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Schnitzler syndrome

Introduction

Schnitzler syndrome is a very rare acquired systemic disease that has many similarities with hereditary autoinflammatory syndromes. Main clinical features include fever, urticarial exanthema, muscle, bone and/or joint pain, and lymphadenopathy. Exanthema and IgM monoclonal gammopathy are the main characteristics of the disease. About 15–20% of patients with Schnitzler syndrome develop lymphoproliferative disease [1], and in rare cases, amyloid A (AA) amyloidosis can occur if the disease is not treated. Activation of the innate immune system, especially of IL-1β, is central to pathogenesis of the disease. Consequently, in 80% of patients, complete control of disease symptoms can be achieved by treatment with the IL-1 receptor antagonist anakinra.

The first cases of this syndrome were reported in 1972 and published as an independent unit in 1974 by Liliane Schnitzler, a French dermatologist. Later more than 300 cases were reported. The age peak lies in the sixth decade of life, men are affected somewhat more frequently than women [2].

Clinical symptoms

The leading clinical symptom of Schnitzler syndrome is urticarial exanthema with an emphasis on the stem. It can be accompanied by chronic relapsing fever, bone and joint pain [3], changes in bone structure, muscle pain, lymphadenopathy, and hepatosplenomegaly. Other non-specific symptoms include headache, exhaustion, and fatigue. Laboratory chemistry shows an increase in inflammatory parameters and monoclonal gammopathy [2]. There is little or no itching; instead, some burning sensations of the skin are reported ([4]; **Table 1**).

Exanthema

Exanthema as the main criteria of the syndrome is, by definition, present in all patients and usually the first clinical sign of disease. It shows pink to red maculae, slightly raised papules, and plaques (**Fig. 1a, b**). It can occur all over the body, but involvement of the face and extremities is rare. Angioedema is very rare [4], and significant mucosal swelling with dyspnea and/or dysphonia is very unusual. The lesions are temporary and usually persist for less than 48 h [1]. The exanthema shows a daytime dynamic, often most pronounced in the evening hours [5]. Varying individually, urticarial exanthema may occur daily over months or years, or may be temporarily interrupted by remission phases of days or several weeks. This rarely lasts longer than 1 month in untreated patients.

Monoclonal gammopathy

Monoclonal gammopathy is associated with a κ-light chain in more than 90% of patients. Normally, IgM levels are low at the time of diagnosis (<10 g/l in 67% of patients), but can increase by about 0.5–1 g/l annually. High IgM values occur when associated with Waldenström disease. There are several reports of Schnitzler syndromes (<10% of reported cases) with an associated monoclonal IgG component. Bence Jones proteinuria was described in about 30% of patients. In about 25% of patients, a lowered IgG or IgA level is found [6]. At the time of diagnosis, bone marrow examination is normal in 80% of patients. The remaining 20% show unspecific, polyclonal, lymphocytic, or plasmocytic infiltrates.

Fever

Almost all patients develop an intermittent fever. The duration of the individual fever episodes is very variable [2]. Body temperature can rise to over 40 °C. The fever is usually well tolerated except for the frequently associated fatigue, and chills are rare [1]. Often there is no temporal connection between fever and

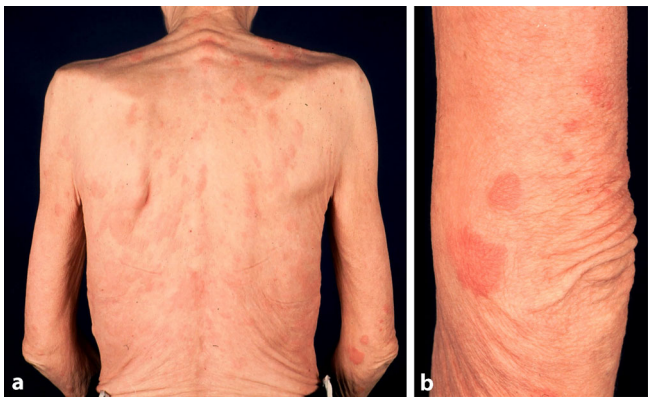

Fig. 1 ◀ Exanthema in a patient with Schnitzler syndrome. **a** The pink urticarial plaques typical for Schnitzler syndrome appear. **b** Close-up

