

CASE REPORT

Refractory urticaria and the importance of diagnosing Schnitzler's syndrome

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Accepted 29 March 2019

SUMMARY

A 52-year-old man presented with chronic urticaria that was refractory to standard chronic spontaneous urticaria (CSU) treatment. Over time, he developed systemic symptoms including fatigue, weight loss, arthralgia and bone pain. His laboratory investigations also became significant for microcytic anaemia, neutrophilia and elevated C reactive protein, erythrocyte sedimentation rate and IgE levels, in addition to an IgM monoclonal protein. He achieved only partial remission with typical medications for CSU including omalizumab, cyclosporine and cetirizine. After 6 years, his worsening symptoms and abnormal investigations led to a rare diagnosis of Schnitzler's syndrome and a trial of the interleukin 1 receptor antagonist, anakinra, which caused a rapid and complete resolution of his symptoms.

BACKGROUND

Chronic urticaria is the occurrence of urticarial wheals and/or angioedema for at least 6 weeks. It is further classified into chronic spontaneous urticaria (CSU) or physical urticaria when symptoms spontaneously arise from unknown causes or are triggered by environmental stimuli, respectively.¹ CSU is a common condition with a point prevalence of 0.5%–1% and is clinically diagnosed based on the presence of recurrent pruritic, migratory, raised, non-scarring, erythematous plaques.² Laboratory investigations are normal, and lesions are responsive to standard CSU therapy.³ CSU is a benign and self-limiting disease lasting between 2 and 5 years.¹ CSU must be differentiated from systemic conditions that can manifest similarly.

Chronic urticaria is the hallmark manifestation in Schnitzler's syndrome, a rare inflammatory disorder. Unlike CSU, patients develop systemic symptoms including recurrent fever, arthralgia and bone pain. Laboratory findings include elevated inflammatory markers and IgM monoclonal gammopathy.⁴ Over 280 cases of Schnitzler's syndrome were reported since 1972, with only four reports described in Canada.⁵ Its pathophysiology remains unclear, although the disease exhibits autoimmune and inflammatory features. Lipsker *et al*'s diagnostic criteria require the presence of recurrent urticaria and IgM monoclonal gammopathy in addition to two minor criteria: (1) recurrent fever, (2) abnormal bone remodelling, (3) elevated C reactive protein (CRP) or leucocytosis and (4) a neutrophilic infiltrate on skin biopsy.^{6,7} Despite the fact that

most cases follow a chronic, non-malignant course, 10%–15% of patients develop lymphoproliferative disorders.⁴

Here, we present a 52-year-old Caucasian–Canadian male patient experiencing chronic urticaria, which remained refractory to standard CSU treatment including antihistamines and immunosuppressive therapies.

CASE PRESENTATION

The patient had a chief complaint of chronic urticaria affecting the neck, torso and extremities. His urticaria became pruritic with reported weekly Urticaria Activity Scores (UAS7) of 30–33 (where 1–6 is well controlled, 7–15 is mild, 16–27 is moderate and 28–42 is severe CSU). The urticarial lesions were migratory, non-scarring, resolved within 24 to 48 hours and exacerbated by heat, upper respiratory tract infections and alcohol consumption. He had no respiratory symptoms or angioedema.

Aside from a remote provoked seizure and a 30 pack-year history of smoking, his medical history was unremarkable. He consumed two alcoholic drinks per week, was not medicated and had no known allergies. He worked as a construction project manager and lived at home with his family, a dog, two cats and a rabbit. There was no family history of autoimmune or inflammatory conditions.

Physical examination was significant for pruritic, erythematous papules and plaques on his trunk, extremities and neck consistent with urticaria (figure 1). There was no lymphadenopathy or hepatosplenomegaly.

INVESTIGATIONS

His allergy skin prick test was positive for house dust mite sensitisation. As shown in table 1, initial laboratory investigations revealed mild leucocytosis, neutrophilia, eosinophilia and elevated IgE, erythrocyte sedimentation rate (ESR) and CRP. Based on the clinical and laboratory findings, he was initially diagnosed with CSU. Creatine kinase should be ordered if musculoskeletal involvement is suspected; however, it was not obtained as part of this patient's diagnostic workup likely because he did not complain of myalgias. Autologous serum skin test (ASST) was also not conducted.

