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Case Report

Diagnostic Delay of Schnitzler Syndrome in an Atopic Patient

I Eguíluz-Gracia[1]*, T Robledo-Echarren[1], C Escobar-Bolaños[1], R Martínez[2], P Villarroel[3], M Fernández-Rivas[1], C Martínez-Cócera[1]

1Allergy Department and IdISSC, Hospital Clínico San Carlos, Madrid (Spain)
2Hematology Department, Hospital Clínico San Carlos, Madrid (Spain)
3Emergency Unit, Hospital Clínico San Carlos, Madrid (Spain)

***Corresponding author:** I Eguíluz-Gracia, Hospital Clínico San Carlos, Allergy Department, c/ Prof. Martín Lagos s/n, 28040 Madrid, Spain

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Abstract

Schnitzler syndrome (SS) is a rare auto-inflammatory disorder with recurrent episodes of urticarial rash and fever and monoclonal IgM gammopathy as the most common findings. SS has been associated to a high rate of AA amyloidosis and lympho-proliferative disorders but not to any other immune mediated disease. We present a 56 year-old woman with respiratory allergy and pressure urticaria that started to develop episodes of urticarial rashes and fever together with diffuse arthralgias. The blood analysis revealed leukocytosis and monoclonal IgM paraproteinemia. Despite fulfilling criteria for definitive diagnosis of SS, she was not diagnosed and treated with anti-interleukin-1 therapy until two years later. The presence of atopic pre-existing conditions might have contributed to this diagnostic delay. With this report we aim to remark that auto-inflammation and allergy can co-exist in the same patient.

Keywords: Schnitzler syndrome; Allergy; Interleukin 1; Urticaria; Gammopathy

What is already known about this topic?

Schnitzler syndrome (SS) is a rare auto-inflammatory disorder with recurrent urticarial rash and fever as clinical hallmarks and monoclonal IgM (or IgG) gammopathy as most relevant analytical finding. Little is known about SS etiology apart from the quick and significant improvement that most patients experience upon initiation of anti-IL-1 therapy. Additionally, AA amyloidosis and lympho-proliferative disorders are more frequent in SS patients than in the general population.

What does this study add?

This case report describes a patient with SS who despite fulfilling criteria for definitive diagnosis was only diagnosed two years later. Pre-existing respiratory allergy and a pressure urticaria might have contributed in this case to the late recognition/diagnosis. We would like to highlight the possibility of the coexistence of both immune mediated disorders –allergy and auto-inflammation-, since the establishment of the diagnosis of SS is crucial for the start of specific therapy and the early recognition of its potential associated co-morbidities.

Main Text

Chronic or recurrent urticarial rashes are frequently a challenge for clinicians in terms of classification and management. A large number of these patients will be diagnosed of chronic idiopathic urticaria (CIU) after negative thorough studies [1]. However, patients with other diseases can develop rashes that resemble CIU and are thus prone to misdiagnosis and treatment delay.

We present a 53 year-old woman with a long-lasting history of seasonal allergic rhino-conjunctivitis who started to develop episodes of prutitic hives in skin areas shortly after exposure to pressure. She was diagnosed of physical urticaria and successfully treated with oral antihistamines (OA). Three years later, after a period of emotional stress, she began to present recurrent episodes of less pruritic urticarial rashes (UR) with trunk predominance (respecting the face) followed by abdominal pain and fever up to 39ºC. The rash preceded several days the appearance of fever, lasted for 1 week, left no residual lesion and did not respond to OA. These episodes were sometimes accompanied by diffuse joint pain with no swelling. The physical examination during symptomatic periods did not reveal palpable adenopathies, organomegalies or any other abnormalities apart from the described skin lesions. An X-ray exam performed during an active phase did not show any bone alteration but in the blood analysis taken at the same time, an elevation in leukocytes (15000 cells/mm^3) with marked neutrophilia (88%) together with increased levels of C reactive protein (CRP) (9.86 mg/dL) and IgM (318 mg/dL) were found. Other serum biomarkers such as creatinine, hepatic enzymes, electrolytes (including calcium), ferritin, all clinically relevant auto-antibodies, complement factors and absolute values of IgA and IgG remained in the normal range or were negative. A biopsy of a skin lesion obtained during a flare-up excluded vasculitis and did not show neutrophilic infiltration. The analysis of the IgM gammopathy revealed a monoclonal peak and a bone marrow (BM) biopsy was decided at this point. The BM immune-phenotyping showed a patchy infiltration by plasma cells bearing monoclonal IgM with kappa light chain (representing the 0.044% of the total cellularity). A positron emission tomography-CT scan did not reveal any signs suggestive of malignancy. All these exams excluded the possibility of a hematologic neoplasm. Treatment with non steroidal anti-inflammatory drugs was prescribed for the symptomatic periods and a close follow-up was established.

