

## Schnitzler's Syndrome in the Absence of a Monoclonal Gammopathy: A Report of Two Cases

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### Abstract

Schnitzler's syndrome is a rare and devastating autoinflammatory syndrome which can be difficult to diagnose. We describe two cases presenting with signs and symptoms consistent with Schnitzler's syndrome with initial or continued absence of monoclonal gammopathy. Both patients responded to anti-IL-1 $\beta$  therapy, consistent with what is known for this disease. From our review of the literature, there has only been one other case of Schnitzler's syndrome without a monoclonal gammopathy documented. Understanding that monoclonal gammopathy may not always be present is important to avoid delay in diagnosis and initiation of proper treatment.

**Keywords:** Schnitzler's syndrome; Fever; Monoclonal gammopathy; Inflammation; IL-1 antagonist

### Introduction

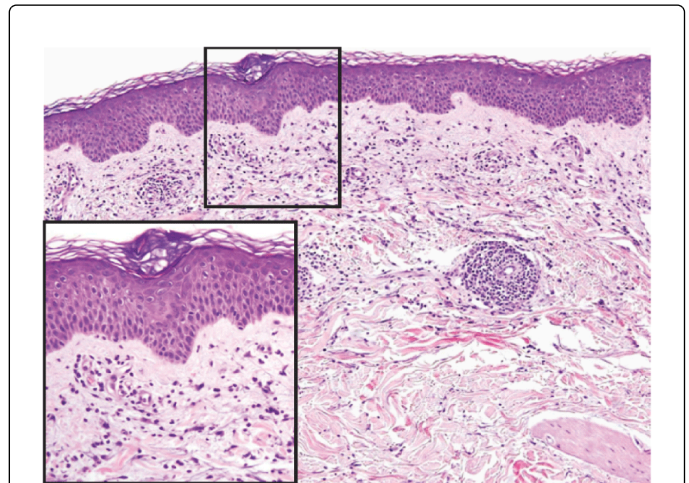
Schnitzler's Syndrome is a rare inflammatory syndrome first described in 1972, and characterized by urticaria, monoclonal gammopathy (IgM or sometimes IgG) and at least two of the following: periodic fever, arthralgias or arthritis, palpable lymph nodes, liver or spleen enlargement, elevated ESR, leukocytosis, or bone pain with evidence of osteosclerosis on imaging [1,2].

We describe two cases, where both patients presented with signs and symptoms consistent with Schnitzler's syndrome, but with the initial or continued absence of monoclonal gammopathy. From our review of the literature, there has only been one other case of Schnitzler's syndrome without a monoclonal gammopathy documented [3].

### Case Report 1

A 58-year-old male construction worker and farmer with pre-existing cardiac disease and a pacemaker presented with a painful, nodular rash on his upper right bicep. This rash spontaneously resolved but recurred in a migratory pattern as urticarial wheels and nodules on the anterior shins, forearms, face and scrotum. A month after the initial rash presentation, he developed morning fevers (up to 38.6°C) which were associated with rigors, arthralgias and fatigue. Laboratory test evaluations were significant for elevation in his ESR (84 mm/hr) and CRP (6 mg/dl). All serologic evaluations, including ANA, ANCA, RF, anti-cyclic citrullinated peptide antibodies, extractable nuclear antigens and cryoglobulins were negative. Serum protein electrophoresis, performed three times over a 12 month interval, initially demonstrated an acute inflammatory pattern without monoclonal gammopathy.

Biopsy of his skin lesions revealed findings consistent with urticaria with a superficial perivascular and interstitial infiltrate with scattered neutrophils (Figure 1). The more nodular skin lesions demonstrated changes consistent with erythema nodosum.



**Figure 1:** Skin lesion demonstrating a superficial perivascular and interstitial infiltrate composed predominantly of neutrophils. (10X, hematoxylin and eosin). Inset 20X, hematoxylin and eosin.

The patient was started on a course of prednisone, 1 mg/kg, with immediate resolution of all symptoms, including the rash, and normalization of his laboratory parameters. However, his fever, arthralgias and fatigue recurred when the dose of prednisone was below 20 mg/day. A thorough malignancy work-up was completed and was unremarkable. A trial of methotrexate was started for steroid-sparing effects; however he was still unable to taper prednisone below

20 mg daily without disease flares. CT of the chest and bronchoscopy for shortness of breath revealed no specific inflammation and negative infectious work-up.

Genetic evaluation for mutations in genes known to cause autoinflammatory conditions was negative. However, because his symptoms were reminiscent of such, he was started on anakinra with improvement in his symptoms and a successful prednisone taper to 12.5 mg daily. Unfortunately, he then developed extensive injection site reactions and the anakinra was discontinued. A trial of etanercept was not effective.

He continued to remain steroid dependent and began a trial of infliximab, 10 mg/kg, 19 months post presentation. The week following his first infusion, he developed a large abscess in his right thigh. Culture of the abscess aspiration revealed *Nocardia* and he was treated with a course of imipenem and trimethoprim-sulfamethoxazole. Repeat CT of his chest revealed a new right lower lobe consolidation abutting the diaphragm with surrounding ground-glass opacity most consistent with pneumonia and two new lung nodules that were likely infectious in etiology. A diagnosis of disseminated *Nocardia* related to inhalational exposure was made. His course was further complicated by an allergic reaction to imipenem infusions. He remained on prednisone but biologic medications were withheld to allow for recovery from infection.

