

# Schnitzler Syndrome in a 27-Year-Old Man: Diagnostic and Therapeutic Dilemma in Adult Auto-Inflammatory Syndromes A Case Report and Literature Review

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**Abstract:** A 32-year-old-man, with a history of chronic urticaria from the age of 27, diagnosed with an adult-onset Still's disease and received a low dose of glucocorticoids, methotrexate and tocilizumab. Despite the long-term combined treatments, he suffered from chronic urticaria, low-grade fever and bone pain. He was found to have high inflammatory markers, hypogammaglobulinemia, monoclonal IgM – kappa light chain in serum and increased radiotracer uptake in the whole bone scintigraphy. No pathological variants for monogenic autoinflammatory diseases were present in the genome exome sequencing. These investigations confirmed the diagnosis of Schnitzler syndrome, which is an exception before the age of 35. Switching from tocilizumab to interleukin 1 receptor inhibitor, anakinra led to a full clinical response and normalisation of inflammatory markers. Patients with a history of fever and chronic urticaria are routinely tested for monoclonal gammopathy in the context of malignancy, but it should also be considered as a sign of the autoinflammatory syndrome. The Schnitzler syndrome and the adult-onset Still's disease share common features, so the diagnosis requires a thorough investigation to establish an optimal treatment. In the diagnostic algorithm, monoclonal gammopathy is usually considered red flag for malignancy but might be overlooked as a criterion of Schnitzler syndrome, particularly in young adults. We confirm that the interleukin 1 inhibitor should be the first line of therapy in Schnitzler syndrome, and in the presented case we found it more effective than the interleukin 6 blockade. The main goal of this paper is to increase awareness of Schnitzler syndrome among health care professionals. We aim to present features which can be helpful in differential diagnosis.

**Keywords:** chronic urticaria, monoclonal gammopathy, tocilizumab, anakinra, autoinflammation

## Introduction

Schnitzler syndrome (SchS) is considered to be a rare disorder characterised by the presence of monoclonal IgM protein in serum, fever and chronic urticaria that is associated with considerable morbidity. SchS symptoms significantly impact a patient's everyday life and in the long term may be followed up by AA amyloidosis. Moreover, up to 20% of SchS patients develop a clinically overt lymphoproliferative disorder such as multiple myeloma, marginal zone lymphomas, and Waldenström's macroglobulinemia (WM).<sup>1</sup> The syndrome is under-recognised and can be present in up to 1.5% patients with IgM monoclonal gammopathy.<sup>2</sup> In the course of the disease patients are consulted by allergy, dermatology, haematology

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and rheumatology specialists for particular symptoms, while a common denominator – autoinflammation – is missed, and patients may be deprived of a highly effective therapy which inhibits interleukin 1 (IL-1).<sup>3</sup>

In this report, we describe the case of SchS with an early disease onset, which was initially diagnosed and treated as adult onset Still's disease (AOSD). We present potential diagnostic and treatment pitfalls in the management of autoinflammatory syndromes in adults.

