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A Modern Look at Schnitzler Syndrome – A Literature Review

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ABSTRACT
Schnitzler syndrome (SS) is an extremely rare acquired systemic disease that shares many similarities with various hereditary autoinflammatory syndromes. It presents as chronic non-pruritic urticarial rash, monoclonal gammopathy, and systemic symptoms, such as recurrent fever, arthralgia, myalgia, bone pain, bone lesions, and enlargement of the spleen and liver. The specific feature associated with SS is its spectacular response to treatment using anti-interleukin-1 (anti-IL-1) agents, such as anakinra or canakinumab. If it remains untreated, the disease can have a devastating effect on the patient's quality of life as well as increased mortality due to systemic complications. Herein, we will summarize the most recent findings in the pathogenesis, diagnosis, and management of SS.

KEY WORDS: Schnitzler syndrome, chronic urticaria, autoinflammatory syndromes

LITERATURE REVIEW

Schnitzler syndrome (SS) is an extremely rare acquired systemic disease that shares many similarities with various hereditary autoinflammatory syndromes (1). It presents with chronic, mostly non-pruritic urticarial rash, monoclonal gammopathy, and systemic symptoms, such as recurrent fever, arthralgia, myalgia, bone pain, bone lesions, and spleen and liver enlargement. The specific feature associated with SS is its spectacular response to treatment using anti-interleukin-1 (anti-IL-1) agents, such as anakinra or canakinumab. Herein, we will summarize the most recent findings in SS pathogenesis in order to raise awareness of this underdiagnosed condition (2).

MATERIALS AND METHODS

A literature search was conducted using the PubMed database by inputting the words "Schnitzler syndrome" in the search engine and filtering the articles published between the years 2010 and 2024. This resulted in 335 articles, out of which we excluded the articles not directly related to the topic, resulting in 30 different publications.

PATHOGENESIS

SS was first observed by French dermatologist Liliane Schnitzler in 1972, with the report published two years later. The pathogenesis of this disorder is not well understood. The key proinflammatory cytokine is interleukin-1β (IL-1β), which corresponds with the fact that anti-IL-1 agents result in complete or nearly complete control of symptoms in most patients. SS is considered to be an acquired autoinflammatory disease in which dysregulation of the innate immune system occurs, namely: the inappropriate production of IL-1β by the inflammasome, the dysregulation of nuclear factor κB (NF-κB) signaling, as

well as incorrect protein folding, cytokine signaling, and ineffective ubiquitination (3). A similar pathology is associated with other hereditary autoinflammatory diseases, such as cryopyrin-associated periodic syndrome (CAPS), where an activating mutation in the NLRP3 gene plays a vital role in its pathogenesis (4). Similarly, some variants of the NLRP3 (most notably NLRP3p.V198M) gene were identified in the myeloid lineage of IgG SS. Rowczenio *et al.* performed an analysis of NLRP3 and 32 other genes and found the same gene mosaicism in one out of 21 patients with SS. Moreover, they found higher levels of apoptosis-associated speck-like protein with Card domain aggregates, IL-6, and IL-18 in the patients' sera, which were higher in patients with SS (5). Unfortunately, the rarity of SS renders it difficult to assess a higher number of patients to properly ascertain the disease mechanisms (6).

EPIDEMIOLOGY

SS is an extremely rare disease with an incidence appraised as less than 1 in 1 000 000 according to the Orphanet Rare Disease Ontology (ORPHA:37748).

Based on the review by Simon *et al.*, the male/female ratio in SS is 1.76, whereas the mean and median ages of the first symptoms are 51.6 years (with a SD of 10 years) and 51 years, respectively (7). Most cases were reported in the United States and Europe among people of Caucasian origin (8). However, a few cases have been reported in China and Japan as well (9-15).

As a shown in a study conducted by the Mayo Clinic, it is important to note that SS may remain underdiagnosed in many cases (16). Due to the quite significant frequency of two major SS criteria – monoclonal gammopathy of unknown significance (MGUS) and urticaria – between 53 and 71 people in a million meet the major Strasbourg criteria. According to El-Khouri *et al.*, the incidence of MGUS in people over 50 years old is more than 10% of the population (17). A comprehensive epidemiological review of chronic spontaneous urticaria assessed its incidence as 8.8% (18). This turns the spotlight on the supposedly low incidence of SS in the general population.

SYMPTOMS AND ADDITIONAL FINDINGS

The two most consistent symptoms of SS are urticaria and the presence of MGUS.

The main skin symptoms in SS are red wheals with a burning rather than itching sensation. The urticarial lesions may be similar to those found in chronic spontaneous urticaria, but the individual lesions are rather symmetrically located, are less itchy, less edematous, and tend to last longer than 24 hours. They are well-rounded, elevated, erythematous, and generally appear on the trunk and extremities. Moreover, red macules, papules, or plaques may also appear (19).

Intermittent fever is the second most common symptom of SS (93% of patients) and it often occurs concurrently with the aforementioned urticarial rash. Joint pain has been observed in two-thirds of the patients and mostly affects the knees, hips, and back, and sometimes the feet and hands. Bone pain is found in more than 50% of patients – mostly in the shins (8). Lymphadenopathy was observed in 6-34% of patients, while hepatosplenomegaly was observed in 26-47%. Other less frequent symptoms of SS are weight loss (16% of patients) and neuropathy (7% of patients) – usually symmetric sensory polyneuropathy (8,20,21). A case of Schnitzler syndrome associated with recurrent subacute thyroiditis and SARS-CoV-2 vaccine has been described (22).

