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Schnitzler syndrome with cold-induced urticaria

Anil Kurian[1], *Jason K Lee*[2], *Peter Vadas*[2]

1. Department of Medicine, McMaster University, Hamilton, Ontario, Canada.
2. Division of Allergy and Clinical Immunology, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

Corresponding author:

Peter Vadas, MD, PhD, FRCPC
Director

Division of Allergy and Clinical Immunology, St. Michael's Hospital, Room 8-161, University of Toronto

Cardinal Carter Wing, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8

E-mail: *vadasp@smh.toronto.on.ca*

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Abstract

Background: Schnitzler syndrome encompasses monoclonal gammopathy, urticaria, inflammation, recurrent fever, bone pain and arthralgia, with occasional lymphadenopathy and/or hepatosplenomegaly. It is a rare condition with approximately 100 cases reported in the literature. To our knowledge, this is the first reported case of cold-induced physical urticaria with Schnitzler syndrome.

Main observations: A 43-year-old woman presented to an allergy and immunology clinic with a 7 year history of chronic urticaria, angioedema with anaphylaxis, monoclonal gammopathy and bone pain. Her urticaria was triggered by cooler temperatures and an ice cube test for cold induced urticaria was positive. In spite of aggressive therapies this patient remains symptomatic.

Conclusions: Schnitzler syndrome is under-recognized, particularly variants of the classical description of Schnitzler syndrome. Other diseases, especially those of hematologic origin, should be ruled out. This condition is largely refractory to conventional therapies, although novel treatments, such as interleukin-1 receptor inhibitor, may show promise.

Introduction

Schnitzler syndrome encompasses monoclonal gammopathy, urticaria, inflammation, recurrent fever, bone pain and arthralgia, with occasional lymphadenopathy and/or hepatosplenomegaly.[1,2] It is a rare condition with approximately 90-100 cases reported in the literature.[1-4] Thorough history and examination are necessary to rule out other diseases, especially those of hematologic origin. To our knowledge, this is the first reported case of cold-induced physical urticaria with Schnitzler syndrome.

Case

A 43-year-old woman presented to an allergy and immunology clinic in Dec 2009 with a 7 year history of chronic urticaria, angioedema, anaphylaxis, monoclonal gammopathy, self-reported weekly fevers, and bone pain. In 2002, she developed hives which were erythematous, raised, and pruritic papules resembling mosquito bites. The hives were associated with dermographism and recurred daily in a generalized distribution. The lesions were not burning or stinging.

In addition to the chronic urticaria, over the past 7 years she had approximately 150 multisystem anaphylactic reactions involving angioedema of her eyelids, lips, tongue, throat, hands and feet. Some of these reactions were associated with manifestations of upper and lower airway obstruction and a few were accompanied by syncope and chest pain but no palpitations or GI symptoms. Cold exposure has been a consistent trigger of the urticaria and angioedema. These episodes would respond to warming and typically last from minutes to a few hours. Ice-cold drinks and frozen foods have caused manifestations of upper airway obstruction. She avoids immersion in cool or cold water. There have been no other triggers of physical urticaria.

Family history was significant in that the patient's mother, maternal aunt, 2 sisters and 2 daughters all have cold induced urticaria. Review of systems revealed chronic numbness and tingling of her hands and lower legs, night sweats, decreased energy level and a tendency to bruise easily. She reported a "deep ache in her bones" for years but had refused to undergo a bone marrow aspirate, biopsy, or nuclear bone scan.

Physical examination was unremarkable and the patient showed no cutaneous manifestations of mastocytosis. An ice cube test for cold induced urticaria was positive.

