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Long Term Efficacy of BID Administration of Anakinra and Canakinumab in Two Refractory Cases of Schnitzler Syndrome

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Abstract

Introduction: Schnitzler Syndrome (SS) is a rare, systemic acquired autoinflammatory syndrome. Its diagnosis is challenging due to confounding factors with systemic autoimmune diseases. In 2013 Strasbourg criteria for SS were validated. Until 2005, no effective therapy was available. The efficacy of IL-1 blockers is supported by several case reports as well as by some clinical studies; however, to date, they are not approved for SS.

Cases: Here we describe two cases of SS who did not respond to daily anakinra, efficaciously treated with anakinra bid and canakinumab, respectively. The two cases also evidence how SS diagnosis can be difficult, mimicking different pathologies.

Conclusion: SS is a complex disease, in which diagnostic process could frequently be long and not linear. A better knowledge of the disease and the possibility to use IL1 blockers modified disease outcome, leading to the achievement of persistent clinical remission.

Keywords: Schnitzler syndrome; Anakinra; Canakinumab

Introduction

Schnitzler Syndrome (SS) is a rare, systemic acquired autoinflammatory syndrome. Its diagnosis is challenging due to specific manifestations, such as fever, arthralgias, increase of inflammatory markers and a wide clinical spectrum, similar to other systemic diseases such as vasculitides, monoclonal gammopathy related diseases, iper-IgD syndrome, acquired C1-inhibitor deficiency, adult Still disease [1]. Therefore, differential diagnosis is essential in order to recognize and promptly treat the disease. In 2013, Strasbourg criteria for SS were validated to help clinician in the diagnosis [2]. Until 2005, different treatment drugs (methotrexate, azathioprine, cyclophosphamide, steroids, NSAIDs, colchicine, immunoadsorption, intravenous immunoglobulins, antihistamines, phototherapy, TNF inhibitors and rituximab) have been tried to resolve systemic

inflammation, with low efficacy. The use of IL-1 receptor antagonist, anakinra, has radically modified the therapeutic scenario, changing the outcome of the disease. The efficacy of IL-1 blockers is supported by several case reports as well as by some clinical studies; however, to date, they are not approved for SS [3-5].

In this paper, we describe two cases of patients who had no response to daily administrations of anakinra but whose disease proved to be efficaciously treatable with anakinra BID and canakinumab, respectively.

Informed consent was obtained by the two patients.

Case Presentation

Case 1

A 46-year-old Caucasian man was evaluated c/o Department of Rheumatology "ASST-Fatebenefratelli-Sacco" in Milan, with the clinical suspicion of urticarial vasculitis, based on recurrent fevers, urticarial rash, overall body itching and arthralgias. During the two years before his admission, laboratory tests showed CRP 98.3 g/L, ESR 38.6 mm/h, monoclonal gammopathy IgM-K 4.1 g/dL, neutrophilic leukocytosis (20000 leukocytes/µl, 87% neutrophils). Abdominal US and chest X-ray were normal; bone marrow aspiration and biopsy were negative for malignancies. Cutaneous biopsy showed a perivascular neutrophilic infiltration. Infectious markers and autoimmunity were negative. The patient had been treated with cyclosporine, azathioprine, iv-Ig, mycophenolate; however, they had been interrupted either for inefficacy or adverse events. An improvement on itching and arthralgias was obtained by using NSAIDs. Prednisone partially controlled rash and fever; recurrence occurred for any dosage lower than 37.5 mg/day.

At clinical examination, we detected urticarial rash at limbs and arthritis on his knees, ankles and wrists (Figure 1) (Table 1). SS was diagnosed by using Strasbourg criteria and subcutaneous anakinra (100 mg daily) was started. After a month, a resolution of arthritis and leukocytosis occurred whilst urticarial rash and itching recurred 12 hours after injection. We increased the dosage to 100 mg BID, followed by a decrease of the monoclonal component to 1.8 g/dL. A complete suspension of steroids/NSAIDs was possible after 2 months of tapering. Six months later, we tried to taper anakinra to 100 mg daily, but a recurrence of urticarial rash and itching was observed; the BID administration was restored without flares within five years of follow-up.