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Table 1 Clinical and laboratory chemical findings according to their frequency in patients with Schnitzler syndrome. (Adapted from Simon et al. [2])

Findings	Frequency (%)
Urticarial exanthema	100
Increased inflammation markers (BSR, neutrophil count, CRP, IL-6, and IL-18)	95
Fever >38 °C to over 40 °C without other cause	93
Monoclonal gammopathy	89
κ-light chains	89
Joint pain	77
Leukocytosis ≥10 gpt/l	76
Bone pain	68
Changes in bone structure	62
Lymphadenopathy	47
Hepato-/splenomegaly	34

BSR blood cell lowering rate, *CRP* C-reactive protein, *IL* interleukin

skin rash. Fever in some patients reacts to non-steroidal anti-inflammatory drugs (NSAIDs) and/or steroids, and can normally be fully controlled by a drug-based interleukin (IL)-1 block [6]. The influence of stress, cold, or infection may cause or aggravate the symptoms [1].

Musculoskeletal system

The involvement of the musculoskeletal system is another important feature of the disease, which affects about 80% of patients. Bone pain in the pelvic bone and tibia is the most characteristic finding, but arthralgia or fully developed arthritis can also occur. Joint destruction and/or deformities have not yet been observed [1, 7]. About 30–40% of patients showed bone lesions in imaging studies [8]. Radiologically, osteocondensation with cortical hyperostosis of the distal femur and the proximal tibia is noticeable. Osteolytic lesions and periosteal appositions have been reported. Magnetic resonance imaging shows thickening of the cortical bone and possibly medullary bone involvement and marrow infiltration, without evidence of a tumor in the affected areas [9].

Lymphadenopathy and hepatosplenomegaly

Palpable lymph nodes are found in about 45% of patients in the axillary and inguinal region and sometimes also in the neck area. They can be permanently enlarged by up to 2 or 3 cm and show non-specific inflammation [1]. In about one third of patients, hepato- or splenomegaly occurs [4, 6].

Further laboratory chemical findings

During the course of the disease, constantly increased inflammatory parameters (blood sedimentation rate, neutrophil count, C-reactive protein [CRP], IL-6, and IL-18) often occur. The complement values are normal or elevated. Inflammatory anemia, sometimes thrombocytosis, is present in up to 50% of patients. Inflammatory anemia can be very severe and symptomatic [6]. Persistent neutrophilic leukocytosis (>10 gpt/l) occurs in more than two thirds of patients [4, 6].

Course of disease

The disease course is protracted and spontaneous remissions have hardly been published so far [1, 10]. The overall prognosis of Schnitzler syndrome depends on the possible development of lymphoproliferative disease, including lymphoplasmocytic lymphoma, Waldenström macroglobulinemia, Richter lymphoma, marginal zone lymphoma, or IgM myeloma [11]. About 15–20% of patients with Schnitzler syndrome develop lymphoproliferative diseases [2, 4]. Lymphoma or Waldenström disease usually occurs more than 10 to 20 years after onset of the first signs of the syndrome. There is no specific predictive factor for the development of lymphoproliferative disorder. Patients without lymphoproliferative disease have unrestricted life expectancy [12]. Due to the chronic inflammation, AA amyloidosis may develop [4]. **Table 1** gives an overview of the frequency of various symptoms.

Diagnostics

Diagnosis of Schnitzler syndrome is based clinically on the typical chronic recurrent exanthema with associated monoclonal gammopathy [2]. These two main criteria as well as the secondary criteria were first defined by Lipsker et al. in 2001 [6]. De Koning slightly extended the criteria by adding the possibility of an IgG variant of Schnitzler syndrome in addition to monoclonal IgM gammopathy [4]. At an international consensus meeting in 2012, the Strasbourg criteria were defined. These comprise two main and four secondary criteria, and distinguish a clear Schnitzler syndrome from a probable Schnitzler syndrome. The main criteria include urticarial exanthema and monoclonal gammopathy with IgM or IgG. The secondary criteria include recurrent fever above 38 °C without any other cause, changes in bone structure visible in imaging with or without bone shearing, neutrophil dermal infiltrate in skin biopsy, and leukocytosis and/or elevated CRP. If both main criteria and at least two secondary criteria for monoclonal IgM or at least three secondary criteria for monoclonal IgG are present, a clear diagnosis can be made. If both main criteria, monoclonal IgM, and one subcriterion, or monoclonal IgG and two subcriteria apply, the diagnosis of Schnitzler syndrome is likely ([2]; **Table 2**).

