swiss medical weekly

CLINICAL REASONING: CASE REPORT
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SARS-CoV2-induced Schnitzler syndrome, inflammatory flare and successful treatment by anakinra during pregnancy: a case report

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Summary

INTRODUCTION: Schnitzler syndrome is a rare acquired autoinflammatory disease characterised by a chronic urticarial rash, recurrent fever, arthralgia or arthritis, bone pain, elevated inflammatory markers, and monoclonal gammopathy. The disease is driven by dysregulated inflammasome activation and excessive interleukin-1 (IL-1) production. Because of its rarity, data on the management of Schnitzler syndrome during pregnancy remain extremely limited. We report the case of a pregnant woman presenting with a SARS-CoV-2-induced inflammatory flare that was successfully treated with anakinra, highlighting both the diagnostic and therapeutic challenges of this uncommon condition in pregnancy.

CASE PRESENTATION: A pregnant woman in her early 40s with previously diagnosed Schnitzler syndrome presented with an acute inflammatory flare triggered by SARS-CoV-2 infection. Clinical manifestations included urticaria and musculoskeletal symptoms consistent with disease reactivation, along with elevated inflammatory markers. The diagnosis of Schnitzler syndrome had previously been established based on clinical criteria, supported by the presence of a chronic urticarial rash and monoclonal gammopathy in accordance with the Strasbourg and Lipsker diagnostic criteria. Due to the severity of the symptoms and the central role of IL-1 in disease pathophysiology, treatment with anakinra, an IL-1 receptor antagonist, was initiated. The patient experienced rapid clinical improvement, with resolution of systemic symptoms and normalisation of inflammatory parameters. Treatment was well tolerated, with favourable maternal and foetal outcomes throughout the pregnancy.

CONCLUSION: This case highlights the importance of recognising Schnitzler syndrome as a rare but potentially severe autoinflammatory condition requiring prompt multidisciplinary management. It also suggests that anakinra may be a potential therapeutic option for inflammatory flares during pregnancy. Early recognition and targeted pharmacological treatment are essential to improving patient outcomes and preventing long-term complications.

Published
19 October 2026

doi
https://doi.org/10.57187/5590

Cite this as
Swiss Med Wkly. 2026;156:5590

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Introduction

Schnitzler syndrome is a rare acquired autoinflammatory disorder that predominantly affects middle-aged adults, with a median age of approximately 50–55 years at symptom onset and a slight male predominance [1]. Like several other autoinflammatory conditions, including adult-onset Still's disease, Schnitzler syndrome typically follows a relapsing course, with inflammatory flares that may be triggered by viral infections. The development of biological therapies, particularly IL-1 inhibitors, has profoundly transformed the pharmacological management of this disease, enabling effective control of both systemic symptoms and the associated biological inflammatory syndrome [2].

The present case is unique in that, to our knowledge, it is the first published report of an inflammatory flare of Schnitzler syndrome occurring during pregnancy. This rarity is likely explained by the epidemiological characteristics of the disease, namely its very low prevalence and its usual onset at an older age, generally beyond the reproductive period. It thus raises important questions regarding the optimal pharmacological management of Schnitzler syndrome during pregnancy. In addition, to our knowledge, this is the first reported case of a Schnitzler syndrome flare occurring

in the context of SARS-CoV-2 infection, a pathogen that was unknown prior to 2019. Insights from the COVID-19 pandemic have demonstrated the pivotal role of the inflammasome in antiviral defence against coronaviruses, while also revealing its propensity for dysregulated activation in severe disease [3, 4]. In this context, viral infections are increasingly recognised as potent triggers of autoinflammatory flares, including during pregnancy. In the present case, SARS-CoV-2 likely initiated innate immune activation, precipitating a disease flare. Within the framework of Schnitzler syndrome, such an infection may have amplified a pre-existing inflammatory cascade, thereby intensifying IL-1–driven disease activity.

This case highlights the importance of considering Schnitzler syndrome even in patients outside the usual epidemiological profile, including during pregnancy, when management can be particularly challenging. Early recognition and timely targeted treatment are essential for achieving rapid disease control and preventing complications.

Case description

We present the case of a woman in her early 40s, initially diagnosed with suspected Schnitzler syndrome in December 2021. Her symptoms began in 2014, with two episodes occurring up to 2021, both of which resolved completely with ibuprofen. These episodes were relatively stereotypical, starting with a sore throat, dry cough, and rhinitis, along with subfebrile temperatures of up to 38°C. Joint pain developed 3-7 days after the first symptoms, with arthralgia in the hands and widespread body pain. In September 2021, the patient presented with a third episode, characterised by diffuse urticarial exanthema, joint pain, and elevated inflammatory markers (C-reactive protein [CRP] 119 mg/l [norm <5 mg/l] and leucocytosis of 14 G/l [norm 3.5–10.5 G/l]), shortly after symptoms resembling a viral upper respiratory infection, with prompt improvement after the initiation of peroral glucocorticoid therapy.

