



## CKJ REVIEW

## Kidney involvement in the Schnitzler syndrome, a rare disease

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### Abstract

The Schnitzler syndrome (SS) is a rare and underdiagnosed entity that associates a chronic urticarial rash, monoclonal IgM (or sometimes IgG) gammopathy and signs and symptoms of systemic inflammation. During the past 45 years, the SS has evolved from an elusive little-known disorder to the paradigm of a late-onset acquired auto-inflammatory syndrome. Though there is no definite proof of its precise pathogenesis, it should be considered as an acquired disease involving abnormal stimulation of the innate immune system, which can be reversed by the interleukin-1 receptor antagonist anakinra. It clearly expands our view of this group of rare genetic diseases and makes the concept of auto-inflammation relevant in polygenic acquired diseases as well. Increasing numbers of dermatologists, rheumatologists, allergologists, haematologists and, more recently, nephrologists, recognize the SS. The aim of this review is to focus on kidney involvement in the SS. Although the literature regarding kidney involvement in the SS is very poor it can be severe, as in our own case here reported, leading us to recommend the systematic search for nephropathy markers in the SS.

**Key words:** acute kidney injury, auto-inflammatory diseases, chronic urticarial rash, membranoproliferative glomerulonephritis, monoclonal IgM gammopathy, Schnitzler syndrome

### Auto-inflammatory diseases and the Schnitzler syndrome

Many systemic diseases affect the kidney and the skin, including relatively common immunologic and inflammatory disorders (e.g. systemic lupus erythematosus, scleroderma, cryoglobulinaemia, Henoch–Schönlein purpura, microscopic polyangiitis and atheroembolic disease), and rare hereditary conditions, such as Fabry's disease [1].

The Schnitzler syndrome (SS) is a rare and acquired systemic disease, which bears in common many features with a group of inherited diseases, referred to as auto-inflammatory syndromes

[2]. Liliane Schnitzler, a French dermatologist, first reported in 1972 the differential signs of the SS [3]. In the following years, cases were reported from all over the world including North America and Japan, but mostly from Europe. The European pre-eminence is probably related to a better knowledge of this entity in the Old World [2]. However, it remains a rare condition, when considering that up to September 2014 only 281 cases have been reported, with a male:female ratio of 1.5 [4]. Furthermore, a review of 94 cases found a median age of onset of 51 years, and only four patients developed symptoms before the age of 35 years [5]. In 2001, Lipsker *et al.* reported four cases and

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performed an extensive literature review, which allowed them to establish diagnostic criteria [6].

Lipsker's diagnostic criteria for the SS define the urticarial skin rash and monoclonal IgM component (or IgG: variant type) as 'obligate criteria' and at least two of the following criteria as 'minor': fever, arthralgia or arthritis, bone pain, palpable lymph nodes, liver or spleen enlargement, elevated erythrocyte sedimentation rate, leucocytosis and abnormal findings on bone morphologic investigations [6]. The more recent Strasbourg diagnostic criteria for the SS define the chronic urticarial rash and monoclonal IgM or IgG as 'obligate criteria'; whereas recurrent fever, objective findings of abnormal bone remodelling with or without bone pain, a neutrophilic dermal infiltrate on skin biopsy, leucocytosis and/or elevated C-reactive protein (CRP) are considered 'minor criteria' [4]. Then, the diagnosis of the SS is considered 'definite' if the two obligate criteria and at least two minor criteria (with IgM gammopathy), or three minor criteria (with IgG gammopathy), are met; the diagnosis of the SS is considered 'probable' if the two obligate criteria and at least one minor criterion (with IgM gammopathy), or two minor criteria (with IgG gammopathy), are met [4]. A multicentre study was conducted between 2009 and 2014 in 14 hospitals in which patients with the SS were followed up [7]. The authors compared the sensitivities and the specificities of the Lipsker [6] and the Strasbourg criteria [4]. Sensitivity and specificity of the Lipsker criteria were 100% and 97%, respectively. For the Strasbourg criteria, sensitivity for definite and probable diagnosis was 81% and 93%, respectively, with a corresponding specificity of 100% and 97%. The conclusion of the study was that diagnostic criteria currently in use to diagnose the SS are reliable [7].

