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Schnitzler Syndrome - Unraveling the Mystery of a Complex Condition

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ABSTRACT

Introduction: This review paper aims to explore the current state of knowledge regarding the underlying mechanisms of Schnitzler syndrome, its clinical manifestations, the diagnostic challenges, and to analyze current treatment approaches, along with potential complications related to the disease.

Materials and Methods: A comprehensive review of the literature was conducted using the PubMed and Google Scholar databases using the following keywords: "Schnitzler syndrome", "Schnitzler-like syndrome", "NETosis", "urticaria", "fever", "monoclonal gammopathy", "neutrophilic dermatosis", "anakinra", "treatment".

Summary: Schnitzler syndrome is a rare autoinflammatory disease that typically affects adults and presents with symptoms such as recurrent urticaria, fever, monoclonal gammopathy, and musculoskeletal pain. The exact cause is still not fully understood, but IL-1 antagonists have shown promising results, indicating IL-1's role in the disease's development. Despite the established diagnostic criteria, the disease still presents significant diagnostic challenges, often leading to delays in recognition or even underdiagnosis. Schnitzler syndrome, particularly if left untreated, can lead to complications such as the development of lymphoproliferative disorders, most commonly Waldenström's macroglobulinemia or, in rare cases, AA amyloidosis.

Conclusions: This review emphasizes the importance of a thorough examination, as its symptoms often resemble those of other diseases, which can lead to misdiagnosis. Due to the complexity of the clinical presentation, effective collaboration among dermatologists, rheumatologists and immunologists is essential. Ongoing research is crucial to better understand the disease's pathogenesis and to develop more effective and personalized treatment strategies.

Keywords: Schnitzler syndrome, neutrophilic urticarial dermatosis, monoclonal gammopathy

Introduction

Schnitzler syndrome is a rare, acquired adult-onset autoinflammatory condition. The first case of a 63-year-old man was identified relatively recently, in 1972. Two years later French dermatologist Liliane Schnitzler classified it as a distinct clinical entity. A few years ago, a proposal was made to change the name of the syndrome to "late onset gammopathy with recurrent urticaria and fever" but it was not implemented. The underlying mechanisms of the disease are still not fully understood, though it shares many characteristics with hereditary autoinflammatory syndromes. Key symptoms include persistent urticaria that does not respond to antihistamines, recurrent fever, monoclonal gammopathy, bone and joint pain, sometimes accompanied by lymphadenopathy or hepatosplenomegaly. There is no approved treatment for Schnitzler syndrome, however, IL-1 blocking agents have proven to be the most effective therapeutic option. In some patients, especially those who are not treated, there may be a risk of developing lymphoproliferative diseases in the future [1, 2, 3, 4].

Epidemiology

Schnitzler syndrome is considered an underdiagnosed and extremely rare autoinflammatory disorder characterized primarily by chronic urticaria and monoclonal gammopathy. Despite being first described in 1972, it remains largely unrecognized in clinical practice, leading to delays in diagnosis and treatment [5]. To date, fewer than 300 cases have been documented worldwide, emphasizing its rarity. The syndrome presents with a range of systemic symptoms, including recurrent fever, bone pain, and fatigue, which can mimic other inflammatory or hematologic conditions, further complicating its identification. Due to its underdiagnosis, many patients may suffer for years without a proper diagnosis or targeted treatment [6].

Between the 1970s and the early 1990s, cases of Schnitzler syndrome were documented exclusively in Western Europe, with France being the most common location. Even today, the majority of diagnosed individuals originate from France, likely because the condition was first described in French by a French physician. Over the past decade, however, reports of the syndrome have emerged worldwide, spanning countries from Australia to the Czech Republic [7, 8]. Most diagnosed patients are of Western European ancestry and white ethnicity, although there are three cases that have been identified in Japan [9, 10, 11]. The reasons behind the relatively low number of reported cases in the United States remain unclear. Given these patterns, as well as the constellation of symptoms, it is highly probable that Schnitzler syndrome continues to be significantly underdiagnosed [1, 12].

The average age at symptom onset is 51 years. The youngest known patient experienced their first episode of urticaria at just 13 years old [13] and only four other individuals developed symptoms before the age of 35 [6]. A considerable delay in diagnosis is observed, varying from a few months to as long as 20 years. In the majority of cases, the time between symptom onset and diagnosis exceeds five years [14].

So far, no risk factors for Schnitzler syndrome have been identified, nor is there any evidence suggesting that it is a hereditary condition - there is only one isolated case without clear genetic implications [6].