Following this episode, the patient was referred to our tertiary centre for further immunological assessment. Serum protein electrophoresis showed a monoclonal immunoglobulin of IgM kappa together with a very weak IgG lambda paraprotein, without a quantifiable M-gradient. Free light chains were within the normal range. IgM was slightly elevated (7.18 g/l, normal range 0.4–2.3 g/l). IgA and IgG were within the normal range. Urinalysis revealed no paraprotein.

A bone marrow biopsy performed in September 2023 revealed trilinear maturing haematopoiesis with no evidence of plasma cell or lymphoid neoplasia. Immunophenotyping revealed no signs of clonality among the lymphocytes or plasma cells, and the aspirate showed only discrete plasma cell proliferation of approximately 2-3%. These findings were most likely compatible with IgM-kappa monoclonal gammopathy of undetermined significance (MGUS). In addition, molecular analysis identified a somatic MYD88 p.L265P (c.794T>C) mutation. Abdominal sonography revealed no evidence of lymphadenopathy or splenomegaly.

In April 2024, the patient presented with another flare (CRP 154 mg/l, interleukin-6 (IL-6) 11 pg/ml, norm <7 pg/ml). A skin biopsy showed perivascular and interstitial mucin-rich dermatitis, with histopathological findings consistent with urticarial dermatitis. Auto-inflammatory gene analysis performed in June 2024 revealed no pathological variants associated with monogenic autoinflammatory diseases among the 59 analysed genes. Due to the shortening intervals between episodes and elevated serum amyloid A (SAA) levels (1920 mg/l), prophylactic treatment with 1 mg/day colchicine was started in August 2024. Because of four pregnancy losses prior to gestational week 10, additional investigations revealed persistently low to moderately elevated anti-cardiolipin IgM antibodies (reference <20 CU; week 0: 40.1 CU, week 12: 34.2 CU). Although the patient did not fulfil the current classification criteria for obstetric antiphospholipid syndrome (APS), the combination of recurrent pregnancy losses and persistent antiphospholipid antibody positivity led to a clinical diagnosis of suspected obstetric APS after rheumatological and other conditions associated with secondary APS had been excluded. Given the pregnancy, the patient was treated accordingly with prophylactic antithrombotic therapy consisting of low-dose aspirin and low-molecular-weight heparin (LMWH).

On 16 January 2025, the patient was hospitalised in our rheumatological department with a new disease flare at week 27 of pregnancy. The urticaria and musculoskeletal symptoms developed following a SARS-CoV-2 infection (positive nasopharyngeal swab polymerase chain reaction). Laboratory findings initially showed highly elevated inflammatory parameters (CRP 185 mg/l). Following treatment with 100 mg/day anakinra, both the symptoms and CRP levels improved dramatically (CRP 7 mg/l on 21 January 2025), allowing discharge on 17 January 2025. Anti-IL-1 ther-

apy was discontinued after 5 days, and colchicine therapy was continued. Obstetric evaluation of the foetus was completely normal. Given the infrequent flares, most likely associated with viral infections, we opted against continuous administration of anakinra for flare prophylaxis.

In mid-March 2025 (gestational week 36), the patient presented again with a typical flare after a respiratory viral syndrome that had also affected several family members (no nasopharyngeal swab was performed in the ambulatory setting). Again, the flare abated rapidly after the initiation of anakinra 100 mg subcutaneously daily. Subsequently, the patient developed purulent cough and nasal discharge, accompanied by a secondary rise in inflammatory markers and radiological evidence of pneumonia and sinusitis. (LE: Please check that your intended meaning is retained.)) Following treatment with amoxicillin 3 × 1 g daily for 5 days, the patient was asymptomatic and CRP was negative (<5 mg/l). Because of the second flare during pregnancy and the complicating bacterial superinfection, we decided to initiate continuous anakinra, in line with the recently published EULAR guidelines [5]. Two weeks later (gestational week 38+3/7), the patient gave birth to a healthy son via Caesarean section, indicated by a history of prior Caesarean delivery.

Discussion

Schnitzler syndrome was first reported in 1972, with the first publication appearing in 1974 by Liliane Schnitzler, a French dermatologist [6, 7]. Diagnosis is based on clinical features combined with biochemical, radiological, and histological findings. Lipsker et al. [8] published the original diagnostic criteria in 2001, which were supplemented in 2012 by the validated Strasbourg criteria [1]. Due to the overlap in clinical presentation with other autoinflammatory conditions and the fact that the diagnosis of Schnitzler syndrome relies exclusively on clinical criteria, comprehensive genetic sequencing is often warranted to confidently exclude alternative diagnoses. Furthermore, the somatic mutation MYD88 L265P, which is usually associated with lymphoplasmocytic lymphoma or Waldenström disease, has been described in some patients with Schnitzler syndrome and is thus also assessed [9].

