The Schnitzler syndrome: chronic urticaria in disguise: a single-centre report of 11 cases and a critical reappraisal of the literature

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Abstract

Objective

The Schnitzler syndrome is a rare inflammatory disorder, with a chronic urticaria-like rash and an IgM (rarely IgG) monoclonal gammopathy as cardinal features. Interleukin-1 β is regarded as the key mediator and the interleukin-1 receptor antagonist anakinra has been proposed as first-line treatment. This case series of eleven patients is intended to enhance disease awareness and to compare our centre's experience with that of literature.

Methods

We describe the clinical features and disease course of 11 patients with a definite Schnitzler syndrome, according to the Strasbourg diagnostic criteria, encountered in the University Hospital, Leuven, Belgium, between 1995 and 2015.

Results

Eleven patients, with a median age of 55 years, were diagnosed with Schnitzler syndrome. All but one were diagnosed during the last decade. Of 6 patients treated with anakinra, 2 had a suboptimal response and 2 had poor tolerance (injection site reaction and neutropenia, respectively). Two of the 11 patients died as a consequence of the disease, culminating in Waldenström's macroglobulinaemia and AA amyloidosis, respectively.

Conclusion

The Schnitzler syndrome is rare, but probably underdiagnosed. In a patient with a chronic urticaria-like dermatosis, minor itch, intermittent fever and bone or joint aches, protein electrophoresis and immunofixation should be ordered. Especially, a finding of a monoclonal IgM kappa fits the diagnosis of Schnitzler syndrome. Anakinra may provide symptomatic relief, although the response is not always spectacular. The outcome is not always benign as fatal complications may occur.

Key words

Schnitzler syndrome, urticaria, monoclonal gammopathy, autoinflammation, interleukin-1

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Introduction

In 1972, Liliane Schnitzler, a French dermatologist, first described the syndrome that was subsequently named after her, in a patient with chronic urticaria, bony lesions and an IgM paraproteinaemia (1, 2). In 2007, 92 published cases were summarised and criteria were proposed (3). In 2013, an international expert group established the so-called Strasbourg diagnostic criteria (Table I) (4). Cardinal features are a chronic urticarial rash and a monoclonal Immunoglobulin (Ig) M (rarely IgG). Minor criteria are intermittent fever, arthralgia or arthritis, bone pain and/or bone abnormalities, lymphadenopathy, hepatomegaly and/or splenomegaly, and elevated acute-phase proteins (3). Increasingly, cases are reported in literature, mainly but not exclusively from Europe and the USA, amounting to >280 (3,5). Still, the Schnitzler syndrome is likely an under-recognised entity.

The present single-centre case series was intended to increase awareness of the disease and allows to critically reappraise the diagnosis, the disease course and the therapy.

Materials and methods

All patients diagnosed at the University Hospitals of Leuven, a large academic tertiary care centre, with a definite diagnosis of Schnitzler syndrome according to the Strasbourg diagnostic criteria are presented (4). Before the diagnosis was established, other diseases were ruled out such as adult-onset Still's disease, systemic lupus erythematosus, the POEMS syndrome, cryopyrin-associated syndrome and other monogenic auto-inflammatory disorders, chronic idiopathic urticaria, and urticarial vasculitis (3, 4). The patient files were revisited and data were extracted, with an emphasis on symptoms, signs, laboratory data, treatment, disease course, and outcome. The study protocol was approved by the ethics committee of the university hospital, Leuven, Belgium. Three of the cases have previously been described in international medical journals (7-9).

Results

Between 1995 and 2015, 11 patients were diagnosed with Schnitzler syndrome in the University Hospital, Leuven: 8 male and 3 female patients, with a median age at diagnosis of 55 (range, 36–77) years (Table II). All but one were diagnosed during the last decade. All patients had Belgian nationality, except one, who originated from Hungary. The interval between first symptoms and diagnosis, maximally 20 years, tended to shorten in recent years (Table II). Urticaria-like dermatosis was the presenting symptom in all but one patient, in whom joint pains predated dermatological symptoms. All monoclonal gammopathies were IgM, and of the kappa subtype in all but one patient. Median total IgM levels at diagnosis were 3.0 g/l (range 1.5–36.2 g/l; reference, 0.46–3.04 g/l). All patients, by default, had a chronic recurrent urticaria-like rash, mostly not or only slightly pruritic. Itching, if present, only developed after a few years and responded poorly to antihistamines. Ten patients reported bone or joint pains, typically involving the larger peripheral joints and without frank arthritis; 9 patients experienced intermittent fevers; weight loss and lymphadenopathies, mostly peripheral, were reported in 7 patients each. Only the one patient, who progressed to Waldenström's macroglobulinaemia, developed hepatomegaly and splenomegaly. All patients had elevated acute-phase reactants before treatment, including elevated C-reactive protein levels and neutrophilic leukocytosis. In 9 patients, skeletal scintigraphy demonstrated bone remodeling. In 6 patients, a skin biopsy was performed, revealing neutrophilic inflammation in 4, and a mononuclear inflammation and a mixed lymphocytic-eosinophilic infiltration in one patient each.