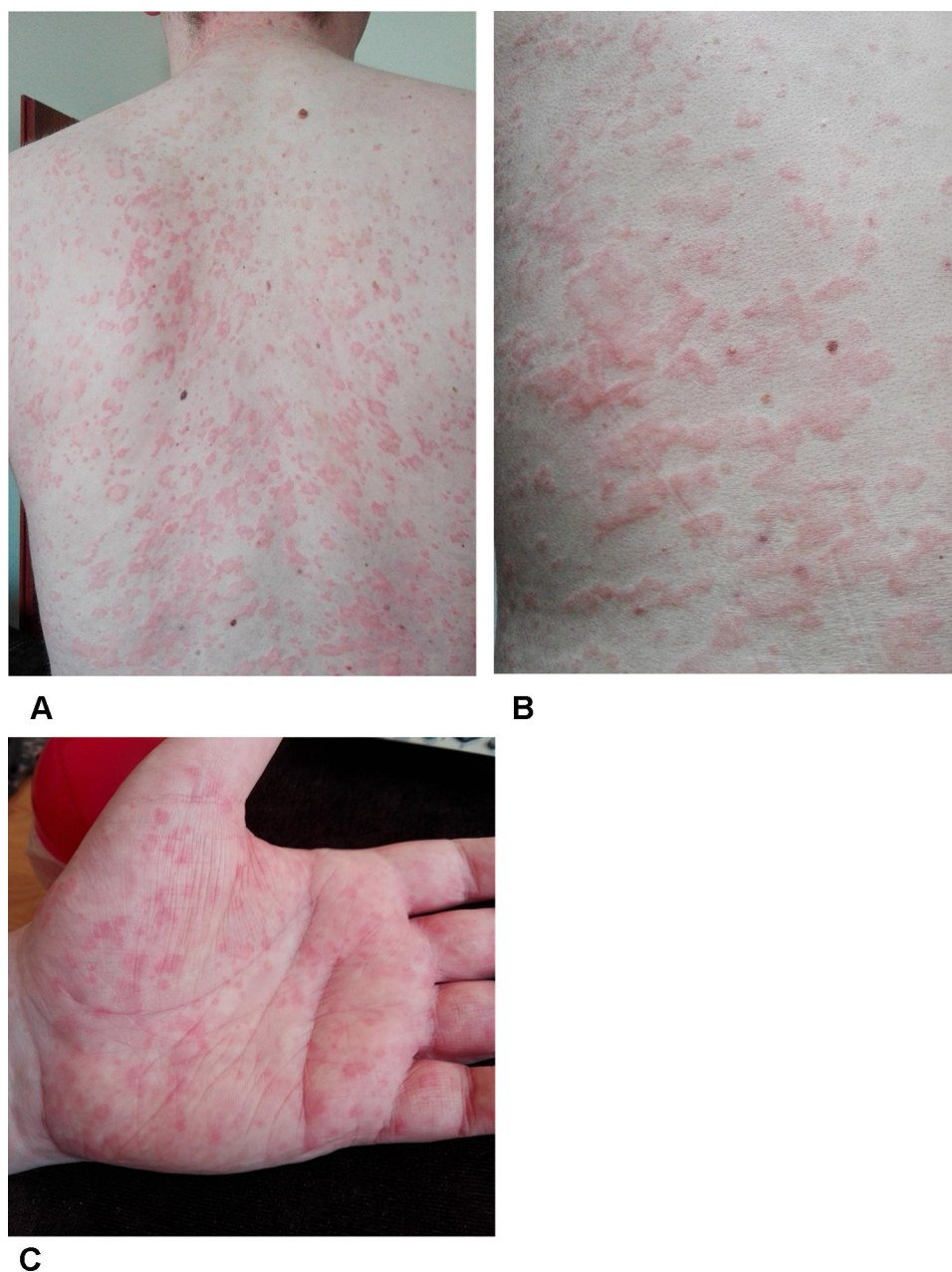
## Case Presentation

The patient was a 32-year-old Caucasian man with chronic urticaria since the age of 27. At the age of 28, it was accompanied by a recurrent fever of over 39 degrees, lasting for 10–14 days. The initial frequency of the fever attacks increased from once per 4–6 months to once every month. His family history of chronic diseases was unremarkable. He was treated symptomatically with non-steroidal anti-inflammatory drugs (NSAID), antihistamine drugs and penicillin. When he was 31, generalised lymphadenopathy, hepatomegaly, peripheral arthralgia occurred. Laboratory tests revealed leukocytosis  $27 \times 10^3/\mu\text{L}$  with neutrophilia (88%), C-reactive protein (CRP) 14.2 mg/dl (0.1–1.0), monoclonal IgM antibody presence, ferritin 537.5 ng/mL (30–400). Anti-CCP antibodies, antinuclear antibodies (ANA), rheumatoid factor (RF), anti-neutrophil cytoplasmic antibodies (ANCA), thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) were negative. C1q, C3 and C4 levels were normal. Lymph node histopathology examination and bone marrow aspirate biopsy showed reactive granulocytosis and excluded malignancy. The consulting haematologist ruled out monoclonal gammopathy and recommended further rheumatological and dermatological diagnostics. The skin specimen biopsy excluded necrotising vasculitis and showed perivascular lymphocyte and slight neutrophils infiltration. He was diagnosed with adult onset Still's disease (AOSD) and received methylprednisolone pulses (500 mg intravenously for 3 consecutive days) followed by glucocorticoids (20 mg prednisolone orally once a day) and methotrexate (25 mg orally once a week), without any effect. Then, tocilizumab (8 mg/kg intravenously once a month) was added with partial response: CRP lowered but the patient continued to complain about pain in thoracic back, hips, sternum and ribs and chronic urticaria. Low-grade fever up to 38 degrees regularly reappeared about one week before the tocilizumab infusions. He was referred to a clinical immunologist for re-evaluation. On admission, his physical examination revealed peripheral lymphadenopathy and