In their article, Lipsker et al. included the chronic infantile neurological cutaneous and articular syndrome (CINCA)/neonatal onset multi-inflammatory disease (NOMID) and the Muckle-Wells syndrome in the differential diagnosis and thus pointed for the first time to similarities between the SS and the auto-inflammatory syndrome, of which the latter are a paradigm [6]. Indeed, the CINCA syndrome, the Muckle-Wells syndrome and familial cold auto-inflammatory syndrome are different phenotypes of the cryopyrin-associated periodic syndromes (CAPS), monogenic diseases involving the innate immune system. Their pathophysiology implies exaggerated activation of the inflammasome, an intracellular multi-protein complex, interleukin-1 (IL-1)-synthesizing cellular machinery, in response to cell stress [8]. Since their definition, inflammasome disorders have been linked to an increasing number of diseases, in which different factors lead to the activation of innate immune cells, causing tissue damage in the absence of autoantigens and autoantibodies. Many inflammasomopathies, such as CAPS, familial Mediterranean fever (FMF), SS, hyper-IgD syndrome (HIDS), periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome and deficiency of IL-1 receptor antagonist (DIRA) [9], include skin signs among the main features. As far as our clinical activity in the field of auto-inflammatory diseases (R.M.) is concerned, our database (1997–2017) includes 460

patients affected by FMF, 80 patients affected by the PFAPA syndrome, 30 patients affected by other auto-inflammatory fevers (TRAPS, CAPS, MVKD, NLRP12-related fevers) and 6 patients affected by the SS. None of these cases has ever been published.

Inhibition of the inflammasome pathway may be a target for future therapies as demonstrated by the efficacy of IL-1 inhibitors in CAPS. Since the SS shares many features with the CINCA syndrome, anakinra, an IL-1 inhibitor, was also tried in the former syndrome and it proved to be the first really efficient treatment of the SS [2]. Besada and Nossent reviewed the literature (in 2010) concerning anakinra treatment in the SS: 24 patients had been successfully treated with anakinra; furthermore, 'seven out of seven patients, that either interrupted or used anakinra every other day, had relapse of their symptoms within 24–48 h; anakinra was restarted in all patients with the same clinical efficiency' [10].

The aim of this review is to focus on kidney involvement in the SS.

### Kidney involvement in the SS

The literature regarding kidney involvement in the SS is very poor (Table 1). O'Hare et al. reported the case of a 34-year-old white male affected by urticarial vasculitis (skin biopsy showed leucocytoclastic vasculitis), renal insufficiency (serum creatinine 2.3 mg/dL) with monoclonal gammopathy (a small IgG- $\lambda$  spike on serum protein electrophoresis) [1]. This patient was markedly hypocomplementaemic and the kidney biopsy findings were characterized by an immune complex-mediated tubulointerstitial nephritis associated with light chain deposition [1]. Prednisone was started, then, as prednisone was tapered, mycophenolate mofetil 1000 mg twice a day was administered. The serum creatinine settled in the 2.0–2.4 mg/dL range [1].

Weshoff et al. reported the case of a 63-year-old male affected by the SS (he had been suffering from chronic urticarial, myalgia, malaise and severe bone pain for almost 10 years). Monoclonal IgM gammopathy was detected; histology of urticarial lesions was compatible with urticarial vasculitis [11]. The patient was normocomplementaemic and his kidney function was only moderately reduced, and glomerulonephritis was deemed improbable since serological findings were normal and there was no proteinuria; therefore, no kidney biopsy was performed. Different treatment modalities, including antihistamines, corticosteroids, azathioprine, colchicine, the cytostatic agent tofosfamide and mycophenolate mofetil, were not sufficient to control the patient's symptoms. Interferon  $\alpha$ -2a combined with six cycles of plasmapheresis achieved only initial improvement. The patient experienced improvement of renal function after treatment with the chimeric anti-CD20 antibody rituximab [11].