ASSTs involve the intradermal injection of a patient's serum and were developed to support an autoimmune mechanism of CSU by providing



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To cite: Nham T, Saleh C, Chu D, *et al*. *BMJ Case Rep* 2019;**12**:e228546. doi:10.1136/bcr-2018-228546

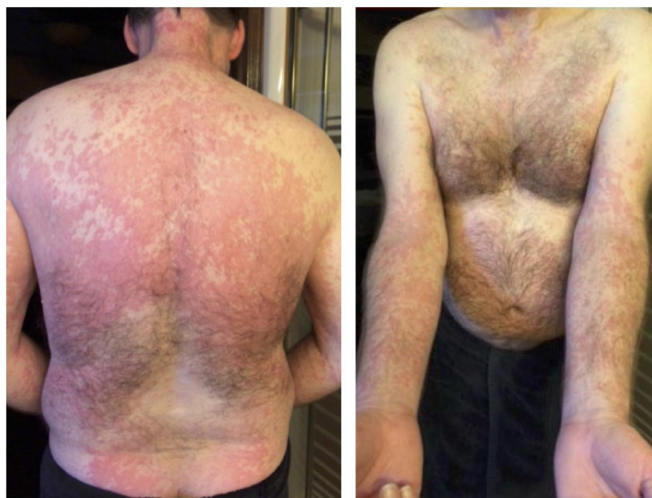


Figure 1 Urticaria as seen across the torso, back and upper extremities.

an *in vivo* assay of mast cell activation caused by patient serum factors.⁸ However, ASSTs are not widely used in clinical practice, since they are neither sensitive nor specific for CSU. Positive ASSTs can be observed in healthy subjects or in patients with other diseases; in fact, one study demonstrated positive results in 53% of patients with CSU, 56% of healthy subjects and 20% of patients with non-allergic asthma/rhinitis.⁹ Therefore, an ASST was not performed as part of this patient's workup.

Over time, the patient experienced worsening systemic symptoms including unintentional weight loss of 12 kg, progressive malaise, fatigue, arthralgia and intense bone pain, associated with worsening anaemia (haemoglobin 87 g/L) and neutrophilia ($13.5 \times 10^9/\text{L}$), which prompted a full clinical and laboratory reassessment (table 1).

Laboratory investigations were significant for microcytic anaemia, markedly elevated inflammatory indices and an IgM monoclonal protein with kappa light chain specificity (2.4 g/L) as shown in table 1. Antinuclear antibody (ANA), antiextractable

nuclear antigens, complement component 3 and 4 and thyroid-stimulating hormone were normal.

A punch biopsy of his urticarial lesion demonstrated slight hyperkeratosis and perivascular lymphocytic infiltrates, with occasional eosinophils and neutrophils in the underlying superficial dermis, which was significant to diagnose urticaria and rule out vasculitis.

Haematological assessment was negative for a clonal lymphocyte population in the peripheral blood and JAK2V617F or BCR-ABL mutations, which would suggest a myeloproliferative neoplasm. His kappa light chain was stable at 122.23 mg/L, and monoclonal protein was 3 g/L. CT imaging of his abdomen and pelvis showed splenomegaly (17 mm craniocaudally), and the skeletal survey revealed bilateral humeral sclerosis and extensive iliac sclerosis (figure 2).

DIFFERENTIAL DIAGNOSIS

Prior to the diagnosis of Schnitzler's syndrome, immunological, haematological and infectious diseases that manifest similarly must be ruled out, as outlined in de Koning *et al*'s concise summary of differential diagnoses.⁴ An approach to patients presenting with chronic urticaria, systemic symptoms and/or IgM monoclonal gammopathy that resemble Schnitzler's syndrome is described below.

A detailed history and physical examination of the dermatological findings can help delineate Schnitzler's syndrome from other diseases. The urticarial lesions in Schnitzler's syndrome affect the trunk, extremities and may start non-pruritic, whereas CSU lesions can be more severe in areas of the body that are compressed by clothing (eg, waistband or axillae), are responsive to antihistamines or omalizumab and are usually not associated with abnormal laboratory investigations.¹²⁴ Painful urticaria (ie, burning sensation or tenderness) may indicate urticarial vasculitis.¹⁰ Vasculitic plaques can persist longer than 24 hours and may leave behind residual pigmentation. Investigations may reveal hypocomplementaemia and positive ANA titres, which are not found in Schnitzler's syndrome. A skin biopsy helps establish the diagnosis of urticarial vasculitis by demonstrating leucocytoclastic vasculitis, fibrinoid deposits and vessel damage.