urticaria which covered his extremities, trunk, palms and soles (Figure 1). The skin lesions were associated with an unpleasant burning sensation. The clinical immunologist put into question the diagnosis of AOSD and referred the patient for further investigation. In total the patient received seventeen doses of intravenous tocilizumab in combination with 7.5 to 10 mg daily of prednisone. In his laboratory investigations leukocytosis with neutrophilia, CRP 3.1 mg/dl (ref 0–0.8), serum amyloid A (SAA) 24 mg/dl (ref <0.64) were present. Serum IgG level was 347 mg/dL (ref. 700–1600), IgA 18 mg/dL (ref. 70–400), IgM 1110 mg/dL (40–230), total IgE <2 IU/mL (10–135), monoclonal IgM – kappa serum-free light chain 892 mg/dl (680–1480), lambda serum-free light chain 180 mg/dL (360–840), kappa to lambda ratio 4.96 (1.35–2.65). The whole-body bone scintigraphy (<sup>99m</sup>Tc-methylene diphosphonate) showed an increased uptake of radiotracer localisers in the ribs, in the right iliac bone, in the vertebrae (thoracic region) and in the distal part of the left femur (Figure 2). Exome sequencing was performed and variants in 289 genes, connected with autoinflammatory diseases and primary immune deficiencies, were analysed and did not reveal pathogenic variants. These findings led to the diagnosis of SchS and the switch from tocilizumab to an IL-1 receptor antagonist. Anakinra 100 mg subcutaneously once a day was started. Urticaria and the fever disappeared within 2 days, SAA normalised within 4 weeks. Glucocorticoids were stopped within the first month of anakinra. An unintentional pause in the anakinra treatment caused the re-occurrence of high fever, and generalised urticaria within 3 days. During a continuous anakinra treatment, the patient remains in clinical remission. After a one-year follow-up his SAA is stable within reference range, IgG is 792 mg/dL, IgA is 50 mg/dl (ref 40–400), IgM 907 g/dl (40–230), light serum kappa-free chain 1168 mg/dl (680–1480), light serum lambda-free chain 320 mg/dl (360–840), kappa to lambda ratio 3.65 (1.35–2.65).

