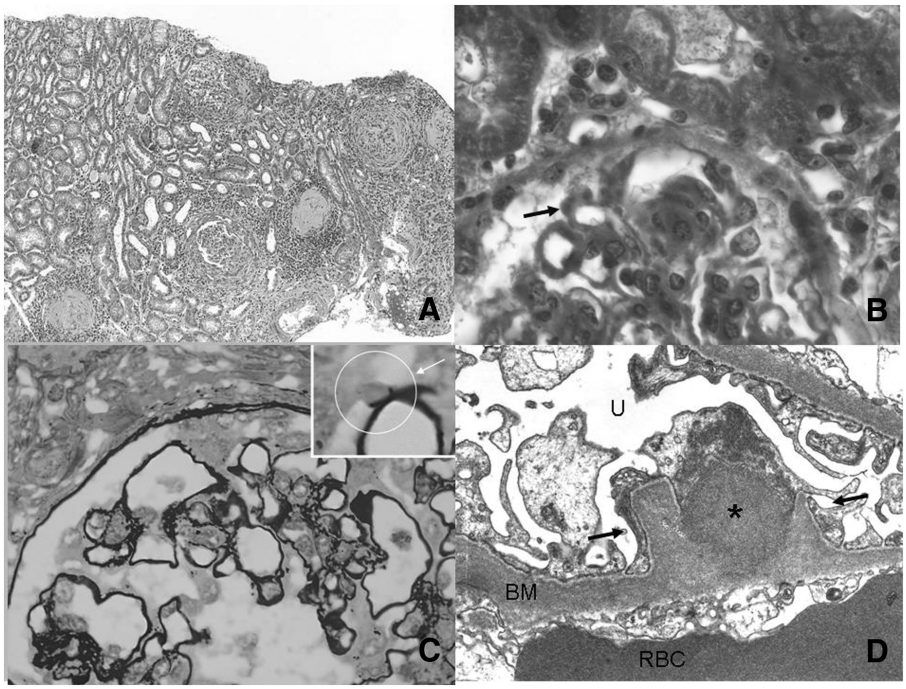


**Fig. 1.** Light and electron microscopy. (**A**) Renal biopsy stained by Masson's trichrome. (**B**) Detail of a glomerulus, showing red humps stained by Masson's trichrome (arrows). (**C**) On this high-power field of a Jones' stain-stained glomerulus, humps are easily demonstrated (arrows). In the inset, they look like pink eggs (immune deposits are eosinophilic) lying on black egg cups (spikes are stained by silver salts). There is a mild mesangial proliferation but no double contours. (**D**) Electron micrograph of two capillary walls, showing one hump (asterisk) flanked by spikes (arrows). The immune deposit is not organized. BM, basement membrane; U, urinary space; RBC, red blood cell.

without clinical manifestations. Antibodies against thyroid peroxidase (163 U, normal range <100) were positive without anti-thyroglobulin antibodies. Thyroid-stimulating hormone was 6.8 mIU/L (normal range 0.3–3.6 mIU/L) with normal thyroxin level consistent with subclinical hypothyroidism. Xerophthalmia was diagnosed by Schirmer's test and xerostomia by salivary gland scintigraphy, and a biopsy of minor salivary glands revealed diffuse lymphocytic infiltration around glandular tissue (grade 4 in the Chisholm scale). A second biopsy was performed with electron microscopy and Ig subclass analysis. Light microscopic was not available. Immunofluorescence showed abundant subepithelial and mesangial deposits staining brightly for IgG1, C3 and kappa light chain (Figure 2). Staining for heavy chains gamma 2, 3, and 4 and for lambda light chains was negative. Electron micros-