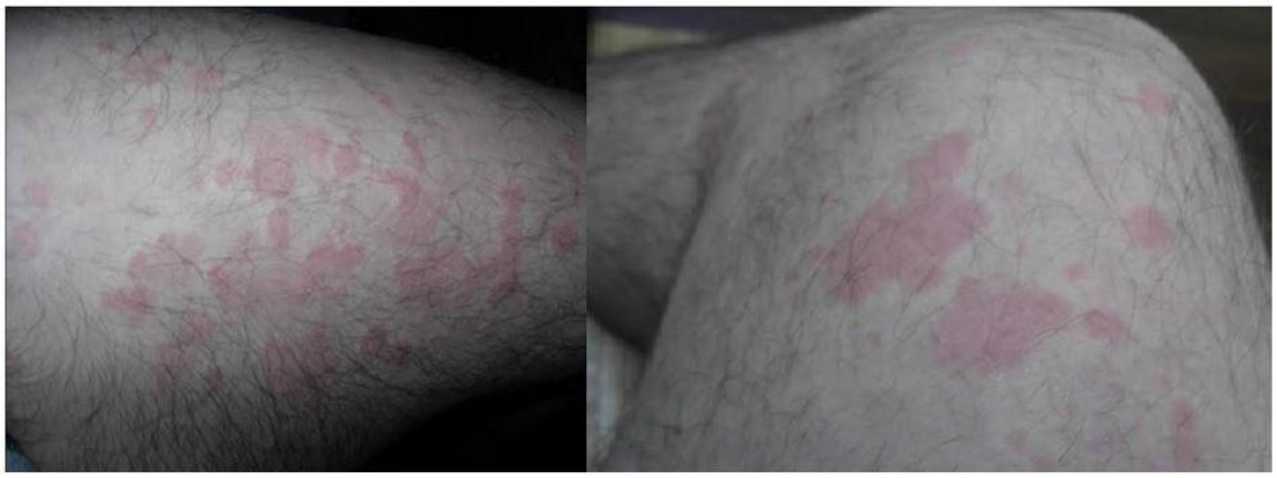

Figure 1: Lower limbs urticarial skin rash.

Table 1: Description of clinical and laboratory findings and treatment course of the two patients.

Case 1	
Clinical examination	**Laboratory tests**
- urticarial rash at limbs - arthritis of knees, ankles and wrists	- Neutrophilic leukocytosis - increase of inflammatory markers (CRP 98.3 g/L, mean ESR 38.6 mm/h) - monoclonal gammopathy IgM-K 4.1 g/dL
Treatment	**Results**
- subcutaneous anakinra 100 mg daily	- arthritis remission - leukocytosis regression - partial resolution of urticarial rash and itching
- increase of anakinra dosage to 100 mg twice a day	- reduction of monoclonal component to 1.8 g/dL - complete clinical and laboratory remission
June 2020: Persistent remission	
Case 2	
Clinical examination	**Laboratory tests**
- MCP, knees, ankles arthritis - Urticarial papular rash - Palpable axillary and latero-cervical lymph nodes	- Neutrophilic leukocytosis (WBC 13980/µl, N 12260/µl) - increase of inflammatory markers (CRP 80,9 mg/L, ESR 76 mm/h) - Monoclonal component IgGK
Treatment	**Results**
October 2017: anakinra 100 mg 1fl SQ/daily	- improvement of arthritis, hypergammaglobulinemia normalization and reduction of CRP and ESR - persistence of papular rash
April 2017: anakinra 100 mg twice a day Steroid dosage was maintained within the range of 5-10 mg of PDN, considering patient's cardiological history	PDN tapering attempt but recurrent rash flares at dosages lower than 7,5 mg
September 2018: canakinumab 150 mg SQ every 8 weeks and slow PDN tapering to 2,5 mg	complete resolution of symptoms and normalization of WBC and acute phase reactants
June 2020: Persistent remission	