Patients with all signs of Schnitzler syndrome—with the exception of skin rash or monoclonal gammopathy—should be referred to as patients with Schnitzler-like syndrome [2].

For the Strasbourg criteria, the sensitivity for a clear and probable diagnosis was 81 and 93%, respectively, with a corresponding specificity of 100 and 97%. These rates can be assessed as reliable [13].

A detailed symptom-oriented anamnesis, physical examination, laboratory checks, skin biopsy, and, if necessary, imaging examinations are decisive for diagnosis of Schnitzler syndrome (**Table 3**; [5]).

The determination of serum amyloid A (SAA) provides additional information on the extent of inflammatory

activity. Permanently elevated SAA may indicate an increased risk of amyloidosis. An increase in the gamma globulin fraction can be investigated by serum electrophoresis. For the exact detection of monoclonal gammopathy, immune fixation in the serum is necessary [2]. If this is positive, lymphoma should be ruled out by bone marrow biopsy and imaging of the thorax and abdomen [2]. Urine status can be used to examine proteinuria associated with amyloidosis.

A skin biopsy from an urticarial lesion is recommended [2]. If a typical plaque is biopsied at a relatively early stage, a neutrophil-rich infiltrate of variable density can be found in the upper corium [1]. In addition, neutrophil epitheliotropism with neutrophil migration into epithelia of epidermis, hair follicles, sebaceous glands, and sweat glands can be observed in Schnitzler syndrome [14].

Optionally, bone scintigraphy or bone MRI can be performed [2].

So far, no established biomarkers are available for Schnitzler syndrome. Various studies have investigated vascular endothelial growth factor (VEGF) [15], the IL-1 receptor antagonist (IL-1-Ra), and the phagocyte-specific proteins S100A8/9 and S100A12 [16, 17]. S100A8/9 and S100A12 may correlate with inflammatory and disease activity.

Differential diagnoses

Due to its rarity, Schnitzler syndrome is an exclusion diagnosis that must be distinguished from diseases with similar symptoms [5]. The most important differential diagnosis is the much more frequent chronic spontaneous urticaria, where there are spontaneous and recurrent wheals at the integument. In contrast to Schnitzler syndrome, however, itching is very pronounced and angioedema is more frequent. Chronic spontaneous urticaria usually responds well to antihistamines and in severe cases to anti-IgE therapy with omalizumab. These drugs have no effect in the treatment of Schnitzler syndrome [5, 18]. In the biopsies of Schnitzler syndrome, increased expression of the cytokines IL-6, IL-1β, IL-18, the neutrophil marker myeloperoxidase, and the inflammasome components ASC (apoptosis-associated speck-like protein containing a CARD) and caspase-1 were found in comparison to chronic spontaneous urticaria, which may allow differentiation [19].

Other diseases characterized by persistent wheal formation, joint pain, recurrent fever episodes, and general fatigue are urticaria vasculitis, cryopyrin-associated periodic syndrome (CAPS), and adult-onset Still's disease (AOSD; [20]; **Table 4**).

The hypocomplementemic form of urticaria vasculitis is clinically difficult to distinguish from Schnitzler syndrome due to fever symptoms, arthralgia, and persistent wheals. The wheals characteristically persist for more than 24 h. A skin biopsy can be helpful, in which for some cases of urticaria vasculitis, leukocytoclastic vasculitis with destruction of the small vessels, cell necrosis, endothelial cell swellings, and fibrin deposition is observed, which is not to be expected in Schnitzler syndrome [12]. Rather, there is neutrophil epidermotropism, which indicates an inflammation rich in neutrophils in inflammatory systemic diseases [14]. The reaction pattern is known as neutrophil urticarial dermatosis (NUD) [21] and can be observed in Schnitzler syndrome, CAPS, and AOSD, but not in urticaria vasculitis [22].

