

Schnitzler syndrome, a rare autoinflammatory disease. Complete response to IL-1 blockade

Paola Faggioli,¹ Antonio Tamburello,¹ Lucia Roncoroni,² Antonino Mazzone¹

¹Internal Medicine Unit; ²Pathology Unit, Legnano Hospital, ASST Ovest Milanese, Legnano (MI), Italy

Abstract

The Schnitzler syndrome (SCS) is a rare, late-onset acquired autoinflammatory syndrome often underdiagnosed. The diagnosis is based on the Lipsker and recently on validated Strasbourg diagnostic criteria (chronic urticarial rash, monoclonal gammopathy, intermittent fever, arthritis, arthralgia, bone involvement, hepatomegaly, splenomegaly, lymphadenopathy, dermal infiltration of neutrophils and laboratory markers of inflammation). Conventional therapies including anti-histamines, anti-inflammatory drugs, corticosteroids and immunosuppressive drugs that are usually ineffective. Recently the gold standard therapy of SCS are considered IL-1 blocking agents as anakinra, canakinumab, rilonacept that led to a significant control of clinical symptoms, even if a relapse could appear at suspension of the treatment. We report a case of a 63-year-old man with a recent diagnosis of SCS - after 6 years of symptoms of disease - refractory to several conventional immunosuppressive therapies and treated with anakinra, with sustained remission of clinic manifestations during treatment at 24 months of follow up.

Introduction

Schnitzler syndrome (SCS) is rare, orphan disease first described in 1972 by Liliane Schnitzler.¹ In 2001, Lipsker *et al.*² suggested diagnostic criteria, revised in 2012 and known as *Strasbourg criteria*.³ They include two obligate criteria (chronic urticarial rash, monoclonal IgM or IgG) and at least one of minor criteria (recurrent fever >38° unexplained, abnormal bone remodeling with or without bone pain, neutrophilic dermal infiltrate on skin biopsy, leucocytosis or/and elevated CRP). Recently *Strasbourg Criteria* have been validated with high sensibility and specificity by a long-term multicentric real life study.⁴ The SCS is rare and there are few

reports published in literature,^{5,6} in fact Gusdorf and Lipsker recently reported in a review only 300 adult cases in literature.⁷ Mean age at the clinical onset is 52-55 y, with male predominance (ratio M/F 1.67) often is present a delay to diagnosis between 3.7-5 y, and no pediatric cases or ethnic predominance have been reported.^{8,9}

The etiology of SCS remains unclear, but elevated levels of proinflammatory cytokines as IL-1 with anti-IL-1 antibodies¹⁰ and elevated levels of IL-6, IL-2 receptor and VEGF suggest a cytokines pathway dysregulation.^{11,12} Furthermore the presence of fever of unknown cause, cutaneous neutrophilic infiltrate and activation of *NLPR3* gene mutation in a few subgroup of patients - as demonstrated in autoinflammatory cryopyrinopathies -, neutrophilia, increase of IL-1 levels, activation of inflammasome by IL-18,¹¹ suggest that SCS could be an acquired autoinflammatory syndrome of adults. Similarly to autoinflammatory syndromes SCS benefit of treatment with anakinra, a recombinant IL-1ra inhibits the binding of IL-1a and IL-1b receptors or other IL-1 blockades.¹³⁻¹⁵ Prognosis of SCS depends on progression to hematological malignancy, as lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, multiple myeloma, marginal zone B-cell lymphoma, whose incidence are higher than the observed in MGUS (45-56%), or amyloidosis, but the data published are underestimated.¹⁶

Case Report

A 63-year-old Caucasian man, affected by arterial hypertension, at age of 57 years, developed many febrile episodes (>38.5°) associated with cutaneous rash diagnosed as urticaria and treated with systemic steroids with remission of fever, but persistence of recurrent itchy rash at the trunk and limbs. A diagnosis of undetermined chronic vasculitis was performed, without cutaneous biopsy or other clinical criteria. At 59 years he developed a mild monoclonal gammopathy IgM K (0.9 g/dL). He underwent to two bone marrow biopsies (BMB) in the same year, negative for hematological malignancies and fever and rash disappeared for 6 months under steroid therapy. At 61 years fatigue, intermittent fever (>38°), weight loss (6 kg in 2 months), diffuse lymphadenopathy and rash on the trunk and on the arms appeared. An elevation of ESR (66 mm/h) and CRP (8.6 mg/dL nv >5), and neutrophilic leukocytosis were present. Common infectious diseases and lymphoproliferative disease were excluded (viral and bacterial serological

Correspondence: Antonino Mazzone, UO Internal Medicine, Legnano Hospital, ASST Ovest Milanese, via Papa Giovanni Paolo II, 20025 Legnano (MI), Italy.
Tel.: +39.0331449305 - Fax: +39.0331449441.
E-mail: antonino.mazzone@asst-ovestmi.it

Key words: Schnitzler syndrome; autoinflammatory disease; IL-1 blockade.

Conflict of interest: the authors declare no potential conflict of interests.

Received for publication: 2 August 2017.
Accepted for publication: 15 November 2017.