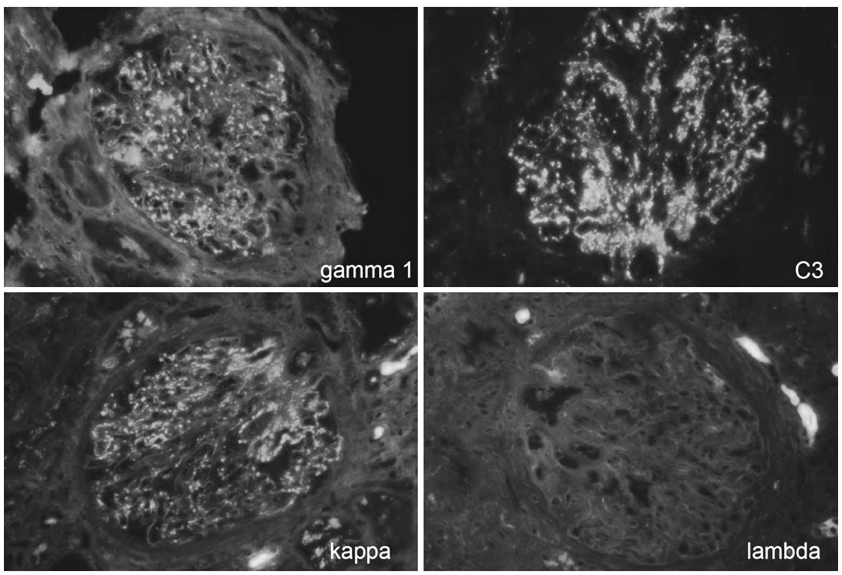


**Fig. 2.** Immunofluorescence pictures show subepithelial deposits that are heavily positive for anti-gamma-1, anti-C3 and anti-kappa antibodies. No reactivity was seen with anti-lambda antibody.

**Table 1.** Membranoproliferative glomerulonephritis in primary Sjögren's syndrome

| Histological lesions | Number of patients | Age (year) | Sex | Treatment | Outcome | Reference number |
|---|---|---|---|---|---|---|
| Membranoproliferative glomerulonephritis in primary Sjögren's syndrome with cryoglobulin | | | | | | |
| Membranoproliferative glomerulonephritis (MPGN) | 24 | 53 | F | CT and CP | Cr 1.3 mg/dL decreased to 0.8 mg/dL Non-Hodgkin lymphoma 5 years later | [5] (8 patients with MPGN with cryoglobulins, 2 cases presented) |
| | | 36 | F | CT and CP | Cr 6.2 mg/dL, haemodialysis (1 year) | [5] (8 patients with MPGN with cryoglobulins, 2 cases presented) |
| | | 63 | F | CT | Ccr 41 mL/min decreased to | [5] (9 patients with MPGN with cryoglobulins) |
| | | 72 | F | PE, CT, CP | 17 mL/min | |
| | | 55 | F | Ccr 52 mL/min decreased to | | |
| | | 62 | F | 7 mL/min | CT, CP | |
| | | 55 | F | CT, CP | NS | |
| | | 64 | F | PE, CT, CP | Partial remission | |
| | | 59 | F | PE, CT, CP | Complete remission | |
| | | 63 | F | PE | Complete remission | |
| | | 32 | F | VT, CP | Ccr 31 mL/min decreased to | |
| | | Ccr stable at 41 mL/min | | | 39 mL/min | |
| | | Ccr stable at 70 mL/min | | | | |
| | | 50 | H | CT | Ccr 20 mL/min increasing to 50 mL/min | [7] |
| | | 34 | F | CT | Deceased 1 year later of disseminated varicella | [7] |
| | | 48 | F | CT | Complete remission | [8] |
| | | 74 | F | CT and CP | Ccr 7 mL/min increasing to 60 mL/min | [9] |
| | | 39 | F | NS | NS | [10] |
| | | 52 | F | NS | NS | [11] |
| | | 58 | F | CT | NS | [12] |
| | | 47 | F | CT | Lymphoma after 148 months | |
| | | 53 | F | CT, PE and CP | Ccr 15.2 mL/min increasing to 55 mL/min | [13] |
| Mixed membranous and membranoproliferative glomerulonephritis (MPGN) | 1 | 34 | F | CT, CP and PE | | [14] |
| Membranoproliferative glomerulonephritis in primary Sjögren's syndrome without cryoglobulin | | | | | | |
| | 4 | 31 | F | | Spontaneous remission of the nephrotic syndrome | [15] |
| | | 73 | F | CT, CP and PE | Died 2 months after admission | [30] |
| | | 53 | NS | NS | NS | [5] |
| | | 38 | NS | NS | NS | [5] |

MPGN, membranoproliferative glomerulonephritis; Cr, creatinine; CCr, creatinine clearance; CT, corticosteroid therapy; CP, cyclophosphamide; PE, plasma exchange; NS, not stated.

copy revealed large, non-organized subepithelial deposits on the glomerular capillary wall, and sparse and small deposits in the mesangium (Figure 1D).