Twenty months post presentation, he finally developed an IgM monoclonal gammopathy (0.1 gm/dL). Bone marrow biopsy revealed a hypercellular (70%) marrow characterized by trilineage hematopoietic maturation with an increased granulocyte:erythroid ratio. Granulocytic hyperplasia was noted with a slight left shift and toxic granulation present. Lymphopenia was present, but no plasmacytosis was noted. Flow cytometry and fluorescence in situ hybridization (FISH) studies were unrevealing for a malignant population. No amyloid deposits were noted on congo-red staining. Serum IL-6 was elevated at 22 pg/ml. An anemia of chronic disease (hemoglobin 9-10 g/dL) developed. ESR remained elevated >100 mm/hr and CRP rose to 20-25 mg/dL despite 20 mg of prednisone per day.

Given his persistent fevers, arthralgias and new presence of an IgM monoclonal gammopathy, a diagnosis of Schnitzler's syndrome was made. He was started on canakinumab 150 mg subcutaneous injection 21 months post presentation. He noted an improvement in his fevers and arthralgias and prednisone was tapered to 15 mg daily; however, his inflammatory markers remained unchanged. His dosing frequency was increased to every four weeks. Three days following his fourth injection, he had a ventricular tachycardia arrest and expired.

## Case Report 2

A 44-year-old woman presented with the history of chronic urticaria for several years (Figure 2), fevers up to 38.3°C persistent throughout the day but breaking with acetaminophen or ibuprofen, arthralgias and recurrent angioedema. She had a history of intermittent elevated inflammatory markers ESR 30 mm/hr, and CRP 2.2 mg/dl (normal <0.5 mg/dl), leukocytosis (20,000/MM3 with 83% neutrophils), hilar lymphadenopathy with biopsy negative for infection, multiple serum electrophoresis with hypogammaglobulinemia and absence of a paraprotein, and normal ferritin. Lesional skin biopsy showed a perivascular infiltrate of lymphocytes with interstitial neutrophils and eosinophils consistent

with urticaria. An extensive autoimmune work-up and periodic fever panel assessment for mutations in 7 genes that are associated with various periodic fevers was negative. Her work-up for hereditary angioedema including C1Q esterase was also negative [2].



**Figure 2:** Urticarial-like lesion on patient forearm.

Due to lack of any other unifying diagnosis, but similarities to autoinflammatory syndromes, she was started on anakinra injections daily and within a week had resolution of her fevers, arthralgias and urticaria. Although she developed severe injection site reactions, she continued therapy as she felt better than she had in years. After review of the literature, there appeared to be good evidence for the use of canakinumab, and due to severe injection site reactions, she was switched to canakinumab and responded well for approximately 4 weeks, when the effect started to wear off. Thus, her dose frequency was changed from every 8 weeks (recommended dose for periodic fever syndromes) to every 4 weeks [4,5]. She continued to do well, until due to insurance issues, there was a lapse in her canakinumab and she had recurrence of her symptoms. Upon resumption of the medication her symptoms resolved and she continues to be asymptomatic until the day of her injection when she occasionally presents with one or two urticarial lesions.

## Discussion

These cases represent a diagnostic challenge, as both patients had chronic, inflammatory symptoms that severely impacted their quality of life without an initial presence of a monoclonal gammopathy that is typical in Schnitzler's syndrome. However, unlike patients with chronic urticaria, these cases had somewhat unusual urticarial-like rashes that responded well to IL-1 $\beta$  blockade, which is typical for rashes associated with autoinflammatory diseases such as Muckle-Wells, familial cold urticaria, or Schnitzler's syndrome [6]. The appearance of symptoms later in life is also more consistent with Schnitzler's syndrome, rather than genetic autoinflammatory conditions, as it tends to affect people in the fourth decade and beyond [2]. Malignancy was ruled out in each patient, leaving Schnitzler's syndrome as the most likely diagnosis.

## Conclusion

Autoinflammatory diseases pose a diagnostic challenge, but a high suspicion can help lead to early diagnosis and treatment, greatly improving patients' quality of life. There has only been one other case reported of Schnitzler syndrome without a monoclonal gammopathy recorded in the literature [3]. Further, our first case suggests that a

monoclonal gammopathy may not be present at the onset of disease but may present later in the course. Thus, we suggest that Schnitzler's syndrome may be an underdiagnosed or alternative period fever syndrome of which physicians need to be aware.

## References

1. Lipsker D, Veran Y, Grunenberger F, Cribier B, Heid E, et al. (2001) The Schnitzler syndrome. Four new cases and review of the literature. *Medicine (Baltimore)* 80: 37-44.
2. de Koning HD, Bodar EJ, van der Meer JW, Simon A (2007) Schnitzler Syndrome Study G. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin Arthritis Rheum* 37: 137-148.
3. Varella TC, Nishimura MY, Machado MC, de Moraes-Vasconcelos D, Rivitti EA (2005) Schnitzler's syndrome without monoclonal gammopathy. *Acta Derm Venereol* 85: 272-273.
4. de Koning HD, Schalkwijk J, van der Meer JW, Simon A (2011) Successful canakinumab treatment identifies IL-1beta as a pivotal mediator in Schnitzler syndrome. *J Allergy Clin Immunol* 128: 1352-1354.
5. Vanderschueren S, Knockaert D (2013) Canakinumab in Schnitzler Syndrome. *Semin Arthritis Rheum* 42: 413-416.
6. Kaplan AP (2012) Biologic agents in the treatment of urticaria. *Curr Allergy Asthma Rep* 12: 288-291.