# Urticaria as a sign of auto-inflammatory disorder: second Indian case report

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Schnitzler's syndrome is an autoinflammatory disorder presenting with wheals, monoclonal gammopathy, and signs of inflammation. A 55-year-old woman presented with reddish, moderately itchy wheals with intermittent fever and arthralgia for two years. Multiple erythematous, edematous plaques were noted all over the body. Dermographism was present. A diagnosis of chronic urticaria was considered and treated with antihistamines. The patient returned six weeks later with partial symptomatic relief. She was then investigated for the cause of chronic urticaria, and the following differentials were considered: systemic lupus erythematosus (SLE), dermatomyositis, urticarial vasculitis, and auto-inflammatory diseases. The patient was febrile, and her blood investigations revealed leukocytosis and a raised erythrocyte sedimentation rate along with IgM gammaglobulinemia and an M band on serum electrophoresis. Skin biopsy revealed a neutrophilic infiltrate in the dermis. Thus, based on the Strasbourg diagnostic criteria, a final diagnosis of Schnitzler syndrome was made. Urticarial rash is one of the most common complaints encountered by dermatologists. Other extremely uncommon diseases like autoinflammatory disorders (for example, Schnitzler syndrome) can mimic chronic urticaria. The appearance of the rash and associated symptoms should be carefully considered to identify these missed cases. Auto-inflammatory syndromes are severely debilitating, with little awareness among healthcare professionals. Thus, they are often recognized with a diagnostic delay of many years. Early diagnosis of such rare diseases is imperative for effective treatment and to prevent devastating long-term complications.

**Keywords:** urticaria, autoinflammatory disorders, dermographism

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## INTRODUCTION

Autoinflammatory syndromes present with recurrent fever and inflammatory cutaneous, mucosal, serosal, or osteoarticular manifestations [1]. These conditions generally result from a genetically driven, dysregulated innate immune system, producing a surplus of cytokines [1]. However, some diseases are also categorized as autoinflammatory on account of their similar inflammatory features but lack an identifiable genetic cause [1], one of them being Schnitzler syndrome. Schnitzler syndrome is an autoinflammatory disease presenting as recurrent



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rash, monoclonal immunoglobulin gammopathy (IgM > IgG), and systemic inflammation [2]. This disease commonly presents with a chronic itchy rash, so the possibility of missing the diagnosis is high. Therefore, a high index of suspicion must be entertained. Herein, we report the case of a middle-aged female presenting to us with a long-standing itchy rash.

## CASE PRESENTATION

A 55-year-old woman presented with transient, reddish, moderately itchy lesions over the body, which had been on and off for two years. This was associated with intermittent fever and knee joint pain. On examination, multiple blanching, erythematous, and edematous plaques (wheals) of various sizes were noted all over the body (Figures 1 and 2). Dermographism was present. A diagnosis of chronic urticaria was considered, and the patient was started on anti-histamines (H1 and H2 blockers) and advised follow-up.

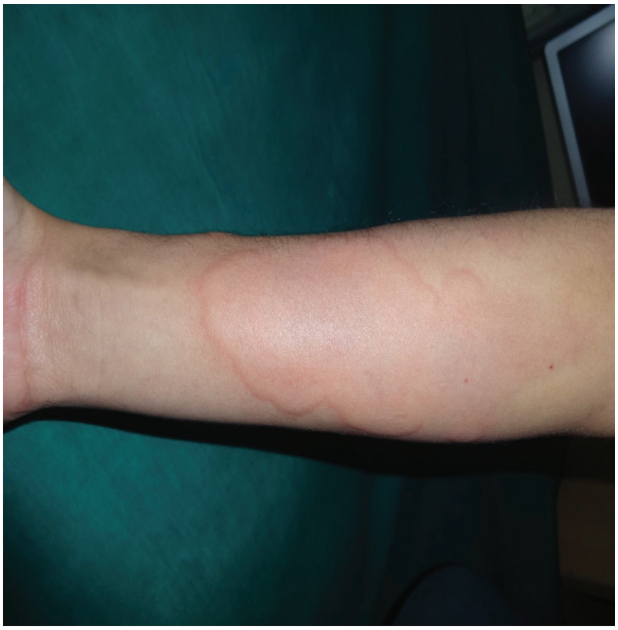

**Figure 1.** Edematous, erythematous wheals over the right forearm.

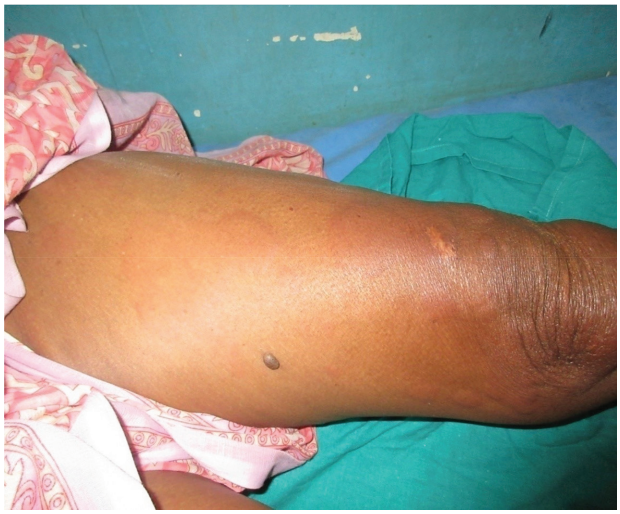

**Figure 2.** Edematous, erythematous wheals over the left thigh.

The patient returned six weeks later with partial relief from itching but no improvement in terms of the appearance of new skin lesions, joint pain, and fever. The patient was then investigated to identify the cause of chronic urticaria, and the following differentials were considered: systemic lupus erythematosus and dermatomyositis, urticarial vasculitis, and autoinflammatory diseases. A detailed history taking and clinical examination were performed to exclude these differential diagnoses. She denied any oral lesions, muscle weakness, photo-exacerbation of rash, or any drug intake prior to the onset of these lesions. She was febrile with a temperature of 39 °C. General and systemic examination was otherwise unremarkable. There was no joint swelling or tenderness or evidence of proximal myopathy.