## Discussion

We describe the young male patient with chronic urticaria, monoclonal IgM gammopathy and systemic inflammation. Although he initially fulfilled the criteria of SchS according to literature<sup>4</sup> some exceptional features were present: his young age, the urticaria of the palms and soles [Figure 1], and the generalised lymphadenopathy, so a more thorough differential diagnosis work-up was needed. We have shown that due to low awareness of the disease, SchS can be missed in an initial differential algorithm of chronic urticaria. The consequence might be a choice of an ineffective or partially



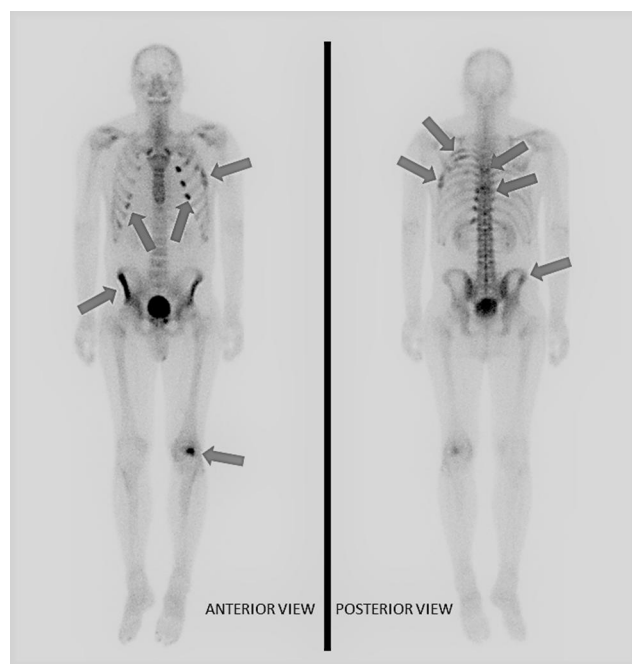
**Figure 1** The trunk (**A** and **B**) and palm (**C**) of the hand covered in urticarial rash observed in a Schnitzler syndrome patient during treatment with tocilizumab.

effective treatment. What is more, we have shown that in the presented case the IL-1 receptor antagonist, anakinra, in a standard dose of 100 mg subcutaneously once a day, was more beneficial than long-term tocilizumab treatment.

SchS was first described by a French dermatologist, Liliane Schnitzler.<sup>5</sup> Its cardinal features include urticarial rash, recurrent fever, monoclonal IgM or, more rarely, IgG gammopathy and elevated acute inflammatory markers. Urticaria is often the first symptom, preceding the fever.<sup>6,7</sup>

The disease occurs worldwide, although the overall incidences remain unknown. The published literature involves case reports, case series and one paper which collected the data from 281 patients.<sup>1,4,8–11</sup> The pathogenesis involves IL-1, interleukin 6 (IL-6), interleukin 17 (IL-17) activation, but the relation to monoclonal gammopathy remains obscure.<sup>12–15</sup>

The diagnosis is based on Lipsker's or Strasbourg's criteria with high sensitivity and specificity.<sup>16–18</sup>



**Figure 2** Whole-body bone scintigraphy ( $^{99m}\text{Tc}$ -methylene diphosphonate) in a Schnitzler syndrome (SchS) patient. Arrows indicate an increased radiotracer uptake.

SchS is included in the autoinflammatory syndromes group, which all are diagnosed per exclusionism, so the differentiation among them can be a challenge.<sup>19</sup> A comparison of main features of discussed autoinflammatory syndromes is shown in Table 1. In the presented case, the initial diagnosis of AOSD was supported by Yamagouchi's criteria: fever, joint pain, leucocytosis with neutrophilia, hepatomegaly, negative RF and ANA.<sup>20</sup> Yet, it was premature. The most important part from the Yamaguchi's criteria is the requirement of exclusion of other rheumatic conditions, malignancies, and infections. However, the autoinflammatory syndrome had not been considered initially. All autoinflammatory diseases share fever as the leading symptom and reveal high acute phase reactants, so an accurate diagnostic work-up is needed. The most helpful laboratory parameter indicating SchS is the presence of monoclonal IgM, while highly elevated ferritin (5 times the upper reference level) suggests AOSD.<sup>21</sup> In the case of our patient, monoclonal IgM led to the search for lymphoproliferative malignancy, but was not considered an indicator of the autoinflammatory syndrome. A bone scintigraphy showed signs of increased bone metabolism are present in 80% of patients with SchS. The bone scans appear to be more sensitive for diagnosis and may correlate with clinical activity better than a positron-emission tomography (PET) scan. Moreover, bone scans may be well positioned to distinguish SchS relapse from