Treatment modalities included acetaminophen, H1-antihistamines, non-steroidal anti-inflammatory agents, colchicine, corticosteroids, azathioprine, methotrexate, cyclophosphamide, chlorambucil, and thalidomide, but efficacies were moderate at best.

Six patients were treated with anakinra (starting dose: 100 mg subcutaneously daily). Fevers abated in all, urticaria-like dermatosis disappeared in 4, and diminished in 2; joint and bone pains dissolved in 4, but persisted in 2, who were

Table I. Schnitzler's syndrome: Strasbourg diagnostic criteria (4).

Obligate criteria
- Chronic urticarial rash
- Monoclonal IgM or IgG

Minor criteria
- Recurrent fever[a]
- Objective findings of abnormal bone remodeling with or without bone pain[b]
- A neutrophilic dermal infiltrate on skin biopsy[c]
- Leukocytosis and/or elevated C-reactive protein (CRP)[d]

Definite diagnosis if
Two obligate criteria AND at least two minor criteria if IgM, and three minor criteria if IgG
Probable diagnosis if
Two obligate criteria AND at least one minor criterion if IgM, and two minor criteria if IgG

[a]A valid criterion if objectively measured. Must be >38°C, and otherwise unexplained. Occurs usually – but not obligatory- together with the skin rash.
[b]As assessed by bone scintigraphy, MRI or elevation of bone alkaline phosphatase.
[c]Corresponds usually to the entity described as 'neutrophilic urticarial dermatosis' (5); absence of fibrinoid necrosis and significant dermal edema.
[d]Neutrophils >10 000/mm^3 and/or CRP >30 mg/l.

Table II. Characteristics of the patients.

Patient number	Gender	Age at first symptoms (years)	Age at diagnosis (years)	Year of diagnosis	M-protein	Anti-IL therapy	Complications
1	Male	48	55	1995	IgM κ	None	Waldenström's macroglobulinaemia, Haemophagocytic syndrome, †2007
2	Male	54	74	2006	IgM κ	None	AA amyloidosis, †2007
3	Male	40	54	2007	IgM κ	Anakinra	
4	Male	33	37	2007	IgM κ	Anakinra, Canakinumab	
5	Male	46	46	2008	IgM κ	Anakinra	
6	Male	77	77	2008	IgM κ	None	Unrelated death, †2013
7	Female	54	55	2012	IgM κ	None	
8	Female	34	36	2013	IgM κ	Anakinra	
9	Male	51	55	2013	IgM κ	Anakinra, tocilizumab	
10	Female	58	59	2013	IgM λ	Anakinra, tocilizumab	
11	Male	41	42	2015	IgM κ	None	

IL: interleukin; M: monoclonal; Ig: Immunoglobulin; κ: kappa; λ: lambda; †: fatal outcome.

recently switched to tocilizumab, a humanised monoclonal antibody against the interleukin-6 receptor. Tocilizumab induced disease remission in one of the 2 patients. One patient stopped anakinra because of injection-site reactions. Another patient developed neutropenia and was switched to canakinumab, a human monoclonal antibody targeted at interleukin-1 beta, with an ongoing excellent control during 4.5 years. Biologicals did not affect the IgM paraprotein levels.

Three patients died. One patient progressed to Waldenström's macroglobulinaemia, 5 years after the onset of joint pains and urticaria-like dermatosis. The disease course was complicated by a myelodysplastic syndrome secondary to chemotherapy and finally by a fatal, histologically proven haemophagocytic syndrome at age 67. One patient developed AA-amyloidosis of colon and kidney, complicated by end-stage nephrotic syndrome, and died at age 75. The last death was considered to be unrelated to Schnitzler syndrome; this patient died at age 82, 5 years after the diagnosis of Schnitzler syndrome, in the aftermath of a complicated colonic diverticulitis.

Discussion

In general, our findings are in keeping with the published experience and may serve to underline the main clinical features of Schnitzler syndrome. Some discrepancies from the literature will be highlighted.