Iwafuchi et al. reported the case of a 62-year-old male with a 6-year history of intermittent urticaria with low-grade fever and recent leg oedema. Protein immunoelectrophoresis revealed an IgM  $\kappa$ -paraprotein in the serum; urinary protein was 4–5 g/24 h [12].

**Table 1.** Summary of the clinical cases reporting kidney involvement in the SS

Authors [reference]	Age and gender	Histologic findings of kidney biopsy	Serum creatinine level (mg/dL)
O'Hare et al. [1]	34-year-old male	Diffuse tubulointerstitial nephritis associated with light chain deposition	2.4
Weshoff et al. [11]	63-year-old male	Kidney biopsy was not performed	1.6
Iwafuchi et al. [12]	62-year-old male	Membranous nephropathy	1.0
Basile et al. (our case)	56-year-old male	Type I membranoproliferative glomerulonephritis	8.5

The histologic findings of the kidney biopsy were compatible with a secondary form of membranous nephropathy. He was treated with pulse intravenous methylprednisolone of 0.5 g for 3 days, followed by an oral prednisolone regimen [12].

Lastly, we report here our own clinical experience about kidney involvement in the SS: as already said, our database includes six patients affected by the SS. Five of them had normal kidney function, neither proteinuria nor haematuria. Only two out of the five patients had anomalies linked to the gammopathy (one patient had traces of cryoglobulinaemia with no C4 consumption, the other a high  $\kappa/\lambda$  ratio without Bence-Jones proteinuria). The sixth case is worthy of being extensively reported because of a very severe kidney involvement: a 56-year-old white male had been in good health until the age of 44, when he had the first episode of polyarthralgias and high spiking fever of variable duration. The clinical picture regressed within a week by means of the administration of paracetamol and antibiotics. Since then, several similar episodes occurred at intervals of approximately 6 months and lasting about 1 week, complicated by the onset of skin rash: each of these episodes was treated successfully by oral diclofenac. Laboratory tests during the acute episodes showed increased levels of some inflammatory markers that returned to normal in the periods of wellness. Skeleton X-rays and total body computed tomography were normal too. When the patient was 47 years old (in 2008), a first episode of non-oliguric acute kidney injury occurred (serum creatinine 2.0 mg/dL); supportive care and oral diclofenac were able to restore his kidney function to normal. When the patient was 51 years old (in 2012), the first admission to our unit was done because of a second episode of oliguric acute kidney injury (serum creatinine 1.7 mg/dL) associated with polyarthralgias, fever and skin rash. The dermatologist described the picture as urticarial non-itching erythema, completely different from a vasculitic erythema, most prominent on the trunk, arms and legs, sparing the palms, soles, head and neck (Figure 1). Increased levels of some inflammatory markers, notably leucocytosis and CRP, were detected. Serum complement (C3 and C4) levels were very low; serum ANA, ANCA, ENA and antibodies to dsDNA levels were normal; cryoglobulins were not detected. For the first time a monoclonal IgG- $\lambda$  gammopathy was detected. He underwent a kidney biopsy, which showed the histologic picture of type I membranoproliferative glomerulonephritis (Figures 2 and 3). Pulse intravenous methylprednisolone (15 mg/kg/day) for 3 days was successful in restoring kidney function to normal. The patient was prescribed a