The clinical symptoms of CAPS can be similar to those of Schnitzler syndrome. In contrast to Schnitzler syndrome, CAPS is a monogenetic disease that often occurs in childhood. In addition, the family history can be helpful. Monoclonal gammopathy is not observed in CAPS [8].

Initially, pharyngitis frequently occurs in AOSD. In laboratory chemistry, ele-

Abstract · Zusammenfassung

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Schnitzler syndrome

Abstract

Schnitzler syndrome is a very rare acquired systemic disease with many similarities to hereditary autoinflammatory syndromes. The main characteristics are generalized exanthema and IgM monoclonal gammopathy. Other clinical features include fever, muscle, bone, and/or joint pain, and lymphadenopathy. About 15–20% of patients with Schnitzler syndrome develop lymphoproliferative diseases and, in rare cases, amyloid A (AA) amyloidosis can occur if the disease is not treated. Activation of the innate immune system, especially interleukin (IL)-1β, is central to the pathogenesis of disease. Consequently, complete control of disease symptoms can be achieved in 80% of patients by treatment with the IL-1 receptor antagonist anakinra.

Keywords

Hereditary autoinflammatory syndrome · Urticarial rash · Interleukin-1 · Anakinra · Systemic disease

Schnitzler-Syndrom

Zusammenfassung

Das Schnitzler-Syndrom ist eine sehr seltene, erworbene Systemerkrankung, die viele Gemeinsamkeiten mit den hereditären autoinflammatorischen Syndromen aufweist. Das Exanthem und eine monoklonale Gammopathie mit IgM sind die Charakteristika der Erkrankung. Zu den klinischen Hauptmerkmalen gehören Fieber, urtikarielles Exanthem, Muskel-, Knochen- und/oder Gelenkschmerzen und eine Lymphadenopathie. Etwa 15–20 % der Patienten mit Schnitzler-Syndrom entwickeln eine lymphoproliferative Erkrankung, und selten kann es zum Auftreten einer AA-Amyloidose kommen, wenn die Erkrankung nicht behandelt wird. Eine Aktivierung des angeborenen Immunsystems, speziell des Interleukin(IL)-1β, ist zentral in der Pathogenese der Erkrankung. Folgerichtig kann bei 80 % der Patienten eine komplette Kontrolle der Krankheitssymptome durch Behandlung mit dem IL-1-Rezeptorantagonisten Anakinra erreicht werden.

Schlüsselwörter

Hereditäres autoinflammatorisches Syndrom · Urtikarielles Exanthem · Interleukin-1 · Anakinra · Systemerkrankung

Table 2 Strasbourg criteria for the diagnosis of Schnitzler syndrome

Main criteria	Chronic urticarial exanthema
	Monoclonal IgM or IgG
Secondary criteria	Recurrent fever
	Objective changes in bone formation with or without bone pain
	Neutrophil-rich dermal infiltrate in a skin biopsy
	Leukocytosis and/or elevated CRP in blood
Secure diagnosis	Both main criteria and
	At least two secondary criteria for monoclonal IgM
	At least three secondary criteria for monoclonal IgG
Probable diagnosis	Both main criteria and
	At least one secondary criterion for monoclonal IgM
	At least two secondary criteria for monoclonal IgG

CRP C-reactive protein

Table 3 Diagnostics of Schnitzler syndrome

Anamnesis [5]	When did the symptoms start?
	What is the course of the disease (continuous/relapsing)?
	What dynamics does the urticarial exanthema show during the course of the day?
	Is there itching and how intense is it?
	Can antihistamines be used to improve symptoms?
	Do the symptoms worsen with cold, stress, or infections?
	Is there pain in the joints, muscles, or bones?
	Is there recurrent fatigue, exhaustion, or a feeling of illness?
	Does chronic recurrent fever occur?
Physical examination [5]	Skin
	Lymph nodes
	Musculoskeletal system
Laboratory testing [2]	Differential blood count
	CRP
	Serum amyloid A → hint for amyloidosis
	Serum electrophoresis → orienting
	Immunfixation → exact detection of a monoclonal gammopathy
	Urine status → exclusion of proteinuria in amyloidosis
Histological examinations [2]	Skin biopsy from lesional skin
	Bone marrow biopsy → exclusion of lymphoma
Imaging (optional) [2]	Bone scintigraphy
	MRI of the bone

CRP C-reactive protein, *MRI* magnetic resonance imaging

vated transaminases and an elevated ferritin level can be observed [2]. The exanthema of AOSD differs morphologically from Schnitzler syndrome due to its rather salmon-colored maculopapular urticarial efflorescence ([23]; ◘ **Table 4**).