Epidemiology

Schnitzler syndrome is an orphan disease that is probably underdiagnosed. Researchers from the Mayo Clinic, USA, estimated that Schnitzler syndrome may be present in up to 1.5% of patients with a monoclonal IgM in the serum (6). In 2014, HD de Koning reviewed 281 published cases (5). The disease is reported all over the world, with most reports coming from Europe. The median age of onset is 51 years and the male-female ratio of 1.5. Historically, the diagnostic delay exceeded 5 years in most cases. Our single centre experience with 11 cases corroborates published case series. However, during the last decade, our patients were diagnosed well within a 5-year interval from symptom onset, probably reflecting an increasing recognition of the disease. In the series of 94 patients reported by de Koning *et al*. (3), symptoms started before the age of 35 years in 5 only (5.3%), whereas 2 of 11 our patients (18%) experienced such an early onset. Thus, Schnitzler syndrome should not be regarded as a disease only encountered in the elderly.

Clinical findings

The skin rash is an obligatory sign and usually the first disease manifestation of Schnitzler syndrome. While chronic urticaria is the descriptive term that is often used, the rash is peculiar, consisting of rose or macules or barely elevated plaques, 0.5 to 3 cm in diameter, which may coalesce (Fig. 1) (10, 11). Usually, the rash involves the trunk and the extremities and is rather symmetrical. Individual lesions vanish within 48 hours without sequel. Flares are variable, with a typical recurrence within one month, although the rash may be continuous. Contrary to genuine urticaria, the skin rash is often non-pruritic at first. Angioedema is usually absent. Response to antihistamines is poor. On

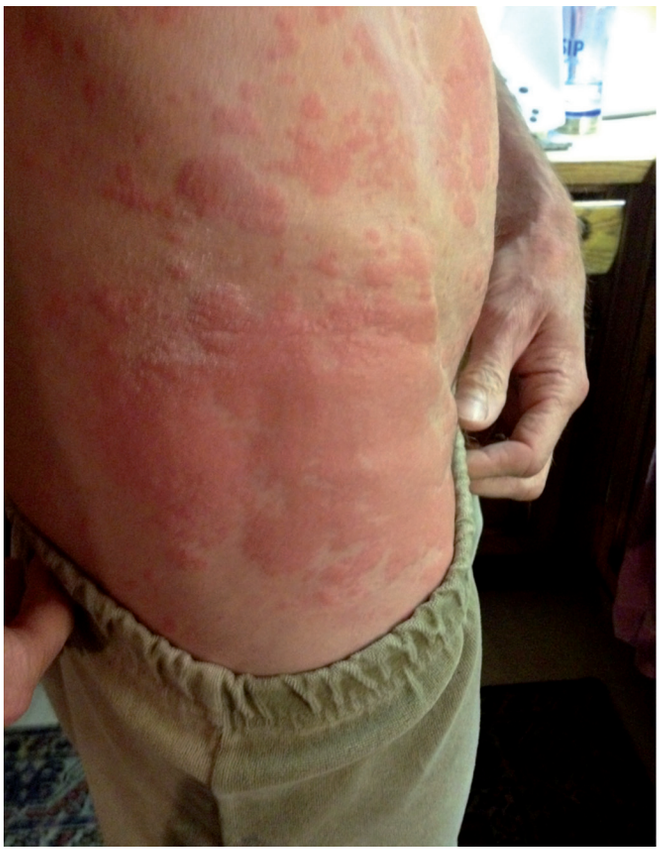

Fig. 1. Typical skin rash in a patient with Schnitzler syndrome.

biopsy, a neutrophilic infiltrate of the dermis is encountered most frequently, with leucocytoclasia, but without vasculitis or significant oedema (10-13). These characteristics serve to delineate the rash of Schnitzler's syndrome from common urticaria, which is usually intensely pruritic, consists of raised hives, responds to anti-allergic agents such as H1-antihistamines, and may be accompanied by angioedema. Typical biopsy findings of chronic idiopathic urticaria include interstitial oedema with a perivascular mixed infiltrate consisting mainly of mononuclear cells (14).

As in published cases, the majority of our patients experienced intermittent fevers. As for the skin rash, the periodicity of the fevers is variable. Although temperatures can increase markedly, fevers are usually well tolerated and chills are rare. Joint or bone pains too are prevalent, with an increased tracer uptake on bone scintigraphy (9). Frank arthritis is rare. Peripheral lymphadenopathy was often present, whereas hepatomegaly or splenomegaly were rarely encountered. Fatigue and weight loss are major complaints in some patients.

Biological findings

Most patients, as in our series, have elevated acute-phase reactants, including elevated C-reactive protein and erythrocyte sedimentation rates, and neutrophilic leukocytosis. Anaemia of chronic disease is often present. Eosinophilia is absent. Complement levels are normal or increased, in contrast with the complement consumption in hypocomplementaemic urticarial vasculitis.