Investigations revealed leukocytosis (total leucocyte count: 14.000/mm$^3$) and an elevated erythrocyte sedimentation rate of 86 mm/hour). There were no platelet or red blood cell count abnormalities. The renal and liver function tests were within normal limits. Serological tests to exclude connective tissue disorders returned normal (rheumatoid factor and antinuclear antibody were negative, and creatinine phosphokinase-MB and lactate dehydrogenase levels were within normal limits). Radiographs of the knee joint showed no abnormality. Serum electrophoresis revealed an M band along with IgM hypergammaglobulinemia (250 mg/dL). Skin histopathology revealed a neutrophilic infiltrate in the dermis. Thus, the patient was diagnosed with Schnitzler syndrome based on the Strasbourg diagnostic criteria. She was given a short course of systemic corticosteroids (oral prednisolone 0.5 mg/kg, tapered rapidly over two weeks) along with oral hydroxychloroquine (200 mg twice daily), colchicine (1 mg twice daily), antihistamines (cetirizine 10 mg tablet in the morning, hydroxyzine 10 mg tablet at night), and ranitidine (150 mg twice daily).

### Ethical consideration

Informed consent was obtained from patient for publication.

## DISCUSSION

In 1972, Dr. Liliane Schnitzler, a French dermatologist, documented the first case of Schnitzler Syndrome [3]. To date, 281 cases have been reported, with a slight male preponderance [3]. After an extensive literature search, we could find only one other reported case from India [4]. The non-specific symptoms of Schnitzler syndrome are often disregarded, leading to an average diagnostic delay of 5-6 years [5]. This syndrome's first and most common symptom is an urticarial rash [3,6]. The second most frequent symptom is an intermittent fever in 72% of patients without a periodic pattern, while two-thirds of patients in a study by Koning H complained of joint pain [3]. These patterns are in accordance with the symptoms experienced by our patient.

Patients commonly present to allergists and immunologists with urticarial rashes in everyday practice [7]. Notably, many seldom-encountered conditions, like autoinflammatory disorders, mimic urticaria [8]. A few entities need to be ruled out before a diagnosis of Schnitzler syndrome is established. Among them are adult-onset Still's disease, cryopyrin-associated periodic syndrome, urticarial vasculitis, SLE, chronic idiopathic urticaria, monoclonal gammopathy of unknown significance (MGUS), and cryoglobulinemic vasculitis. For this purpose, a set of criteria were developed to definitively establish the diagnosis of this rare disease [2]. Our patient satisfied both major criteria with two minor criteria (chronic urticarial rash with monoclonal immunoglobulin M and recurrent fever, neutrophilic infiltrate in dermis, and leukocytosis), thus was diagnosed as a definite case of Schnitzler syndrome.

The complications seen in patients of Schnitzler syndrome include inflammatory AA amyloidosis [6], possible evolution into a lymphoproliferative disorder [6,9], sensorimotor polyneuropathy, and anemia [10]. Thus, this disease can pursue a devastating course, necessitating stringent monitoring over a prolonged duration. Fortunately, our patient has not developed any such complications so far.

There are subtle points of differentiation between the rash of urticaria and that of autoinflammatory syndromes, which should be borne in mind during the clinical examination. The rash appears as erythematous patches and flatter wheals with more indurated and stable lesions compared with a chronic urticarial rash [7]. It is usually distributed symmetrically, and pruritus may even be conspicuously absent, while pain and burning may be prominent [7]. This rash does not respond to antihistamines and is associated with systemic symptoms like fever, arthralgias, and fatigue, as we observed in our case [7]. Also, these patients have elevated systemic markers of inflammation (e.g., erythrocyte sedimentation rate and C-reactive protein) [7], as illustrated in our case. These features must give the clinician a clue to look for autoinflammatory syndromes in patients who are misdiagnosed as urticaria and are unresponsive to treatment. Identifiable aggravating factors like emotional and physical stress, spicy foods, and alcoholic beverages should be avoided [11]. Recommended treatment modalities include colchicine, short-course non-steroidal anti-inflammatory drugs, and anakinra based on the degree of quality of life and inflammatory markers [11]. Our patient was given a short course of systemic corticosteroids to hasten the symptomatic relief.

## CONCLUSION

Schnitzler syndrome shares plenty of clinical, biological, and therapeutic aspects with a multitude of diseases under the purview of "autoinflammatory diseases," a category hitherto assigned to disorders with Mendelian inheritance [12]. Autoinflammatory syndromes are severely debilitating chronic diseases with limited awareness. Thus, they are either missed completely or often recognized with a diagnostic delay of many years or even decades. Timely diagnosis, though challenging, can facilitate appropriate management and avert long-term complications like amyloidosis. Urticarial rashes are often the initial and most pronounced symptoms in autoinflammatory disorders. This group of rare disorders deserves to be considered as a potential differential diagnosis of refractory chronic spontaneous urticaria.

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### Authors' contributions

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**Conflict of Interest:** None declared.

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