other aetiologies of bone, joint, or muscle pain.<sup>22</sup> In our case, the scintigraphy showed an increased radiotracer uptake, which correlated with bone pain, but the alkaline phosphatase was normal. Urticaria is a common symptom in SchS and has to be differentiated from chronic spontaneous urticaria (CSU). In CSU individual lesions usually appear, enlarge and then resolve within 24 hours and are accompanied by severe pruritus. A rash in SchS is more painful and burning, often lasting for longer than 24–48 hours. The skin biopsy should be obtained. Infiltration of neutrophils without evidence of vasculitis further supports the diagnosis of autoinflammatory syndromes.

The skin biopsy showed no evidence of vasculitis and only a slight neutrophilic inflammation which occurred in 50% of patients,<sup>4</sup> however, it was helpful to exclude spontaneous chronic urticaria and urticarial vasculitis.<sup>14,23</sup> Our patient fulfilled both Lipsker's and Strasbourg's diagnostic criteria for SchS. However, he was only 27 at the disease's onset. The presence of monoclonal gammopathy is very rare before 40 and the average age at the onset of SchS is 51–54 years.<sup>4,11,24</sup> Until now, a SchS diagnosis before the age of 35 has been an exception.<sup>10</sup> In our opinion, due to phenotypical similarities to NLRP3 related diseases, a late onset of monogenic autoinflammatory disease has to be included in the diagnostic work-up in such cases. No pathological variants in exome sequencing were found. Genetic testing for monogenic autoinflammatory syndromes in such cases is an open question.<sup>25</sup> Somatic mosaicism of NLRP3 mutations in the myeloid lineage has been reported in two patients with variant SchS; however, the further study of 21 patients with SchS did not support somatic mosaicism in NLRP3, TNFRSF1A, NLRC4, or NOD2 genes. NGS analysis of 32 genes associated with inherited autoinflammatory diseases failed to reveal any common susceptibility factors for SchS.<sup>11</sup> In addition, we searched for MYD88 mutations, which may predict the development of Waldenström's macroglobulinemia, and the results were negative.

The next unique issue in the presented case was hypogammaglobulinemia. In rheumatic and hematologic conditions hypogammaglobulinemia can be primary or secondary and can be a warning sign for immunodeficiency.<sup>26</sup> In our case, hypogammaglobulinemia was not clinically significant, we did not observe increased susceptibility for any common or atypical infection during the immunosuppressive or tocilizumab treatment. In our opinion, the hypogammaglobulinemia was related to tocilizumab, as IgG and IgA normalised after the tocilizumab was ceased.



**Table 1** Comparison of Main Features of Schnitzler Syndrome (SchS), an Adult-Onset Still's Disease (AOSD) and Cryopyrin-Associated Periodic Syndrome (CAPS)<sup>32–36</sup>

	SchS	AOSD	CAPS
Age	>50	15–26 and 36–46	Childhood
Fever	Yes	Yes	Yes
Sore throat	No	Yes	No
Skin rash	Urticaria	Salmon pink rash	Urticaria
Skin biopsy	Neutrophilic inflammation	Neutrophilic inflammation	Neutrophilic inflammation
Joints and bone	Bone pain	Arthralgia, arthritis	Bone pain, arthralgia, transient arthritis
CRP	↑↑↑*	↑↑↑*	↑↑↑*
Ferritin	↑*	↑↑↑*	↑*
Leucocytosis with neutrophilia	Typical >80% neutrophils	Typical >80% neutrophils	Might be present during flares
Alkaline phosphatase	↑↑*	No data	No data
Bone scintigraphy	Increased bone metabolism	No data	No data
Paraproteinemia	Always present	Absent	Absent
GCS	No response	May respond	No response
DMARDs	No response	May respond	No response
IL-1 inhibitor	Effective (90%)	Effective	Effective
IL-6 inhibitor	May be effective	Effective	May be effective
Complications	Lymphoproliferation AA amyloidosis	HLH Joint damage Rare cases AA amyloidosis	AA amyloidosis The hearing deficiency
Genetics	Polygenic Mosaics described	Polygenic	Monogenic (AD inheritance, NLRP-3 related)