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Clinics and Practice 2017; 7:1018
doi:10.4081/cp.2017.1018

tests, FDG-PET, lymph node biopsy, BMB) and he was discharged with diagnosis of chronic lymphadenitis and steroid therapy (prednisone 50 mg daily followed by tapering) with benefit (disappearance of fever and lymphadenopathy, but persistence of skin lesions). After 6 months FDG-PET and a computed tomography (CT) showed a hepatic infiltrative lesion of 3 cm diameter and splenomegaly. Fine needle liver aspiration was indicative of neutrophilic infiltrate compatible with *probable systemic inflammatory disease*. A therapy with cyclosporine 200 mg/daily started with benefit on fever and cutaneous lesions, but after 4 months fever appeared again, cyclosporine was stopped and azathioprine 100 mg daily and prednisone 10 mg/daily were introduced with benefit. In November 2014 at 63 years he was hospitalized for increasing of urticarial skin lesions (Figure 1), appearance of diffuse bone pain, myalgias and arthritis of knees and wrists, remitting fever, diffuse lymphadenopathy, leukocytosis (WBC 19,000/mm³ neutrophil cells 90%), elevated CRP (24 mg/dL), ESR (80 mm/h) and increase IgMk (2.3 g/dL). A cutaneous biopsy was performed and showed a neutrophil infiltrate in dermis without signs of vasculitis. A BMB and a lymphonodal biopsy excluded lymphoproliferative diseases (Figure 2). Finally a diagnosis of SCS was performed in according to Strasbourg diagnostic criteria. A treatment with anakinra subcutaneously 100 mg/daily started. Seven days after anakinra therapy an important clinical improvement was achieved with disappearance of fever, arthritis, skin lesions, regression of leuko-

cytosis, inflammatory markers. A mild reduction of monoclonal component IgMk was observed (1.7 g/dL). The therapy was well tolerated without adverse reactions or side effects except a mild flitting erythema in side injection. The patient tapered the steroid until 5 mg/daily of prednisone. Three months after of starting therapy the patient was in complete clinical remission of the disease. Serological markers of inflammations were normalized, but a mild monoclonal component IgMk remained present (1.6 g/dL). We decided to stop temporarily anakinra, but ten days after, skin rash and mild fever (37.8°C) reappeared, so anakinra was resumed and maintained in therapy once a day. After 12 months the patient remained asymptomatic, then anakinra was administered 3 times a week. At 24 months of follow up, under anakinra therapy the patient persists asymptomatic (see photo 3), blood inflammation indices are normalized, monoclonal component IgMk is stable (1,5 g/dl) and no evolution on myelo-lymphoproliferative disease was observed. The patient gave permission to reproduce his photos, although he could not be identifiable.

Discussion

There is none codified therapy for the Schnitzler syndrome. Many immunosuppressive treatments had been used as colchicine, corticosteroids, azathioprine, cyclosporine, but little effective and only on symptoms. Similarly to other autoinflammatory syndromes, IL-1 blocking agents are the most effective therapies in SCS and especially the IL-1 receptor antagonist anakinra. Anakinra is the most commonly used agent to treat Schnitzler syndrome and recommended as of first choice treatment by a consensus conference of expert in 2012.⁷ So many authors suggest that the treatment with anakinra or others IL-1 blockade represent the gold standard in treatment of SCS when the conventional therapies are inefficacies.¹⁷ Unfortunately the administration of anakinra is daily, but unlike the others IL-1 blockades its half-life is short (6 h), does not strongly depresses the immune system and the side effects are tolerable. All the IL-1-blockade drugs, are strong effective in regulating inflammation, but they show a little effect on B cell and plasmacells on reducing monoclonal paraproteinemia, possible expression of a not downregulable.

Chronic cytokine pathway activation

Despite treatment with anakinra leads to a clinical remission, there is no evidence



Figure 1. Urticarial skin lesions at the diagnosis.

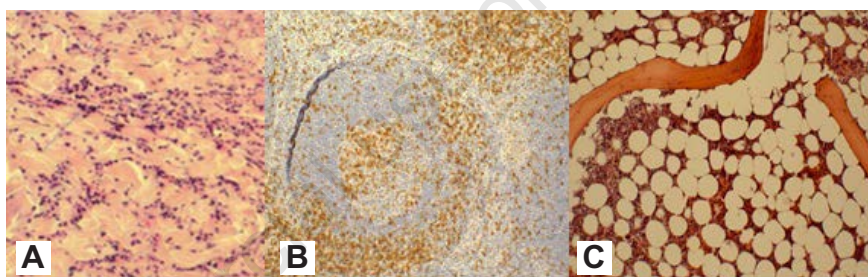


Figure 2. Histological aspects of: A) skin lesions biopsy; B) lymphonodal biopsy; C) bone marrow biopsy.



Figure 3. Complete regression of cutaneous lesions after 24 months of anakinra therapy.

that this drug prevents progression to lymphoproliferative disorders, although anakinra is usually considered safe in neoplastic syndrome.¹⁸ Moreover, the lack of response to IL-1 blocking therapies should lead to reconsider the diagnosis of Schnitzler syndrome and a rapid response to anakinra could also become a diagnostic criteria.

Other IL-1 blocking therapies are employed in randomized placebo-controlled multicenter studies as canakinumab and rilonacept.¹¹ These studies showed a significant efficacy versus placebo in reducing clinical and laboratory findings, but also an increase of adverse events such infections injection-site reactions, neutropenia (due perhaps to their higher half-life).

The treatment with IL-1 blocking therapies leads to complete remission in about 83% of pts affected by SCS.¹⁹

However, some patients do not respond to anti-IL-1.²⁰ In this cases anti-IL-6 treatment such as tocilizumab can be proposed, together to a reconsideration of Schnitzler syndrome diagnosis.

Conclusions

The Schnitzler syndrome is now considered among the rare acquired autoinflammatory syndromes, and often the diagnosis is difficult, delayed and *per exclusionem*. The role of monoclonal paraproteinemia remains unclear, as the possible evolution to hematological malignancies. IL-1 blocking agents remain the most effective therapies and the first choice therapy, and particularly anakinra.⁷ Despite treatment with anakinra leads to a clinical remission, there is no evidence that this drug prevents or promotes progression to lymphoproliferative disorders, and a strictly follow up is recommended in patients affected by Schnitzler syndrome.

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