Table 1 Laboratory investigations during his disease course and following the initiation of anakinra 100 mg/day subcutaneous injections

Laboratory	Initial presentation	5.6 years after initial presentation	1–6 months after starting anakinra	11 months after starting anakinra	Reference range
Hb (g/L)	124	87	136	148	130–180
MCV (L)	79.7	74.0	79	86	82–99
Ferritin (µg/L)	96	296	N/A	N/A	22–275
Leucocytes ($\times 10^9/\text{L}$)	11.1	15.8	9.4	9.3	4.0–11.0
Platelets ($\times 10^9/\text{L}$)	248	296	228	159	150–400
Eosinophils ($\times 10^9/\text{L}$)	1.0	0.5	0.9	0.6	0.0–0.4
Neutrophils ($\times 10^9/\text{L}$)	7.6	13.5	5.4	6.5	2.0–7.5
ESR (mm/hour)	26	N/A	17.5	4.0	<20.0
CRP (mg/L)	145.6	150.0	5.7	3.5	<5.0
LD (U/L)	N/A	136	N/A	N/A	100–220
CK (U/L)	N/A	N/A	42	N/A	<200
IgE (kU/L)	250	N/A	N/A	27	<100
IgM (g/L)	1.53	2.40	N/A	2.77	0.41–2.07

CK, creatine kinase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; LD, lactate dehydrogenase; MCV, mean corpuscular volume; N/A, not available.

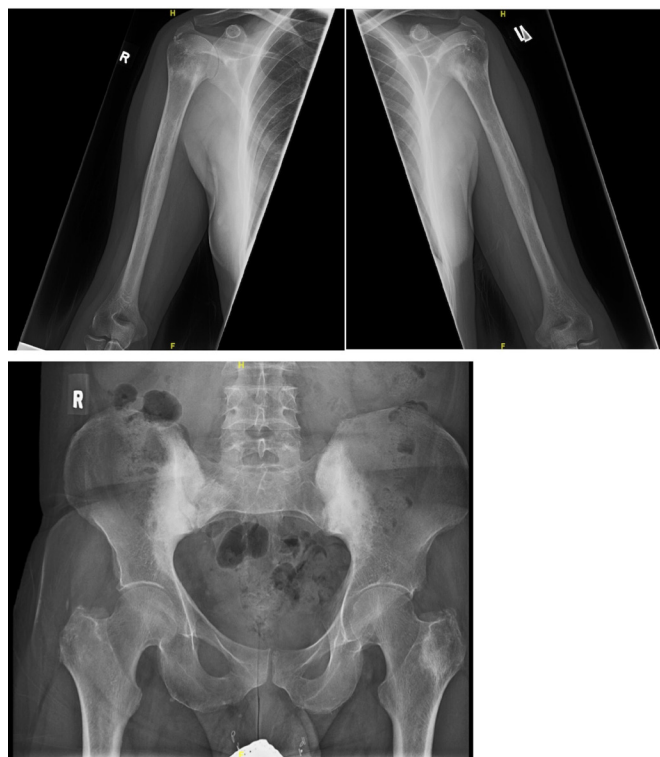


Figure 2 Skeletal survey of right (top left) and left (top right) humerus and pelvis (bottom) demonstrating bilateral humeral sclerosis and extensive bilateral iliac sclerosis.

Urticaria is also the hallmark manifestation of cryopyrin-associated period syndromes, in addition to elevated inflammatory markers, arthralgias and fever.⁴ They are a group of disorders arising from autosomal dominant point mutations in *NLRP3* causing inappropriate interleukin 1 (IL-1) β activity. The presence of positive family history, presentation at a young age, *NLRP3* mutations and the lack of a monoclonal paraprotein help distinguish them from Schnitzler's syndrome.

