Complete Remission of Schnitzler Syndrome and Waldenström Macroglobulinemia under Rituximab-Cyclophosphamide-Dexamethasone

Achille Aouba a, g Claire Pressiat b Maria Pricopi a Sophie Georgin-Lavalie f François Boue a Maria-Angela Lievre-Castilla c Anne Marfaing-Koka d Sophie Prevot e Audrey Decottignies b

Departments of a Clinical Immunology and Internal Medicine, b Pharmacy, c Nuclear Medicine, d Hematology and e Pathology, Hôpital Antoine Béclère, AP-HP, Université Paris 11, Clamart, d Department of Internal Medicine, Hôpital Tenon, AP-HP, Université Paris 6 Pierre et Marie Curie, Paris, and g Department of Internal Medicine, CHU Côte de Nacre, Caen, France

Key Words
Anakinra · Cyclophosphamide · Rituximab · Schnitzler syndrome · Waldenström macroglobulinemia

Abstract
In Schnitzler syndrome, which is mostly diagnosed with a low and asymptomatic monoclonal peak, anakinra has always exhibited a complete but only transient control of the auto-inflammatory signs, which are induced by interleukin (IL)-1 auto-activation. We focused on the treatment of a case of Schnitzler syndrome with moderate macroglobulinemia peak. Anakinra failed to improve the severe inflammatory anemia and the dysglobulinemia, but rituximab-dexamethasone-cyclophosphamide chemotherapy alone allowed a complete response. The correlation between the clinical, pro-inflammatory cytokines and dysglobulinemia complete controls with chemotherapy proves the following: (1) the dual action of this treatment in both the auto-inflammatory and dysglobulinemia components of the syndrome and (2) a different but entangled cytokine network in the pathogenesis of the auto-inflammatory and dysglobulinemia components of the syndrome.

Introduction
Schnitzler syndrome (ScS) is a rare and probably underdiagnosed entity, which includes an auto-inflammatory component and a dysglobulinemia component with mostly an IgM-κ monoclonal peak, typically in a small amount [1, 2]. Initial diagnosis of ScS can be difficult and delayed. Its spontaneous evolution can lead to the development of lymphoproliferative disease (10–15% per year), including Waldenström macroglobulinemia (WM), as observed in the princeps case [3].

Because of its unknown physiopathology, its treatment remains unclear and only symptomatic. The different conventional therapeutic approaches (corticosteroids, interferon, pefloxacin, various disease-modifying anti-rheumatic drugs, and immunosuppressants) get highly variable responses, often partial and transient [4, 5]. Given the demonstrated involvement of interleukin (IL)-1 in the pathogenesis of the auto-inflammatory component, the logical proposal of anakinra shows a quasi-permanent and dramatic but only suspensive response in all symptoms of ScS [6, 7].

We hereby report the dual, rapid and complete efficiency of a treatment with rituximab, cyclophosphamide and dexamethasone (RCD) in a case of ScS associated with moderate-to-high WM peak, for which a first-line treatment with anakinra allowed control of only auto-inflammatory signs. We then discuss the pathogenic difference between these two associated nosological entities in the light of the two therapeutic evolutions.
A 63-year-old woman, without medical history, was hospitalized for inflammatory arthralgias of peripheral large joints, thoracic pruriginous maculopapular lesions (fig. 1a) and slight asthenia lasting for 3 years. Physical examination found two left axillary lymph nodes of 2 cm.

Laboratory investigations showed aregenerative normocytic anaemia (10.2 g/dl), neutrophilia (11 g/l), accelerated erythrocyte sedimentation rate (64 mm) and C-reactive protein (CRP) increase (54 mg/l). Serum protein electrophoresis and immunofixation showed a monoclonal IgM-λ peak to 17 mg/dl. Free light chain dosage showed an increase of that same light chain to 90%.

Cutaneous biopsy showed a neutrophilic pericapillary urticaria (fig. 1b). Bone marrow smear showed a lymphoplasmacytic infiltration of 21% and a slight excess of morphologically normal mast cells, all findings corresponding to WM. Lymphocyte immunophenotyping showed no abnormality.