In addition, exanthemas can be considered as differential diagnoses in the context of autoimmune diseases such as systemic lupus erythematosus and monoclonal gammopathy of unclear significance (MGUS) [2].

Pathogenesis

Schnitzler syndrome belongs to the group of systemic autoinflammatory diseases characterized by an intermittent or chronic inflammatory process mediated by the innate immune system [24]. Characteristic are neutrophil activation in blood and skin and an increased concentration of the cytokines IL-1β, IL-18, and IL-6 in blood and skin [25]. IL-1β and IL-18 are generated by the activation of a large intracellular multiprotein complex, the inflammasome. Inflammasome stimulators have not yet been defined in Schnitzler syndrome. Dermal mast cells and blood mononuclear cells are thought to be the source of IL-1β in patients with Schnitzler syndrome [26]. IL-1β promotes IFN (tumor necrosis factor)-γ/T-bet induction in T-helper (Th)17 cells and suppresses their immunomodulating IL-10 secretion [27]. In patients with Schnitzler syndrome, the IL-10-mediated inhibitory effects of Th17 cells were significantly limited, suggesting involvement of the adaptive immune system in pathogenesis. Under systemic IL-1 blockade, IL-10 production of the Th17 cell subpopulation normalized. IL-6 levels in serum appear to correlate with disease activity [28]. The pathogenetic significance of this cytokine is suggested by the successful treatment with IL-6 antagonists in patients who did not respond to IL-1 blockade [29].

Schnitzler syndrome shares many clinical and biological features with CAPS, which is caused by activating mutations in the *NLRP3* (nucleotide-binding oligomerization domain leucine-rich repeat containing pyrin domain 3) gene [30]. *NLRP3* encodes important components of the inflammasome. A gain-of-function mutation in this gene caused by overactivity of caspase-1 increased the release of IL-1β and IL-18 [24]. In both diseases, patients suffer from recurrent fever, urticarial exanthema, proliferation of neutrophils in skin and blood, inflammasome activation in the skin, and an increase in inflammatory parameters (CRP) [26]. Schnitzler syndrome has no germline mutation in the *NLRP3* gene. Somatic mutations or polymorphisms of unclear phenotypic relevance have been detected [30]. In the affected patients, however, the possibility of a late manifestation of CAPS was also discussed. A current genetic investigation could not find any relevant mutations in genes of the inflammasome signaling pathway [1, 31].

Table 4 Common and different findings of the most important differential diagnoses of Schnitzler syndrome

Differential diagnosis	Common findings	Different findings
Chronic spontaneous urticaria	Recurrent spontaneous wheal formation	Angioedema up to 50% Severe itching Response to antihistamines Response to Anti-IgE therapy Reduced expression of IL-6, IL-1β, IL-18, myeloperoxidase, ASC, and caspase-1 in skin biopsy
Hypocomplementemic urticaria vasculitis	Persistent wheals joint pain Recurrent fever attacks General fatigue	Histologically true leukocytoclastic vasculitis
Cryopyrin-associated periodic syndrome		Monogenetic diseases First manifestation in childhood No monoclonal gammopathy
Adult-onset Still's disease		Initial pharyngitis Elevated transaminases Highly elevated ferritin level Salmon-colored maculopapular exanthema

ASC apoptosis-associated speck-like protein containing a CARD

The role of monoclonal gammopathy in the pathogenesis of Schnitzler syndrome remains unclear. On the one hand, monoclonal gammopathy may be the result of the increased release of IL-1β, IL-6, and IL-18. On the other hand, monoclonal gammopathy could be the cause of the disease and lead to a reduction of IL-1 clearance via an agonistic effect at the IL-1 receptor [1]. The observation of an association between macroglobulinemia in Waldenström disease and mutations in the *MYD88* gene [32] raises the question of a possible association between the IgM paraprotein and autoinflammation in Schnitzler syndrome. In fact, MyD88 is a toll-like receptor signal transduction molecule that serves as an adapter for IL-1 signal transduction by interacting with the IL-1 receptor complex and IL-1 receptor-associated kinase, whereby increased IL-1 stimulation could contribute to monoclonal IgM production.