A monoclonal protein is present by definition, although levels may be very low at onset. In over 90% of cases, the monoclonal component is IgM kappa (3-5). A so-called variant Schnitzler syndrome is characterised by the present of monoclonal IgG instead of IgM (3). In this instance, however, diagnosis should be made after even more scrutiny, as the Strasbourg diagnostic criteria suggest (Table I) (4). The pathogenesis of Schnitzler syndrome is uncertain. Notably, the association with the monoclonal protein, most frequently IgM kappa, is puzzling. Increasingly, Schnitzler syndrome is regarded as an acquired autoinflammatory syndrome (11). It has phenotypic features in common with other rare autoinflammatory syndromes such as the cryopyrin-associated syndrome, with which it shares the response to interleukin-1-blockade. Recent reports suggest that the monoclonal IgM may rather be a byproduct of the ongoing inflammation, rather than a pathogenic trigger (5).

Treatment

The number of therapies that have been tried in patients with Schnitzler syndrome is remarkable (3). Most pharmacological agents, however, had no or only modest effects. The treatment paradigm shifted with the advent of the anti-interleukin-1 agents, including anakinra especially, canakinumab and rilonacept. A prompt response to the interleukin-1 receptor antagonist anakinra was even forwarded as a diagnostic criterion (11). Indeed, initial case reports documented a dramatic improvement (15). In a French multicentre study, 29 of 42 patients were treated with anakinra, inducing a complete remission in 24 (83%) and a partial remission in 5 (17%) (16). In the Mayo Clinic, 5 of 20 patients received anakinra; only 1 patient had dramatic improvement, the second had minimal benefit, and 3 were lost to follow-up (13). Recently, 3 patients have been described in whom therapy with anakinra failed and who recovered after therapy with the anti-interleukin-6 agent tociluzimab (17). Weekly injections of rilonacept, another interleukin-1 neutralising agent, induced a complete or near complete remission in 4 of 8 patients (18). Limited data suggests that the longer acting agent canakinumab, that inhibits only interleukin-1β, is highly effective in the majority of cases (8, 19).

In the present series, not all patients treated with anakinra had a complete and durable remission, or tolerated therapy. Also, symptoms tend to recur after cessation of interleukin-1 blockade and the treatment does not affect the levels of monoclonal protein. Thus, although interleukin-1 blockade offers symptomatic relief in the majority of patients, therapy is not curative. Moreover, interleukin-1 neutralising agents are not licensed for this indication and are not readily available in every country (including Belgium).

Disease course

Patients with Schnitzler syndrome, if left untreated, experience recurrent and often debilitating symptoms. Spontaneous remission seems to be extraordinarily rare (11, 20). The most important complication is the development of a haematological malignancy, most frequently Waldenström's macroglobulinaemia or lymphoma (5). The index case, described by L. Schnitzler, died of Waldenström's macroglobulinaemia 23 years after the diagnosis (21) The rate of increase of the monoclonal protein is comparable to the rate in patients with a monoclonal protein of unknown significance (MGUS). Evolution to AA amyloidosis, as occurred in one of our patients, has been described (5). Thus, although no reduction in survival was postulated, Schnitzler syndrome (3), due to the incapacitating symptoms and its association with haematological malignancies and AA amyloidosis, cannot be regarded as a benign disease. In our series of 11 patients, 2 deaths were related to the disease.

Conclusion

We present the current case series to increase the awareness among clinicians of Schnitzler syndrome. Patients present with a so-called urticaria-like eruption. However, itch is not prominent, lesions are not or only slightly raised, antihistamines do not produce relief, angioedema is rarely present and skin biopsy mostly shows neutrophilic inflammation. More strikingly, systemic symptoms such as fever, fatigue, weight loss, bone and joint pains, corroborate the picture. In such a constellation, a diagnosis of Schnitzler syndrome should be entertained and a lab work-up is warranted, including acute-phase reactants and especially serum protein electrophoresis and immunofixation. In case of bone aches, a low threshold should be applied to order bone scintigraphy, which often shows increased osteoblastic activity. Complications include Waldenström's macroglobulinaemia and AA-amyloidosis. Anakinra, can induce dramatic symptomatic relief in Schnitzler syndrome, but response in our experience was not always that spectacular or straightforward as described in the literature. Moreover, symptoms tend to recur once interleukin-1-antagonists are interrupted. Thus, while anakinra presented a breakthrough in the treatment, it does not seem to be a panacea for every patient. Comparative studies with other, longer-acting interleukin-1 antagonists, and other biologicals such as interleukin-6 antagonists are warranted.

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