Pathogenesis

The pathophysiology of Schnitzler syndrome remains incompletely understood and may be complex. The effectiveness of treatment with IL-1 antagonists suggests the involvement of this cytokine in the development of the disease [2]. Significant similarities have been observed with cryopyrin-associated periodic syndrome (CAPS). CAPS is a monogenic autoinflammatory disorder characterised by skin rash, recurrent fever and joint pain. It is caused by a gain-of-function mutation in the NLRP3 gene, which encodes the NLRP3 protein (cryopyrin). NLRP3 belongs to intracellular pattern recognition receptors, which are activated by pathogen-associated or danger-associated molecular patterns (PAMPs or DAMPs). These include, for example, uric acid crystals and nucleic acids. Upon stimulation, the NLRP3 protein oligomerizes, which subsequently activates caspase 1. This enables the conversion of pro-IL-1β and pro-IL-18 into mature, active cytokines [15, 16]. Mutations in the NLRP3 gene have not been identified in patients with classical Schnitzler's syndrome. However, somatic NLRP3 mosaicism has been detected in some patients with the non-classical form of the syndrome [17].

It has been observed that patients with Schnitzler syndrome had higher blood levels of IL-6 and IL-18. Moreover, peripheral blood mononuclear cells (PBMCs) spontaneously release elevated levels of IL-1β, IL-1α, IL-6 and TNFα. The lipopolysaccharide stimulation further increased the production of these cytokines [15]. It has been shown that mast cells present in the skin of patients with Schnitzler syndrome can also be a source of IL-1. This cytokine enhances the accumulation of neutrophils. Their activation initiates the process of releasing neutrophil extracellular traps (NETs), known as NETosis [2, 15]. This process plays a crucial role in the body's immune response. NETosis aims to neutralize pathogens, but its dysregulation can lead to tissue damage [18]. Increased NETosis has been linked to the progression of autoimmune diseases, such as systemic lupus erythematosus (SLE). It is therefore suggested that the worsening of skin lesions in Schnitzler syndrome may follow a similar mechanism [17]. Elevated IL-1 levels also stimulate the production of the chemokine CCL2 by activated PBMCs and skin fibroblasts. CCL2 acts as a chemoattractant for monocytes, which can then differentiate into osteoclasts. This may be associated with bone-related symptoms in patients with Schnitzler syndrome [15].

Symptoms

Urticarial rash

Recurrent urticarial exanthema is usually the first symptom in patients with this syndrome. Urticaria may occur many years before other symptoms appear. It consists of rose or red spots, slightly raised papules or plaques that may merge. The rash is typically non-itchy. The lesions usually resolve within 48 hours, most often not lasting more than 24 hours. Sometimes dermographism is present. Angioedema occurs very rarely. The most common locations are the trunk and the limbs. The lesions typically do not appear on the face, palms or soles. It is characteristic that the rash in Schnitzler syndrome is resistant to treatment with antihistamines [1, 15]. Interestingly, it has been noted that the rash tends to intensify in the evening. Most patients with Schnitzler syndrome report having a rash daily, while others experience it only a few times a year [19]. Common triggers include infections, stress, alcohol, physical exercise or exposure to cold [20, 21].

Recurrent fever

Intermittent fever is the second most frequent clinical symptom. It is present in nearly all patients with Schnitzler syndrome. The body temperature typically exceeds 38°C, although it can occasionally reach as high as 40°C. Chills are usually absent. The fever may be relieved after taking non-steroidal anti-inflammatory drugs or glucocorticoids. There is generally no association between the onset of the rash and the fever [1, 3].

Bone and joint pain

Musculoskeletal complaints are experienced by approximately 60% to 80% of patients with Schnitzler syndrome [21, 22]. Patients with this condition most commonly reported pain in the tibia and the pelvis, although some also experienced pain in the spine or long bones, such as the forearm, femur or clavicle. These symptoms may be associated with the remodeling and alteration of the bone tissue structure.

Patients frequently reported arthralgia, although joint inflammation was rarely observed [15, 23]. In some cases, peripheral neuropathy was an associated symptom [17, 21].

Other symptoms

Other physical examination findings are lymphadenopathy in about 40% of patients and enlargement of the liver or spleen in about 30% of cases. The enlargement of lymph nodes most often occurred in the axillary, inguinal and cervical regions. Less common complaints include pruritus, chronic fatigue and weight loss [2, 12, 23]. Individual case reports described intercostal neuralgia, headache and even pancreatitis [21].