The main complications of Schnitzler syndrome include the development of lymphoproliferative disease in 15-20% of patients, a percentage similar to that observed in other patients with IgM MGUS, and, in rare cases, AA amyloidosis resulting from persistent uncontrolled inflammation [1].

The syndrome is presumed to be driven by dysregulated inflammasome activity, resulting in excessive IL-1β production. Since its initial description, considerable research has been conducted, leading to a better understanding of the underlying pathophysiology and, subsequently, to the development of targeted therapeutic agents. However, due to its rarity, the exact molecular mechanisms responsible for autoinflammation and monoclonal gammopathy remain incompletely understood, and ongoing research aims to elucidate these underlying processes. Furthermore, the relationship between inflammasome activation leading to the production of IL-1 and clonal B-cell expansion remains unclear, particularly regarding the role of the paraprotein and whether it acts as a driving factor or represents a secondary consequence of the disease process [2]. While some theories propose that chronic inflammation may drive plasma cell clonality and the subsequent emergence of paraproteinemia, as supported by reports of delayed paraprotein detection up to four years after symptom onset [10], other hypotheses suggest a direct pathogenic role for the paraprotein, based on rare instances of symptom remission following treatment with cyclophosphamide or rituximab [11, 12]. Nonetheless, the lack of impact of IL-1 and IL-6 blockade on the monoclonal component and on progression to lymphoproliferative disorders, despite the rapid clinical efficacy of these treatments, suggests the involvement of additional pathogenic mechanisms [2, 13]. Schnitzler syndrome thus requires multidisciplinary management, including long-term malignancy screening despite successful symptomatic treatment.

Although IL-1 inhibitors represent the cornerstone of treatment [2], other therapeutic approaches are used in clinical practice, including IL-6 blocking agents, colchicine, and Bruton's tyrosine kinase inhibitors [2, 14]. By analogy with other autoimmune or autoinflammatory diseases, such as cryopyrin-associated periodic syndromes (CAPS), tumour necrosis factor receptor–associated periodic syndrome (TRAPS), and rheumatoid arthritis, IL-1 inhibition is considered safe during pregnancy. This therapeutic approach was also endorsed in the 2024 update of the EULAR recommendations for the management of rheumatic diseases during pregnancy and lactation [5]. Unlike

IgG-based biologic agents, anakinra lacks an Fc region and is thus not actively transported across the placenta via the FcRn-mediated pathway. Consequently, placental transfer of anakinra is expected to be limited.

In the present case, intermittent administration of anakinra, an IL-1 receptor antagonist, during inflammatory flares resulted in a rapid and complete clinical and biological response of the Schnitzler syndrome flares. Therapeutic intensification, with the initiation of continuous maintenance therapy during the third trimester of pregnancy (at 36 weeks of gestation), a period considered sensitive for the foetus due to maximal placental transcytosis of immunoglobulins, led to optimal control of maternal disease activity. This strategy was not associated with any maternal or foetal perinatal complications. Overall, this clinical observation is consistent with currently available literature supporting the safety of IL-1 inhibitors during pregnancy. In addition, the clinical and laboratory findings were suggestive of obstetric antiphospholipid syndrome, although the current classification criteria were not fully met, and the patient was thus treated with prophylactic low-dose aspirin and LMWH.

The main limitations of this report are the rarity of Schnitzler syndrome and the absence of previously reported cases describing its management during pregnancy. Consequently, no disease-specific guidelines are currently available to guide treatment in this setting. Therapeutic decisions were thus based on clinical judgment and extrapolation from recommendations and safety data for anakinra in other autoimmune and autoinflammatory diseases. As a single-case observation, this report cannot establish the efficacy or safety of anakinra in pregnant patients with Schnitzler syndrome, but it may provide useful clinical experience for the management of similar cases.

In conclusion, this clinical observation reinforces the currently available evidence supporting the safety of IL-1 inhibitors during pregnancy and highlights their central role in the management of Schnitzler syndrome, even in atypical patient populations. Importantly, our case demonstrates that anakinra can be both effective and well tolerated in the context of pregnancy-associated disease flares triggered by SARS-CoV-2 infection, in accordance with current EULAR recommendations. Further prospective studies and registry data are warranted to better characterise disease behaviour and optimise treatment strategies in women of reproductive age affected by this rare autoinflammatory condition.

Notes

Informed consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Use of AI: The authors used AI-assisted tools solely for language editing and writing improvement. All scientific content and conclusions are the responsibility of the authors.

Financial disclosure

The authors did not receive any financial support for the preparation of this manuscript.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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