Thoraco-abdominal-pelvic CT showed a homogeneous hepatomegaly and some mediastinal and mesenteric lymphadenopathy of 1.5–2 cm. Joint X-rays were normal, but bone scan showed symmetrical pathological uptakes of knees, ankles, wrists, and elbows (fig. 1c). The diagnosis of ScS was retained and, due to non-clear active evolution of the dysglobulinemia, anakinra (100 mg/day, s.c.) was proposed, allowing a dramatic and rapid control of urticaria and arthralgias. In contrast, after 3 months of treatment, CRP levels, lymphadenopathy and hepatomegaly exhibited only a partial decrease, and the anaemia and asthenia worsened, while the monoclonal peak remained stable (fig. 2a).

RCD treatment was then decided, showing a rapid and complete remission of both ScS and WM signs, including the iconographic features (fig. 1d).

Figure 2a and b shows favourable and rapid evolution of haemoglobin, CRP and monoclonal peak from the onset of RCD to the 6-month follow-up. Furthermore, correlated normalization of IL-1β, IL-6 and CRP levels was observed at complete remission of both auto-inflammatory and lymphoproliferative signs under RCD, in contrast of that seen under anakinra (table 1).

Discussion

The prognosis of ScS depends on the occurrence of lymphoproliferative complications from the dysglobulinemia component such as lymphoma, IgM myeloma or WM [3, 8].

Two major points make this clinical case a unique occasion to discuss and make assumptions about the differential pathophysiology of the two components: firstly, the advanced stage of the dysglobulinemia with active WM at the time of ScS diagnosis and, secondly, the dissociated then parallel responses of the components, respectively, with anakinra and RCD. Indeed, in the literature the vast majority of ScS diagnosed are associated with indolent and/or asymp-
tomatic low-peak dysglobulinemia (monoclonal immunoglobulin around 1–5 mg/dl). Therefore, the treatment with anakinra allows almost always perfect and dramatic control of all symptoms only related to the auto-inflammatory component of ScS [5, 7]. Some authors have then suggested that the response to anakinra could be used as a diagnostic criterion of ScS [8]. A failure of anakinra should lead one to reconsider the diagnosis of ScS, except for its association with active moderate-to-high peak WM and considering that the failure should be partial. Indeed the outcome of anakinra in our case should be analysed, on the one hand, as a good response of the probable exclusive auto-inflammatory manifestations (cutaneous and articular signs) and, on the other hand, as a partial response of other involvement for which the pathogenic role of WM was probably predominant (anaemia, CRP increase, tumoral syndrome).

The pivotal role of IL-1β in the pathogenesis of ScS is demonstrated in vitro (culture of myelomonocytic cells) and in vivo, notably with the continued effectiveness of anakinra, which is a specific inhibitor of this cytokine [9]. Conversely for WM, the pathogenic pro-inflammatory roles of the activation of nuclear factor kappa-B (NF-κB) and IL-6 are currently admitted [10]. The cytokine profiles of our case are in correlation with these pathogenic hypotheses. Besides the direct activation of IL-6 production by IL-1β, the direct production of IL-6 [11] by the NF-κB signalling network ac-
Correlated increased levels of IL-1β, IL-6 and CRP at diagnosis; at the time of partial response concerning only the auto-inflammatory signs under anakinra (at the 8th week of treatment), IL-6 and CRP levels remained increased, whereas IL-1β level normalized. At complete remission (at the 6th monthly treatment of RCD) auto-inflammatory and lymphoproliferative signs and the values of all inflammatory parameters were within normal values. TNF-α values were always normal. Bold and non-bold sections correspond to high and normal values, respectively.

**Conclusion**

This case suggests both entanglement and difference in the leading cytokine profile inducing the systemic inflammatory syndrome, which is common in ScS and possible in WM alone. Given that the effect of IL-1 blockade is only suspensive and probably does not modify the natural evolutionary risk of the background lymphoproliferative component, partial efficacy or secondary therapeutic escape under anakinra should be considered in ScS. This should lead to a reappraisal of the diagnosis and an assessment of the malignant progression of the associated dysglobulinemia. Therefore, earlier or first-line chemotherapy in curative intent should be discussed in the context of ScS when some symptoms are related to an overt lymphoproliferative disease, whatever the rate of the monoclonal spike.

**Disclosure Statement**

The authors have no conflicts of interest to declare.

---

**References**

1 Schnitzler L: Lésions urticariennes chroniques permanentes (érythème pétaloïde?). Cas clinique 46B. Journée dermatologique d’Angers, October 28, 1972.


8 Lipsker D: The Schnitzler syndrome. Orphanet J Rare Dis 2010;5:38.