Diagnostic tests

Laboratory findings

A characteristic feature and an essential criterion for the diagnosis of Schnitzler syndrome is monoclonal gammopathy. In over 90% of cases it involved IgM and kappa light chains. About one-third of patients also showed the presence of Bence-Jones protein composed of light chains in the urine. Initially, IgM levels may be low, but as the disease progresses, they may increase. Very high levels of IgM may indicate the development of Waldenström macroglobulinemia. In some cases, the monoclonal gammopathy involves IgG or even IgA. Patients without monoclonal gammopathy in laboratory tests but with the presence of other symptoms listed in the criteria are diagnosed with Schnitzler-like syndrome [9, 23, 24, 25].

In patients with Schnitzler syndrome, elevated levels of inflammatory markers have been observed. Laboratory tests in most individuals show an increase in ESR and CRP. A characteristic feature is leukocytosis with a predominance of neutrophils. In approximately 50% of patients, inflammatory anemia is observed. In some cases, thrombocytosis occurred. Complement levels are usually normal, although in rare cases, a deficiency of the C4a component has been noted [6, 23].

In the blood of patients with Schnitzler syndrome, elevated levels of bone formation markers produced by osteoblasts, such as bone-specific alkaline phosphatase and osteocalcin, have been observed. It is suggested that high levels of IL-1 predispose to bone remodeling by stimulating the production of VEGF and the promotion of angiogenesis [15].

Imaging studies

Imaging studies in patients with Schnitzler syndrome may reveal various bone structural abnormalities. In most cases, the femoral and tibial bones are affected, particularly around the knee joints. The most frequently observed findings include foci of osteosclerosis and cortical hyperostosis. Additionally, an intense periosteal reaction may be present. Magnetic resonance imaging (MRI) can also provide insight into these changes, showing thickening of the cortices of long bones. In some cases, osteolytic lesions have also been observed [3, 23]. Furthermore, bone scintigraphy using 99mTc-HDP revealed symmetric areas of increased tracer uptake in the femur and tibia [26].

Skin biopsy

In Schnitzler syndrome, neutrophilic urticarial dermatosis is observed. In the early stages of plaque development, histopathological examination reveals a normal epidermis, a dermal infiltrate of granulocytes and clusters of neutrophils surrounding the sweat ducts [20]. Moreover, skin biopsy specimens showed the presence of an inflammation with perivascular infiltration of neutrophils and leukocytoclasia, but no signs of vasculitis. The similar histopathological pattern may also be present in CAPS or SLE [15, 27, 28]. In one patient with Schnitzler syndrome, infiltration with basophils was also detected [29]. Immunofluorescence studies also revealed the presence of immunoglobulin deposits, mainly consisting of IgM [23].

Diagnosis

The first diagnostic criteria were developed by Lipsker et al. in 2001. They consisted of the presence of urticarial rash and monoclonal IgM gammopathy, along with 2 of the following symptoms: fever, arthralgia or arthritis, bone pain, bone structure abnormalities, lymphadenopathy, liver or spleen enlargement, leukocytosis, elevated ESR.

In 2013, the diagnostic criteria for Schnitzler syndrome were updated and became known as the Strasbourg criteria (**Tab.1**). A definite diagnosis is made with two obligate criteria and at least two minor criteria if IgM is present, or three minor criteria if IgG is present. A probable diagnosis is made with two obligate criteria and at least one minor criterion if IgM is present, or two minor criteria if IgG is present [2, 20].

Tab. 1 Strasbourg diagnostic criteria of Schnitzler syndrome

OBLIGATE CRITERIA	MINOR CRITERIA
Chronic urticarial rash	Recurrent fever (> 38°C and otherwise unexplained)
	Objective findings of abnormal bone remodeling +/– bone pain (scintigraphy, MRI or elevation of bone alkaline phosphatase)
Monoclonal gammopathy (IgM or IgG)	A neutrophilic dermal infiltrate on skin biopsy (absence of fibrinoid necrosis and significant dermal edema)
	Leukocytosis and/or elevated CRP (Neutrophils >10,000/mm^3 and/or CRP >30 mg/l)

Due to the occurrence of patients who do not meet the main diagnostic criteria but respond well to anti-IL-1 treatment, the establishment of a new disease has recently been proposed.

This condition could be a precursor to Schnitzler syndrome. It has been suggested to name it paraprotein negative IL-1 mediated inflammatory dermatosis (PANID) [30].