Laboratory investigations revealed an elevated ESR at 75 mm/Hr, an unremarkable complete blood count and differential, and a homogeneous IgG kappa monoclonal spike consistent with monoclonal gammopathy of unknown significance (MGUS). There was no reciprocal suppression of other immunoglobulin classes. An anti-nuclear antibody was weakly positive at a titre of 1:8. Flow cytometry showed an absolute CD3+ of 1.013 E9/L, CD4+ of 0.598 E9/L, CD8+ of 0.435 E9/L, CD 16/56 of 0.118 E9/L, and a low absolute lymphocyte count of 1.303 E9/L. Cryoglobulins and cold agglutinins were both negative. C3 and C4 levels were within the normal range and rheumatoid factor was negative.

A review of her previous x-ray imaging was unremarkable. The patient declined a bone marrow biopsy as she felt a previous attempt caused her anaphylaxis when she disrobed for the procedure. Electromyography was not performed.

Ongoing medications include diphenhydramine 50 mg tid (up to 400 mg daily), montelukast 20 mg daily, ranitidine 150 mg daily, and ketotifen 4 mg bid. In addition, due to persistent symptoms of anaphylaxis, an outside physician began intravenous immunoglobulin (IVIG) therapy with Gammagard® (Baxter, Canada) at 65 g at 2 week intervals (corresponding to 971 mg/kg). In spite of these measures, she continues to experience breakthrough symptoms.

The symptoms and findings described above are consistent with Schnitzler syndrome. However, the cold-induced urticaria and anaphylaxis is a novel aspect as it has not been linked to Schnitzler syndrome. With a family history of cold-induced urticaria, a potential differential diagnosis of familial cold auto-inflammatory syndrome (FCAS) arises, however, she does not have the more typical diagnostic features of FCAS, namely, fever, conjunctivitis, and painful rash. Moreover, typically in the autosomal dominant cryopyrin associated periodic syndromes (CAPS) involving the NLRP3 (C1AS1) gene, there is leukocytosis and the ice cube test5 is negative.

Discussion

In 1972, the French dermatologist Liliane Schnitzler described a syndrome which included monoclonal IgM gammopathy, chronic urticaria, inflammation, recurrent fever, bone pain and arthralgia, with occasional lymphadenopathy and/or hepatosplenomegaly.[6] It is a rare condition with approximately 100 cases reported in the literature.[4,6-8]

Schnitzler syndrome occurs predominantly in Western Europeans with a slight male predominance sex ratio (1.45:1, males:females). Patients with Schnitzler syndrome range from age 13-71 with the mean age at diagnosis of approximately 60 years. On average, there is a diagnostic delay of 5 years or more after the symptoms onset.[6]

Clinical Features

Urticaria is a consistent feature. The eruption usually affects the trunk and limbs and spares the face and neck.[9] Individual lesions measure 0.5-2 cm in diameter but may coalesce. They clear completely within 12-24 h. New lesions usually develop every day, although lesion-free periods of 1-2 weeks may occur. Pruritus is minimal or absent initially then develops over time in about 30% of cases. Recurrent fever of about 40˚C occurs in 90% of patients but is not related to timing or presentation of urticaria.[4] Lymphadenopathy is found in 50% of patients. The nodes measure 2-3 cm and are usually located at the axillary and inguinal sites, although the cervical chain may be involved. Hepatosplenomegaly is seen less commonly. Bone pain is a feature in about 70% of patients.[4] On rare occasions, peripheral neuropathy with or without anti-myelin-associated glycoprotein antibodies has been reported.[10]

Diagnostic Imaging

Radiographs show foci of osteosclerosis, which are visible as hot spots by bone scintigraphy.[8] In the distal femur and proximal tibia, a periosteal reaction with increased radionuclide uptake is present. On MRI scans, the metaphyses generate low signal on T1 images and high signal on T2 images. Bone marrow biopsies are normal or contain non-specific infiltrates of inflammatory cells. Inflammatory arthralgia and arthritis occur in 60% of patients.[8]

Laboratory Findings

The presence of a monoclonal immunoglobulin is a hallmark of Schnitzler syndrome with IgM monoclonal protein isotype being the most predominant.[11] In classical Schnitzler syndrome, the monoclonal component was overwhelmingly IgM and the light chain was kappa in 90% of cases. However, in 6 recent cases there was a single IgG monoclonal component, with a light chain kappa in 5 cases, and lambda in one.[8] At diagnosis, most patients meet criteria for MGUS. The titre of the component is low and there is no plasma cell proliferation. Histology shows non-specific reactive hyperplasia.