Treatment

There is currently no approved treatment for Schnitzler syndrome. The disease does not respond to antihistamines [5]. Anti-inflammatory drugs such as NSAIDs, glucocorticoids, and colchicine only lead to a slight improvement of symptoms. Provided disease activity does not impair quality of life, these drugs can be used for low inflammatory parameters (CRP <30 mg/l) or as supportive therapy to an IL-1 blocker [2].

The availability of antagonists of the IL-1 signaling pathway has revolutionized the treatment of Schnitzler syndrome. They lead to a rapid clinical response even in severe disease progressions. Inflammation parameters are significantly reduced. The therapeutic effect lasts for the duration of treatment. With anakinra, rilonacept, and canakinumab, three IL-1-neutralizing drugs are available [2].

Anakinra is approved in Europe and the US for treatment of rheumatoid arthritis and since April 2018 for treatment of AOSD. It is an IL-1 receptor antagonist and was first used in the treatment of Schnitzler syndrome. The symptoms of the disease return after pausing the drug [2]. A multicenter retrospective analysis in France examined 42 patients with Schnitzler syndrome, 29 of whom received the IL-1 receptor antagonist anakinra. In two cases, Waldenström disease developed during the course of disease, in one case AA amyloidosis. All 29 patients with anakinra responded to treatment over a median observation period of 36 months, without loss of efficacy. Three patients developed grade 3 to grade 4 side effects, 24 patients achieved complete remission (83%), 5 patients achieved partial remission (17%). Six patients developed severe infections [33].

Rilonacept is a dimeric fusion protein that blocks IL-1α, IL-1β, and IL-1 receptors. In a prospective study, rilonacept resulted in a rapid response and a sustained and significant improvement in health with good tolerability in 8 patients [34].

Canakinumab is approved in Europe and the US for treatment of CAPS, systemic juvenile idiopathic arthritis, AOSD, and therapy-resistant gout. An open, single-arm study evaluated 8 patients receiving 150 mg canakinumab once a month for 6 months. This led to complete remission in all patients after 14 days [35]. In the follow-up period of 3 months, 4 patients developed a relapse, the other 4 patients achieved a remission of several months after the end of the study. Another randomized, placebo-controlled, multicenter phase II study investigated 20 patients with active disease in four German study centers [17]. In the canakinumab arm, significantly more patients ($p = 0.001$) achieved complete remission ($n = 5$ of 7) than in the placebo arm ($n = 0$ of 13).

General side effects of anti-IL-1 therapy are reactions at the injection site and a slightly increased risk of serious infections. It is recommended that tuberculosis be excluded and vaccinations against influenza and pneumococcus be refreshed before starting treatment. No live vaccination should be administered during ongoing therapy. Every 3 months, blood count and CRP should be checked, serum electrophoresis or immune fixation performed, and immunoglobulins quantitatively determined [2].

For patients who do not respond to IL-1 blockade, treatment with the IL-6 antagonist tocilizumab may be indicated. Krause et al. reported remissions in 3 patients [29].

Practical conclusion

- **Schnitzler syndrome is a very rare autoinflammatory disease that can**

be diagnosed on the basis of the Strasbourg criteria.
- The main criteria are chronic recurrent exanthema with associated monoclonal gammopathy.
- Various differential diagnoses such as chronic spontaneous urticaria, cryopyrin-associated periodic syndrome, or urticaria vasculitis should be excluded.
- The IL-1 receptor antagonist anakinra is a very effective therapy for Schnitzler syndrome that can significantly improve patients' quality of life.
- The prognosis of Schnitzler syndrome depends on the development of lymphoproliferative disease, which can occur in 15–20% of cases.

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Compliance with ethical guidelines

Conflict of interest F. F. Gellrich and C. Günther declare that they have no competing interests.

For this article, no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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