Schnitzler's syndrome must also be differentiated from disorders that have urticaria or urticaria-like lesions and systemic symptoms including adult-onset Still's disease, systemic lupus erythematosus and amyopathic dermatomyositis. Adult-onset Still's disease presents with dermatological and systemic symptoms that respond to IL-1 antagonists.^{4 11} Patients with adult-onset Still's disease have a classic evanescent, macular or maculopapular lesion that is rarely pruritic and comes and goes with daily fevers. Like Schnitzler's syndrome, patients can have arthralgias and neutrophilic leucocytosis; however, adult-onset Still's disease is associated with severe pharyngitis, markedly elevated ferritin levels and can be classified using Yamaguchi's diagnostic criteria. Although CSU is commonly associated with systemic lupus erythematosus (and has a prevalence of up to 22%), systemic lupus erythematosus has classic dermatological findings including malar rash, photosensitivity and discoid lesions.¹² It is also strongly associated with positive ANA titres. The typical dermatological features of amyopathic dermatomyositis like a heliotrope rash, Gottron's papules, photodistributed poikiloderma and holster sign can be extremely pruritic resembling urticaria.¹³ However, patients have characteristic proximal skeletal muscle weakness and/or pain, elevated serum muscle enzymes and characteristic myopathic changes on electromyography, which are several features of Bohan and Peter's diagnostic criteria for dermatomyositis.

Chronic urticaria and monoclonal gammopathy of undetermined significance (MGUS) can coexist as the prevalence of CSU is up to 1% in the general population and that of MGUS is 3% in individuals over 50 years old.^{2 4 14} However, if dermatological findings and monoclonal gammopathy are found especially in the presence of systemic symptoms, plasma cell dyscrasias (eg, multiple myeloma) or lymphomas (eg, Waldenstrom macroglobulinemia) should be considered.

TREATMENT

Standard CSU therapy starts with the administration of a second-generation H1 antihistamine at increasing doses in adjunct with other H1/H2 antihistamines and leucotriene-receptor antagonists.¹⁵ This patient's urticaria was refractory to these measures including fexofenadine as needed, cetirizine (20 mg two times per day), desloratidine (5 mg two times per day) plus ranitidine (150 mg two times per day). First-generation antihistamines were avoided in this patient's treatment due to the previous seizure association.

Patients intolerant to initial CSU therapy have refractory CSU and are managed with additional anti-inflammatories such as short-term glucocorticoid therapy, dapsone, tacrolimus, cyclosporine or omalizumab.¹⁵ In this patient, prednisone (50 mg/day for 5 days) was temporarily effective for some exacerbations. Therapy with antihistamines and tacrolimus (1 mg two times per day) or dapsone (50 mg/day) was also unsuccessful at alleviating symptoms. Only the combination of omalizumab (600 mg intramuscularly every 4 weeks), cyclosporine (100 mg two times per day) and cetirizine (20 mg two times per day) led to a partial improvement in his symptoms for about 4 years. The patient reported a 50% improvement in his symptoms for 10–12 days following each omalizumab injection. Unfortunately, his urticaria would return near the time of his next omalizumab dose.

Based on the combination of his symptoms and laboratory findings, the patient fulfilled all of Lipsker *et al*'s criteria and was diagnosed with Schnitzler's syndrome.¹⁶ He started the IL-1 receptor antagonist anakinra (100 mg/day subcutaneously) and experienced full remission of his symptoms (UAS7 of 0) and laboratory abnormalities (table 1).

OUTCOME AND FOLLOW-UP

After a year of daily anakinra injections, he maintained the resolution of his clinical symptoms, anaemia, leucocytosis and elevated inflammatory markers (table 1).

DISCUSSION

Schnitzler's syndrome is a rare inflammatory disorder that presents similarly to more common, benign conditions like CSU leading to delayed recognition. Diagnosis and clinical monitoring are essential due to its association with the development of lymphoproliferative disorders.⁴ In a review of 281 cases of Schnitzler's syndrome at a median follow-up of 8 years, 12% of patients developed a haematological malignancy including Waldenstrom macroglobulinemia (lymphoplasmacytic lymphoma), non-Hodgkin's lymphoma, other B-cell lymphomas, multiple myeloma and rarely, acute myeloid leukaemia. The treatment of choice for Schnitzler's syndrome is the IL-1 receptor antagonist anakinra. Although it can dramatically induce symptom remission, this effect is not curative since the withdrawal of anakinra causes symptom recurrence within days. It is unknown if anakinra provides any morbidity or mortality benefit in Schnitzler's syndrome since the longest treatment duration is currently 11 years.¹⁷