long-term outpatient treatment including low-dose steroids and immunosuppressive drugs (among them cyclosporine and azathioprine). This treatment was unable to prevent the occurrence of new episodes, characterized by the same cohort of clinical signs and symptoms and laboratory data as described above. Specifically, the occurrence of acute kidney injury led to four admissions in our unit (in 2013, 2014, 2015 and 2016) with a serum creatinine level ranging from 2.8 to 8.5 mg/dL. During the last hospitalization in 2016 anuria and the highest serum creatinine level (8.5 mg/dL) occurred, requiring renal replacement therapy (five haemodialysis sessions). Pulse intravenous methylprednisolone (15 mg/kg/day) for 3 days was successful in restoring kidney function to normal in all four hospital admissions. We finally made the diagnosis of the SS in March 2016. Then, a long-term treatment with subcutaneous daily administration of the IL-1 receptor antagonist anakinra (100 mg/day) was prescribed. The patient decided not to adhere to this prescription, but accepted to be treated at the very early beginning of symptoms of a new potential episode with the immediate subcutaneous administration of anakinra. Actually, two new episodes occurred in October 2016 and February 2017: they were treated successfully with three daily doses of anakinra (100 mg/day) and did not require any hospital admission. Furthermore, as of today, kidney function is normal.

## Discussion

The SS is characterized by a recurrent febrile rash, joint and/or bone pain, enlarged lymph nodes, fatigue, a monoclonal IgM component, leucocytosis and systemic inflammatory response [2]. A monoclonal IgM component is the biological hallmark of the disease; variant cases of the IgG subtype constitute 7% of the reported cases [4]. Diagnosis of the SS relies on a combination of clinical, biological and radiological findings as well as on exclusion of another cause. Especially, the following diseases/entities need to be excluded: cryoglobulinaemia, hypocomplementaemic urticarial vasculitis, adult-onset Still's disease, systemic lupus erythematosus, angioedema, and haematological disorders such as lymphoma or IgM gammopathies of undetermined significance (MGUS) [4]. Furthermore, a spectacular and immediate response to anakinra is another finding that supports the diagnosis, as already suggested by Gilson *et al.* [13].

About 15–20% of patients with the SS will develop a lymphoproliferative disorder, a prevalence shared with other patients with MGUS [14]. AA amyloidosis is a concern in untreated



Fig. 1. The typical rash of the SS, which corresponds to a neutrophilic urticarial dermatosis: red eruptions consisting of flat macules are visible on the back and abdomen.



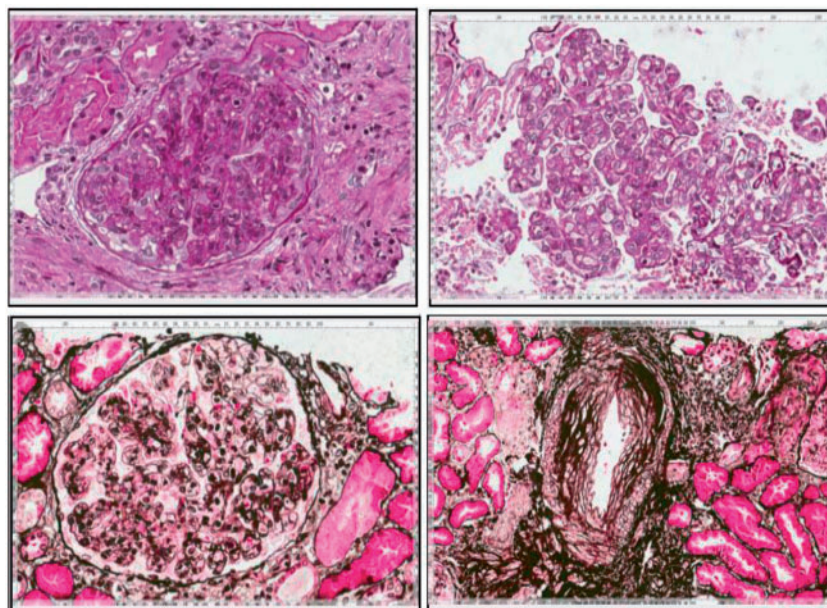


Fig. 2. Kidney biopsy, light microscopy. Left and right upper panel: hypercellular glomeruli with endocapillary and mesangial proliferation (PAS staining). Left lower panel: double contour aspect with splitting and duplication of the glomerular basement membrane and expansion of the mesangial matrix (silver staining). Right lower panel: intimal thickening with lamellation of the elastic membrane of an artery (silver staining).