Because of the monotypic IgG1-kappa deposits and the presence of humps, we performed an extensive search for lymphoproliferative and infectious disease, respectively. Bone marrow biopsy, blood and bone marrow immunophenotyping, bone marrow smear, and clonality were normal. Coloscopy and abdominal and chest CT scan did not show any anomaly. Fluor-FDG positron emission tomography did not reveal any abnormal fixation. Numerous blood cultures remained negative. All infectious serologies including those of hepatitis B, hepatitis C, human immunodeficiency virus (HIV), Parvovirus B19, *Chlamydia pneumoniae*, *Chlamydia psitacci*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, *Brucella*, *Salmonella*, *Rickettsia* and *Coxiella burnetti* were unremarkable. The antistreptolysin titre was normal. Transoesophageal and transthoracic echocardiography did not show anomaly. Because of the C3 deposit, we explored the alternate pathway of complement, but the C3 antigen was normal (953 mg/L, normal range 660–1250 mg/L).

Given the association of xerostomia and xerophthalmia, and diffuse lymphocytic infiltration of the salivary gland and antibodies against SSA and SSB, a diagnosis of primary Sjögren's syndrome was made. Prednisone was started at the dose of 0.5 mg/kg/day. At the time of treatment onset, proteinuria was 1.1 g/day (proteinuria over creatinine ratio 814 mg/g, normal range ≤300 mg/g), and serum creatinine was 120 μmol/L (MDRD 44 mL/min/1.73 $m^2$, normal range ≥90 mL/min/1.73 $m^2$). Clinical outcome was favourable with improvement of proteinuria (580 mg/day) and serum creatinine (1 mg/dL) after 1 year. A third biopsy showed stable renal lesions. Seven years after onset of the disease, the patient had no sign of lymphoproliferative disorder, and serum creatinine was normal (72 μmol/L; MDRD 81.2 mL/min/1.73 $m^2$, normal range ≥90 mL/min/1.73 $m^2$) with no proteinuria or haematuria.

## Discussion

We report on an unusual form of proliferative glomerulonephritis with humps and monotypic IgG1-kappa deposits during pSS. The diagnosis of pSS was made according to the revised version of the European Classification Criteria [1]. The occurrence of glomerulonephritis in a patient with pSS is a rare phenomenon which should always raise the question of associated disease, particularly systemic lupus erythematosus (SLE) and related connective tissue disease, lymphoproliferative disorder, and infection. However, we found no evidence of those disorders, suggesting that the glomerulopathy was linked to pSS through expansion of a benign IgG1-kappa excreting B-cell clone.

Renal failure in pSS is well recognized, but the real incidence of the renal disease is not well known. Kidney diseases have been reported in 4–70% of patients depending on the criteria used for renal involvement [2–4]. Most of the patients present with indolent, subclinical interstitial nephritis, while clinically significant renal disease occurs in only 5% of patients [4]. Overt renal tubular acidosis occurs in ~5% of patients, but this percentage rises to 20–40% when acid load tests are performed. Glomerular lesions are particularly rare in pSS, with only scattered cases reported in the literature. A recent study by Ren *et al*. reported an unexpected high rate of 'glomerular' involvement in 18 out of 130 patients (14%), but a renal biopsy was performed in only eight patients [5]. The three main histological types of glomerulopathy in pSS are membranoproliferative glomerulonephritis (MPGN), membranous nephropathy and pauci-immune crescentic glomerulonephritis (Tables 1 and 2). Twenty-nine patients with MPGN and pSS have been reported [5–15]. In 25 of them, the link between MPGN and pSS was a cryoglobulin. In the largest series of 20 patients with renal involvement in the setting of mixed cryoglobulinaemia without evidence of hepatitis C virus infection [6], nine patients had pSS, and in all of them, typing revealed type II cryo-