Pathogenesis and Etiology

The pathophysiology of Schnitzler syndrome is still not well defined. Monoclonal IgM deposits are found along the basement membrane of the skin or within the capillaries in 30% of cases.[8] Using immunoelectron microscopy studies and immunoblotting, IgM-kappa anti-skin autoantibodies were identified at the dermal-epidermal junction.[11] The presence of anti-skin autoantibodies having the same isotype as the circulating monoclonal component suggests deposition of the monoclonal component in the skin. However, it is questionable that IgM deposits cause the eruption, as some patients lack IgM deposits. In addition, anti-skin IgM autoantibodies have been identified in individuals who do not have Schnitzler syndrome.

IL-1α is a known mediator of inflammation, and its injection into the skin causes persistent erythema. One report noted that the serum from 6 of 9 patients with Schnitzler syndrome contained polyclonal immunoglobulin G (IgG)-type autoantibodies directed against IL-1α.[12] These autoantibodies have been shown to prolong the half-life of IL-1α, to change its tissue distribution, and to enhance its effects. Therefore, this increase in IL-1α activity could account for the

symptoms of urticaria and fever. As Schnitzler's syndrome has been associated with the development of lymphoproliferative disorders (marginal B-cell lymphoma, IgM myeloma, and Waldenström macroglobulinemia), it is a pre-malignant condition.[7]

Treatment

Schnitzler syndrome never remits spontaneously and its course is characterized by recurring symptoms that are difficult to treat and/or prevent. There have been a number of reports describing treatment of Schnitzler syndrome with the IL-1α and IL-1β receptor antagonist, anakinra, leading to complete remission.[8] This supports the notion that IL-1 plays a key role in the pathophysiology of this condition. IL-1 is known to cause systemic inflammation as well as inflammation of the skin, and is also a potent stimulator of bone resorption.[6] Nevertheless, the exact role of IL-1 in the pathophysiology of Schnitzler syndrome is unknown. Anakinra binds to the IL-1 receptor and thus inhibits the binding of IL-1α and IL-1β.[4] The majority of patients with Schnitzler syndrome require daily dosing with IL-1 receptor antagonist.

Rituximab has also been tried in some case reports. There are cases of patients with Schnitzler syndrome refractory to rituximab who responded to anti IL-1 therapy.[13,14] Other treatments that have also been reported to be successful including cyclosporine[15,16] and in some cases psoralin UV-A therapy.[17] Recently IL-1 β receptor selective antagonist Rilonacept has also been successfully applied supporting the role of IL-1 in the pathophysiology of Schnitzler syndrome.[18]

A dramatic response to pefloxacin, a fluroquinolone analogue, was reported in 10 of 11 patients with Schnitzler syndrome by Asli *et al.*[19]

Prognosis

In a recent review of 94 patients with Schnitzler syndrome, none experienced spontaneous complete remissions.[2] However, mortality was not significantly increased during a mean follow-up of 9.5 years.[2] Nonetheless, there is a reported 10-year risk of 15% of developing a lymphoproliferative disorder, most notably Waldenstrom's macroglobulinemia.[2] Three cases of type AA amyloidosis associated with Schnitzler syndrome were also reported in this cohort.[2]

Conclusion

Herein, we report a patient with monoclonal gammopathy, chronic urticaria, bone pain and elevated ESR, all of which are typical of Schnitzler syndrome. However, this female also had disabling reactions induced by cold exposure, ranging from urticaria to anaphylaxis. Her symptoms were refractory to all suppressive medications taken to date, including IVIG therapy.

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