It is thought that IL-1 plays a major role in the pathogenesis of Schnitzler's syndrome largely due to the observation that IL-1 receptor antagonists can induce symptom remission in patients who have failed other immunomodulatory regimens.^{3 18 19} Moreover, the pathogenesis is thought to be mast-cell independent. This report is the first to document elevated IgE levels in Schnitzler's syndrome, which may have contributed to this patient's clinical presentation since partial remission was achieved with a combination of omalizumab, cyclosporine and cetirizine. To our knowledge, there are no previous reports demonstrating elevated IgE levels in Schnitzler's syndrome or the efficacy of using the anti-IgE monoclonal antibody omalizumab in this setting.^{20 21}

Although its mechanism for improving CSU is not well elucidated, it is known that omalizumab is an IgE-directed IgG antibody that rapidly depletes IgE antibodies from the circulation. As circulating IgE levels decrease, high-affinity cellular IgE receptors (FcεRI) are internalised and downregulated on mast cells. Circulatory IgE antibodies sensitise mast cells to release inflammatory mediators in response to antigens, and it was demonstrated that circulatory IgE plays a crucial role in stabilising and increasing mast cell FcεRI expression. This allows mast cells to become more sensitive and have a diminished threshold for antigens, with the ability to release abundant inflammatory markers at lower concentrations of external stimuli.^{21–23} Therefore, although elevated IgE levels were not previously implicated in the pathogenesis of Schnitzler's syndrome, in the context of this patient's elevated circulatory IgE levels and his positive response to omalizumab, IgE appeared to contribute to the pathophysiology of his urticarial lesions.

Learning points

- Schnitzler's syndrome is a rare inflammatory disease that can present similarly to chronic spontaneous urticaria (CSU). Consider Schnitzler's syndrome in patients presenting with CSU accompanied by systemic symptoms and abnormal investigations including elevated C reactive protein (CRP), erythrocyte sedimentation rate and IgM monoclonal gammopathy.
- Lipsker *et al*'s diagnostic criteria include the presence of a recurrent urticarial rash and an IgM monoclonal protein in addition to two of the following minor criteria: (1) recurrent fever, (2) abnormal bone remodelling, (3) elevated CRP or leucocytosis and (4) a neutrophilic infiltrate on skin biopsy.
- Interleukin 1 (IL-1) receptor antagonists like anakinra are the treatment of choice and highly effective in inducing symptom remission. Despite its efficacy, withdrawal of anakinra causes symptom recurrence within days, and it remains unclear if treatment with an IL-1 receptor antagonist has mortality or morbidity benefit in Schnitzler's syndrome since its longest duration of use for this disease is currently 11 years.
- 12% of patients with Schnitzler's syndrome progress to develop lymphoproliferative disorders and require close follow-up with haematology, immunology and rheumatology.
- IL-1 is known to play a major role in the pathogenesis of Schnitzler's syndrome mainly due to IL-1 receptor antagonist efficacy in inducing symptom remission. This report highlights IgE may contribute to its pathogenesis by increasing the density of FcεRI on effector cells and decreasing their activation threshold, as demonstrated through this patient's partial responsiveness to an IgE antagonist (omalizumab).

This report highlights the importance of diagnosing Schnitzler's syndrome since its disabling symptoms have a highly efficacious treatment (anakinra) and patients require close follow-up with involvement from haematology, immunology and rheumatology due to high rates of progression to lymphoproliferative disorders. Further research is needed regarding the long-term outcomes of patients with Schnitzler's syndrome receiving anakinra.

Acknowledgements We would like to acknowledge this work was presented as a poster at the 2018 Canadian Society of Allergy and Clinical Immunology Annual Scientific Meeting in Halifax, Nova Scotia, Canada. It was not published as a conference abstract.

Contributors TN organised and interpreted the clinical data, created the manuscript figures and wrote the article. CS, DC and DMS participated in the conception and design of the article, interpreted the data and revised the manuscript. SLV participated in the conception of the article, acquired and interpreted the data and revised the manuscript. JAO participated in the conception and design of the article and revised the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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