**Table 2.** Pauci-immune crescentic glomerulonephritis and membranous nephropathy in primary Sjögren's syndrome

| Histological lesions | Number of patients | Age (year) | Sex | Treatment | Outcome | Reference number |
|---|---|---|---|---|---|---|
| MPO-ANCA-associated pauci-immune crescentic glomerulonephritis | 4 | 62 | F | CT and CP | Haemodialysis during 1 month, then Cr decreased to 1.6 mg/dL | [31] |
| | | 74 | F | CT | Cr 2.6 mg/dL decreased to 1.6 mg/dL. | [32] |
| | | 67 | F | PE and CT | Cr 2.8 mg/dL decreased to 1.8 mg/dL | [21] |
| | | 49 | F | CT | Cr 2 mg/dL decreased to 1 mg/dL | [19] |
| Pauci-immune crescentic glomerulonephritis without ANCA | 1 | 72 | F | CT | Cr 2.3 mg/dL decreased to 1.8 mg/dL | [23] |
| Membranous nephropathy | 9 | NS | NS | NS | NS | [5] |
| | | 72 | H | CT | Remission of the nephrotic syndrome Ccr 35 mL/min increasing to 78 mL/min | [5] |
| | | F | 52 | NS | NS | [10] |
| | | 71 | F | None | Unknown | [12] |
| | | 19 | F | CT | Remission of the nephrotic syndrome | [16] |
| | | 40 | F | CT and CP | Remission of the nephrotic syndrome | [17] |
| | | 64 | F | CT | Cr 2.1 mg/dL decreased to 1.1 mg/dL Remission of the nephrotic syndrome | [18] |
| | | 30 | F | CT | Haemodialysis | [19] |
| | | 43 | F | NS | NS | [20] |

globulinaemia including a monoclonal IgM-kappa associated with polyclonal IgG. Only one of the nine patients developed a lymphoma. Membranous nephropathy was observed in nine patients without cryoglobulinaemia or ANCA [5,7,10,12,16–20]. We retrieved five patients with pauci-immune crescentic glomerulonephritis, four of them having MPO-type ANCA [21–25] and a fifth patient presenting with a pauci-immune vasculitis, but criteria for diagnosis of pSS were incomplete, with SSA and SSB antibodies both being negative [26]. In addition, three cases of focal segmental glomerulonephritis and one case of 'minimal change disease' with glomerular IgA deposits without cryoglobulinaemia or ANCA were reported [5,25,26].

Our patient presents a very atypical form of pSS-associated glomerulonephritis. Interestingly, the renal manifestations preceded xerophthalmia and xerostomia, which is quite unusual. Two main features of the glomerulopathy are the deposited monotypic IgG1-kappa, which was not detected in the blood, and the absence of organization of the deposits appearing as humps by light microscopy. An extensive search for lymphoproliferative disorder and infectious disease was negative. The aspect of the deposits excludes a diagnosis of fibrillary or immunotactoid glomerulonephritis, but is reminiscent of the entity described by Nasr *et al*., as proliferative glomerulonephritis with monoclonal Ig deposits which may occur with or without overt monoclonal gammapathy [27,28]. No case of autoimmune disease including pSS was reported in this setting.

Because of the low circulating amounts of the IgG1-kappa which prevented further immunochemical studies, the pathophysiology of the lesions remains obscure. One can hypothesize that the monoclonal IgG1-kappa recognized a glomerular antigen leading to the *in situ* formation of immune complexes, or that this Ig was prone to precipitation or aggregation owing to unusual physicochemical properties [29].

From a therapeutic point of view, glomerular injury must be recognized early in the course of pSS because of its sensitivity to steroids used alone or with cyclophosphamide (Tables 1 and 2). In our patient, estimated creatinine clearance almost doubled after 5 months of treatment.

In conclusion, this observation describes a new type of pSS-associated glomerulonephritis in the absence of cryoglobulin and raises the question of the pathogenesis and the frequency of monotypic deposits in patients with pSS. In those patients that present glomerular proteinuria, a kidney biopsy should be performed, and investigations should include electron microscopy and detailed immunofluorescence studies with kappa/lambda staining and IgG subclass typing in case of dysbalance of light-chain isotypes.

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