Case 2

A 57-year-old Caucasian man was visited in the Department of Rheumatology, "AOU Citta della Salute e della Scienza of Turin" Hospital in 2017. In 2007, tibio-tarsic and metacarpo-phalangeal arthritis, persistent low-grade fever, scalp rash and increased inflammatory markers appeared. Infectious markers and autoimmunity were negative. A seronegative arthritis was diagnosed and he was treated with methotrexate, which was suspended for adverse events. Sulfasalazine and chloroquine were tried and suspended for adverse events as well. Antibiotics and cyclosporine had to be suspended for inefficacy. In 2008, vasculitis or SS were suspected whereas a skin biopsy was inconclusive. In order to control the rash, dapsone was introduced but it was suspended after 6 months for inefficacy; prednisone 12.5 mg daily allowed a partial resolution. In 2012, in an effort to control joints manifestations, adalimumab 40 mg/2 weeks was prescribed for 6 months without efficacy. A Positron Emission Tomography (PET) revealed an uptake at the major groups of lymph-nodes but bone marrow and 2 lymph-node biopsies were negative. In 2013, a new PET showed both splenomegaly (maximum diameter: 20 cm) and lymph nodes uptake. In May 2014, the patient autonomously interrupted steroids for wellness; however, their reintroduction appeared to be mandatory (mean dosage 12.5 mg/daily) in September 2014, since a cutaneous flare occurred. For the further increase of his splenomegaly, splenectomy was performed in September 2017; during this time, the patient was diagnosed with an NSTEMI which was strictly

treated with a triple coronary by-pass. Due to cardiovascular complications, steroids were interrupted; however, a papular rash and arthritis flare appeared. The dermatologist suspected erythema elevatum diutinum, based on hypergammaglobulinemia and papular rash; however, in the past dapsone proved to be ineffective. In 2017, we evaluated the patient for the first time. Given the Strasbourg criteria, we diagnosed SS (Table1). Information about clinical course and treatment are summarized in table 1. In October 2017, anakinra 100 mg daily plus prednisone 7.5 mg/daily were introduced with improvement of arthritis, inflammatory markers and hypergammaglobulinemia but persistence of the rash. No variation after the increase of anakinra dosage to 200 mg daily was observed and steroid tapering under 7.5 mg proved to be impossible due to rash recurrences. In September 2018, we switched the patient to canakinumab 150 mg SQ every 8 weeks. The patient showed a complete and persistent remission as the steroids were reduced to 2,5 mg without flares.

Discussion

Schnitzler syndrome is a rare acquired autoinflammatory syndrome. The pathogenesis of the disease is not clarified yet. It has been hypothesized that different alterations in innate immunity pathways could be implied in the initiation of the disease. [1,2,6]. IL-1β and IL-6 were found to be increased in peripheral blood mononuclear cells of SS patients stimulated by lipopolysaccharide, in comparison to healthy controls, suggesting an increased inflammasome activity similar to other autoinflammatory disorders [6]. The role of IL-1 pathway in monoclonal gammopathy has not been elucidated [2]. IL-1 blockers efficacy in disease treatment has been emerging during the last decades. Anakinra, recombinant IL-1 receptor antagonist and canakinumab, human anti-IL-1β monoclonal antibody, are nowadays the only effective drugs for SS patients [1-6].

In the 1st case we described, anakinra standard dosage was unable to control all inflammatory symptoms, while the patient achieved complete remission with the BID prescription. It is still unclear if IL1 blockers could prevent the development of lymphoproliferative disorders associated with monoclonal gammopathy. A long follow-up is useful to control the disease course and to better understand other advantages linked to IL1 blockers.

In the 2nd case we highlighted the challenging nature of the diagnostic process of SS, with consequent delay in the therapeutic approach. In this case, disease symptoms were refractory to anakinra treatment, requiring canakinumab administration. A recent systematic review points out that canakinumab is effective in inducing a complete response in the majority of SS patients [7].

Conclusion

SS should be suspected in patients with urticarial rash in presence of one or more of the following symptoms: fever, fatigue, joint pain, enlarged lymph nodes, splenomegaly, neutrophilic leukocytosis, increased inflammatory markers, monoclonal gammopathy. IL-1 blockers rapidly provide persistent clinical response in the majority of patients; in refractory cases, standard dosage could be ineffective or the first course of IL-1 block could produce only a partial remission.

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