Treatment

For many years, no therapy had been consistently effective [1]. Antihistamines, for instance, do not alleviate the rash and therefore are not recommended. Their ineffectiveness points to a histamine-independent underlying mechanism [6].

Corticosteroids provide significant symptom relief in 39% of patients, but their use is limited due to the need for high doses, which often lead to adverse effects. Colchicine has shown strong efficacy in a small subset of patients [6].

Several promising treatment options have been identified, though the number of patients receiving them remains limited. Initially, interferon-alpha appeared to be an effective choice [31, 32]. In one case, after multiple therapies failed to alleviate symptoms, IFN-2b led to a significant reduction in both urticarial lesions and bone pain over an 18-month follow-up period. The patient experienced three relapses of urticaria, two of which occurred when discontinuation of IFN-alpha was attempted. Notably, the treatment was well tolerated in this individual [31].

Pefloxacin has shown effectiveness in treating a small number of patients, demonstrating promising results in symptom management. However, its use is limited due to a considerable risk of tendinopathy, a condition that can lead to painful inflammation and even rupture of tendons. This potential adverse effect makes long-term treatment with pefloxacin a concern, especially for patients who may already experience musculoskeletal symptoms. Additionally, access to this medication remains restricted, as it is not widely available in many countries, further limiting its practical application as a standard therapy for Schnitzler syndrome [12].

Anakinra, a synthetic equivalent of the naturally occurring IL-1 receptor antagonist, has proven to be highly effective in the treatment of Schnitzler syndrome. In all eight documented cases, patients achieved complete remission following its administration. This effect was observed in both the classical and variant forms of the disease, making it a universally effective option regardless of the specific presentation of Schnitzler syndrome. The longest recorded follow-up period now extends to three years, during which patients have continued to experience persistent remission without any signs of relapse [6]. Given these promising results, anakinra stands out as a breakthrough treatment for Schnitzler syndrome, particularly in contrast to other therapeutic options that often provide only partial or temporary symptom relief. However, while its efficacy appears consistent, further long-term studies are needed to confirm its safety profile and optimal dosing regimen for broader patient populations [33]. Anakinra is not recommended for patients with known hypersensitivity to the drug or those with severely impaired kidney function, specifically when renal clearance falls below 30 ml/min. In cases of renal insufficiency, careful consideration of the benefit-to-risk ratio is essential before initiating treatment. If anakinra is deemed necessary, dosage adjustments should be made to minimize potential adverse effects [34].

Pregnancy is an uncommon occurrence in individuals with Schnitzler syndrome, as the average age at which symptoms first appear exceeds 50 years. However, discontinuation of anakinra is advised in case of pregnancy. In situations where stopping treatment is not feasible, a thorough risk-benefit assessment should be conducted.

Although clinical data on the use of anakinra during pregnancy is extremely limited, available evidence suggests that the drug does not cause congenital abnormalities and may be used with caution when no safer alternatives exist. Nonetheless, close monitoring is essential to ensure the well-being of both the mother and the developing fetus [12].
Canakinumab has been officially approved in both Europe and the United States for the treatment of several inflammatory conditions, including Cryopyrin-Associated Periodic Syndromes (CAPS), systemic juvenile idiopathic arthritis (sJIA), adult-onset Still's disease (AOSD), and gout that does not respond to conventional therapies. Its potential effectiveness in managing Schnitzler syndrome has also been explored in clinical research [35]. Canakinumab can provide rapid and effective symptom control in Schnitzler syndrome, though the durability of remission may differ among individuals. Further studies with larger patient populations and extended follow-up periods are needed to determine its long-term efficacy and optimal dosing strategies for sustained disease management [1].

Complications

In general, Schnitzler syndrome is associated with a positive long-term outlook regarding mortality, as studies indicate a 91% survival rate after 15 years. This suggests that the condition itself does not significantly reduce life expectancy. Given that the average age at which symptoms first appear is around 51 years, this survival rate aligns closely with that of the general population within the same age group [6].
While Schnitzler syndrome can significantly impact a patient's quality of life due to chronic symptoms such as urticaria, fever, and bone pain, it does not appear to substantially shorten lifespan. However, potential complications, such as progression to hematologic malignancies like Waldenström's macroglobulinemia, lymphoma or AA amyloidosis, require continuous monitoring. Most patients can achieve effective symptom control with appropriate treatment, particularly with targeted therapies [7, 36].

Disclosure

Author's contribution

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