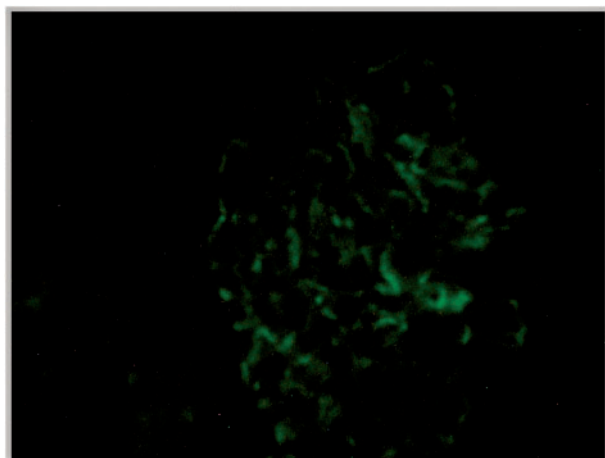


Fig. 3. Kidney biopsy, immunofluorescence microscopy. Bright deposits scattered along the capillary walls and in the mesangium detected with an antibody to complement component C3.

patients [5]. The reviews performed by Lipsker *et al.* in 2001, de Koning *et al.* in 2007 and de Koning *et al.* in 2014 summarize most published cases [4–6].

Antihistamines are not effective in treating the hives in this condition. It may respond to immunosuppressive drugs such as corticosteroids, cyclo-oxygenase inhibitors, interferon  $\alpha$ , IL-1 receptor antagonist anakinra, pefloxacin, colchicine, cyclosporine or thalidomide. The hives may respond to treatment with PUVA, and the bone pain may respond to bisphosphonates. The IL-1 receptor antagonist anakinra relieves all symptoms within hours after the first injection [10]. Because the SS is so rare, the efficacy of different treatments cannot be compared using statistics. Nevertheless, case studies provide evidence that anakinra is much more effective for the SS than any other drug, and that the improvement in symptoms associated with this treatment is dramatic [10].

Theories concerning the pathophysiology of the SS include hypothetical autoimmune properties of the paraprotein, a

haematological origin and more recently, interference with the inflammasome, the activator of cytokines of innate immunity [4]. After the recognition of the SS as a potential auto-inflammatory disorder, research focused on the role of pro-inflammatory cytokines, IL-1 $\beta$  in particular [15, 16]. The effect of the IL-1 receptor antagonist anakinra provided the first evidence for the crucial role IL-1 plays in the pathophysiology of recurrent fever in the SS [15, 16]. The recurrence of the systemic inflammation, due to IL-1 $\beta$  over-activation, in presence of the monoclonal gammopathy, is the most puzzling aspect of the SS. Accumulating data suggest that the monoclonal gammopathy is caused by the systemic inflammation rather than vice versa [4].

In conclusion, during the past 45 years, the SS has evolved from an elusive little-known disorder to the paradigm of a late-onset acquired auto-inflammatory syndrome. Though there is no definite proof of its precise pathogenesis, it should be considered as an acquired disease involving abnormal stimulation of the innate immune system, which can be reversed by the IL-1 receptor antagonist anakinra. It clearly expands our view of this group of rare genetic diseases and makes the concept of auto-inflammation relevant in polygenic acquired diseases as well [2]. Increasing numbers of dermatologists, rheumatologists, allergologists, haematologists and, more recently, nephrologists, recognize the SS. Although the literature regarding kidney involvement in the SS is very poor however, it can be severe, as in our own case here reported, leading us to recommend the systematic search for nephropathy markers in the SS.

### Conflict of interest statement

None declared.

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