During the following year the frequency and severity of symptomatic periods significantly increased. Two treatment cycles with oral corticosteroids and chloroquine were unable to control the disease and the patient was finally referred to our Allergy Outpatient Clinic. Basal tryptase was 6.92 µg/L. Adult-onset

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Still disease, urticarial and cryoglobulinemic vasculitis, systemic lupus erythematous, mastocytosis, monoclonal gammopathy of unknown significance, POEMS (Poly-neuropathy, Organomegaly, Endocrinopathy, M-protein and Skin abnormalities) syndrome, Waldenström macroglobulinemia and delayed pressure urticaria were ruled out after careful re-evaluation of both clinical history and the mentioned complementary studies. Periodic fever syndromes (PFS), also referred as inherited auto-inflammatory syndromes, closely resembled the clinical picture of our patient, even though PFS tend to appear in younger individuals and do not usually show monoclonal paraproteinemia [2]. These observations guided us to the diagnosis of Schnitzler syndrome (SS), which is a paradigm of late in life acquired auto-inflammatory disorders. Monoclonal IgM, recurrent episodes of fever, UR and leukocytosis are sufficient for the definitive diagnosis of SS [3].

Several anti-inflammatory drugs and systemic immunosuppressors failed to provide symptomatic relief in SS patients [3]. However, since some PFS such as cryopirin-associated periodic syndromes (CAPS, a subgroup of PFS) respond to anti-interleukin 1 (IL-1) therapy [4], several drugs targeting this cytokine have been used in SS patients [5-7]. Most of the published studies show a dramatic improvement of both clinical and analytical parameters in SS patients following this therapeutic approach [3]. In our case the quality of life of the patient was significantly affected and the initiation of anti-IL-1 therapy was decided. Treatment with 100 mg/day of subcutaneous anakinra (Kineret®, Amgen, Thousand Oaks, CA, USA), a competitive inhibitor of IL-1 receptor [8], was started during a symptomatic phase of the disease. The patient was informed about off-label use of the drug and provided written consent. Anakinra therapy produced an immediate (< 24 hours) resolution of both fever and UR, whereas the normalization of leukocyte counts and CRP was achieved within a week. On the other hand, IgM levels did not decrease with this measure. Since spontaneous remissions of SS have been described [9], after 18 months of daily anakinra therapy with optimal clinical control, the discontinuation of the drug was decided. Forty-eight hours after the administration of the last dose, the patient developed a new episode of fever, nausea and UR that did not respond to a combination of high dose oral corticosteroid and antihistamines. The re-introduction of the therapy produced an immediate resolution of signs and symptoms. To date the patient has been on anakinra treatment for 30 months showing persistent elevated IgM (up to 1715 mg/dl) together with excellent clinical control and no adverse side effects. The inability of anti-IL-1 therapy to decrease paraproteinemia in SS individuals had been previously reported [7]. The patient continues nowadays under close follow-up by a team of physicians including allergists, haematologists and internits. This multi-disciplinary evaluation is crucial for patients with uncommon diseases affecting several organs and systems.

Even though the clinical similarities with PFS provide some clues, the etiology of SS is still largely unknown. PFS comprise CAPS (like Muckle-Wells syndrome or familial cold anti-inflammatory syndrome) and other entities like hyper-IgD syndrome [2]. These disorders are monogenic diseases with established mutations affecting the functionality of innate immune system. In CAPS, a mutation in *NALP3* gene determines the hyper-function of cryopirin, an innate immunity receptor. This abnormality leads to the exaggerate activation in antigen presenting cells and other cell subsets of the inflammasome, a complex formed by several intracellular proteins. This cellular machinery is responsible for the conversion of pro-IL-1β (and other cytokines) into their active forms [3]. IL-1β is a well-known pro-inflammatory and pyrogenic cytokine with key roles in many immune mediated diseases. Several clinical features of CAPS patients could be explained by this IL-1 β hyper-function. Even though a study from 2010 described a SS patient with a gain of function mutation on *NALP3* [10], in many of the case reports and series published to date an obvious genetic or immune link between inflammasome and SS is lacking. These observations might imply that the interaction of variable genetic factors (polymorphisms or mutations with variable penetrance) with (yet unknown) extrinsic triggers could lead to the development of the clinical and analytical picture that defines SS [11].

The pre-existing physical urticaria and respiratory allergy might have contributed to the late diagnosis in this patient, as skin symptoms could have been considered as manifestations of her atopic background. No association between allergy and auto-inflammation has been reported to date, but SS patients are more prone to AA amyloidosis and lympho-proliferative disorders than the general population [12]. Physicians taking care of patients with UR should be also aware of auto-inflammatory syndromes in order to improve patient's quality of life by an early initiation of the therapy, and also perform an early recognition of putative co-morbidities once the diagnosis is established.

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