**Abbreviations:** \*↑↑↑, highly elevated; ↑↑\*, elevated; ↑\*, might be elevated; CRP, C-reactive protein; GCS, glucocorticoids; DMARDs, disease-modifying antirheumatic drugs; IL, interleukin; HLH, hemophagocytic lymphohistiocytosis; AD, autosomal dominant; NLRP-3, nucleotide-binding oligomerization domain-like receptor with a pyrin domain 3.

The most effective treatment in SchS is IL-1 inhibition. The majority of patients respond to anakinra or canakinumab.<sup>27–29</sup> A lack of response to IL-1 blocking therapies should lead to reconsideration of the diagnosis of SchS, while a rapid response to anakinra could also become a diagnostic criterion. The inhibition of IL-6 can be effective, but data is limited to rare cases.<sup>7,30</sup> In the case of our patient, we did not observe a clinical response to the IL-6 blockade – only CRP lowered, but urticaria, low-grade fever and bone pain persisted. A difference in response to tocilizumab and anakinra was previously observed in AOSD patients.<sup>31</sup> Another explanation is the need to use higher doses of tocilizumab or more frequent administration – for example, every two weeks; however, it would be burdensome for the patient, as it is administered in hospital, and leads to absence at work, which is inconvenient in long-term treatment and raises concerns of a higher cost.

The open question is how long the IL-1 blockade should be conducted. Our experience and data from literature

showed that even a short break in anakinra led to the recurrence of symptoms.

The next point to discuss is the prognosis of SchS. At the early observation stage, SchS was considered a benign condition; however, a further follow-up revealed long-term complications.<sup>4,7,10,17</sup> Lymphoproliferative disease occurred in 12% of 281 patients after a median 8 years from the diagnosis.<sup>4</sup> These were particularly Waldenström's macroglobulinemia [WM] (in 21 patients of 35 reported cases) and single cases of non-Hodgkin lymphoma. One patient had acute myeloid leukaemia.<sup>4</sup> It is not clear if good control of inflammation has any impact on the risk of progression to lymphoproliferation, and, if in this group, the risk factors are similar to a monoclonal gammopathy of unknown significance (MGUS).<sup>24</sup> In MGUS the risk of progression to multiple myeloma or another plasma-cell or lymphoid disorder is higher if the ratio of the kappa to lambda chain is abnormal and monoclonal protein IgM is  $\geq 1.5$  g/dl. A deficiency of two other main immunoglobulin classes is also disadvantageous.<sup>24</sup> In our case, IgA and IgG normalised, and the IgM threshold

was stable. Another complication might be AA amyloidosis that justifies the careful control of SAA during treatment.<sup>3</sup>

## Conclusion

SchS and AOSD share common features and the differential diagnosis requires a thorough investigation to establish the optimal treatment. Interleukin 1 inhibitor is the first-line therapy in SchS and in the presented case we found it more effective than tocilizumab. Patients with a history of recurrent fever and chronic urticaria are routinely tested for monoclonal gammopathy. However, when malignancy is excluded, the presence of monoclonal protein can represent a sign of SchS. Due to the potential development of lymphoproliferative disorder, SchS requires a long-term haematological follow-up.

## Ethics Statement

Based on the regulations of Clinical Hospital of the Ministry of National Defense, Military Institute of Medicine in Warsaw an institutional review board approval is not required for case reports.

## Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Disclosure

The authors report no conflicts of interest in this work.

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