MGUS is the main laboratory finding in patients with SS (>90% of patients). It is usually a monoclonal IgM or IgG gammopathy, the first having been described more often. Kappa light chains are often elevated in blood serum. Other laboratory results often found in SS are: elevated ESR (95% of patients), leukocytosis – mostly neutrophilia (75% of patients), anemia (63% of patients), and Bence Johnson proteins in urea (8).

The histopathology of a skin biopsy often reveals neutrophilic urticaria, albeit with other immune cells are sometimes also being present: lymphocytes, macrophages, and eosinophils. Vasculitis can be observed in 20% of biopsies. Immune deposits are usually absent (70%), but IgM (23%), C3 (14%), or IgG (2%) deposits can sometimes be found (8).

In conventional radiography, the findings are often within the normal range, but hyperostosis or sclerosis (39-64%) is sometimes described. Bone scintigraphy can show increased uptake of radioactive material in 85% of patients. Bone alkaline phosphatase can be elevated (8,23).

Due to the fact that the diagnosis of SS is often delayed, it is worth noting that further complications may develop. These are AA amyloidosis, sensorimotor neuropathy, anemia due to chronic inflammation, and hearing loss (8,24).

DIAGNOSIS

Due to the scarcity and rarity of diagnosed cases as well lack of specific laboratory tests, the diagnosis of SS is based on a long list of exclusions. The first major attempt to categorize SS was performed by Lipsker *et al.*, who presented four cases of the disease

Table 1. The Strasbourg criteria for Schnitzler syndrome

Major criteria	Minor criteria
Urticarial skin rash Monoclonal IgM gammopathy (or IgG)	Intermittent fever[I] A neutrophilic dermal infiltrate on skin biopsy[II] Elevated ESR and/or leukocytosis[III] Objective findings of bone remodeling abnormalities[IV]
I – otherwise unexplained fever >38 C II – neutrophilic urticarial dermatosis with the absence of fibrinoid necrosis and significant dermal edema III – leukocytes count >10 000/mm^3 and/or CRP >30 mg/L IV–- assessed by MRI, scintigraphy, or elevation of bone alkaline phosphatase	

and performed a literature review, which resulted in the formation of the first criteria for the diagnosis of SS (25). Subsequent cases were reviewed in 2007 by De Koning *et al.* and consisted of 94 patients with SS (24). In 2013, a group of experts led by Simon *et al.* reported another 102 different cases of SS and, after merging them with de Koning's *et al.* results, presented the Strasbourg diagnostic criteria (Table 1) (7). A probable and definite diagnosis can be established based on these criteria. It should also be noted that several different diseases should be excluded before the diagnosis of SS is made – these are presented below (Table 2) alongside comments regarding their most significant differences.

TREATMENT AND FOLLOW-UP

According to the report by Simon *et al.* from 2013, patients with significant alterations in the quality of life and/or increased blood serum inflammatory parameters (such as CRP ≥30 mg/L) should be treated using anti-IL-1 agents, such as anakinra, canakinumab, or rilonacept (26,27). Anakinra in a dose of 100 mg daily applied subcutaneously is considered to be the first line of treatment for all the patients requiring systemic treatment. The long-term effects of this procedure have been well-documented and have proven effective – in a French follow-up from 2014, all 29 patients with SS responded rapidly, with complete remission occurring in 24 and partial remission in 5 patient (28). Notably, treatment with the anti-IL-1 agent is effective regardless of the presence of MGUS (29). It is also worth noting that classical pharmaceuticals used in treating chronic urticaria (such as anti-histamine drugs) are ineffective in SS. Moreover, systemic steroids provide little improvement in patient symptoms. Milder cases of SS may be effectively treated using anti-neutrophilic agents such as colchicine (1-2 grams daily) – 25% of patients showed clinical improvement with this treatment method (24,30).

Table 2. Differential diagnosis of Schnitzler syndrome

<u>For skin lesions and inflammatory phenotype</u>
Systemic juvenile idiopathic arthritis/adult Still's disease
Cryopyrin-associated periodic syndrome (i.e. Muckle-Wells syndrome, familial cold autoinflammatory syndrome)
Different auto-inflammatory disorders (i.e. TRAPS or mevalonate kinase deficiency syndrome)
Urticarial vasculitis and cryoglobulinemic vasculitis
Systemic lupus erythematosus
Chronic idiopathic urticaria
<u>For monoclonal gammopathy</u>
Monoclonal gammopathy of unknown significance (MGUS)
Multiple myeloma
Monoclonal IgM gammopathy
Waldenström's macroglobulinemia

CONCLUSION

Schnitzler syndrome is a very rare diagnosis, but due to its nefarious and elusive symptoms, the number of undiagnosed or misdiagnosed patients may be high. It is necessary for physicians of different specialties (dermatologists, rheumatologists, hematologists, radiologists, pathologists) to be able to recognize potential cases and properly address the patient needs, due to the fact that that treatment is highly specific. Moreover, if it remains untreated, the disease can have a devastating effect on the patient's quality of life as well as resulting in increased mortality due to systemic complications.

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