Schnitzler syndrome and Schnitzler-like syndromes

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Abstract

Schnitzler syndrome is a rare disease of adult-onset with main features including chronic urticarial rash, recurrent fever, arthralgia or arthritis, monoclonal gammopathy of undetermined significance (MGUS), and marked systemic inflammation. Schnitzler syndrome is often underdiagnosed. Patients with Schnitzler syndrome may present to dermatologists and allergists for urticaria, hematologists for MGUS, or rheumatologists for arthritis. It is important to recognize Schnitzler syndrome for its remarkable response to interleukin (IL)-1 blockade. Besides, many cases of Schnitzler-like syndromes do not meet the diagnostic criteria of classical Schnitzler syndrome but display excellent response to IL-1 inhibitors. The overly produced IL-1 is the result of a somatic mosaic gain of function mutation of *NLRP3* (nucleotide-binding oligomerization domain [NOD]-like receptor [NLR] family pyrin domain containing 3) gene in some patients with Schnitzler-like syndromes. Inflammasome activation is evident in patients with classical Schnitzler syndrome although no *NLRP3* gene mutation is identified. Collectively, Schnitzler syndrome and Schnitzler-like syndromes represent a spectrum of IL-1 mediated adult-onset autoinflammatory diseases.

Keywords: Schnitzler syndrome; Schnitzler syndrome-like conditions; Interleukin-1; Chronic urticarial rash

Introduction

Schnitzler syndrome was first described by a French dermatologist, Dr. Liliane Schnitzler in 1972,[1] and was further defined in 1974.[2] Patients with classical Schnitzler syndrome present with chronic urticarial rash and monoclonal gammopathy of undetermined significance (MGUS), the two essential features required for diagnosing the condition.[3,4] It is now recognized that Schnitzler syndrome is an adult-onset autoinflammatory disease. Because of its rarity, many cases in earlier reports remained underdiagnosed for several years.[5] Recognition of Schnitzler syndrome is important since untreated patients suffer from severe morbidities from systemic inflammation. Interleukin (IL)-1 blockade therapy is highly efficacious and the vast majority of patients can achieve and maintain a long-term remission. It has been reported that cases who present with similar clinical features but do not meet diagnostic criteria for Schnitzler syndrome also have a dramatic response to IL-1 blockade treatment. Collectively these cases are referred as Schnitzler-like syndromes which extend the spectrum of IL-1 mediated adult-onset autoinflammatory conditions. The purpose of this review is to bring this rare but well treatable condition to a broader audience to increase its recognition for receiving proper therapy, to update current understanding of this spectrum of conditions, and to discuss future research for better understanding them.

Classical Schnitzler syndrome

Epidemiology

Schnitzler syndrome is very rare. It is estimated that >300 cases are reported in the literature. The majority of reported cases are from the United States, France, and Germany; and patients are of Caucasian origin.[5] A few cases have been reported in Chinese and Japanese,[6-12] which expand the ethnic groups of Schnitzler syndrome patients beyond European origin. The actual prevalence of Schnitzler syndrome is not available but it is highly likely that many cases are under diagnosed. This is reflected by the findings of a retrospective study conducted at Mayo Clinic.[13] In the interval between 1972 and 2010, a total of 62 cases were found to meet the Lipsker diagnostic criteria for diagnosis of Schnitzler syndrome,[3] but only 16 were actually diagnosed. The other 46 cases were identified by cross-referencing between 4103 patients with IgM MGUS and 8439 patients with chronic urticaria. This indicates that 1.5% of patients with a monoclonal IgM have Schnitzler syndrome in this cohort, but up to 74% of

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these Schnitzler syndrome patients were not recognized. Interestingly, given the prevalence of MGUS at 2.4% of the population,[14] and 15% to 20% of them are IgM monoclonal,[15,16] 53 to 71 cases per million population will meet the two major diagnostic criteria for Schnitzler syndrome.[3,4] However, since a definitive diagnosis of Schnitzler syndrome requires two additional minor criteria, a precise prevalence of Schnitzler syndrome in a general population could not be estimated from these data. Nevertheless, Schnitzler syndrome does not seem to be so rare.

Diagnostic considerations

Only 48 cases of Schnitzler syndrome were reported in the literature before Lipsker diagnostic criteria were proposed in 2001 when four additional cases were reported.[3] Lipsker diagnostic criteria [Table 1] require two essential features: "urticarial skin rash" [Figure 1] and "monoclonal immunoglobulin M (IgM) component," plus at least two out of eight other features. The diagnostic criteria were used by almost all the subsequent reported cases and the number of cases being reported has substantially increased. The monoclonal IgM component was later expanded by the addition of monoclonal IgG as a variant.[17] However, IgM monoclonal is present in the majority of the patients (94%) with κ light chain overwhelmingly skewed (85%), and IgG comprises of a minority (6%) among the 281 cases reported.[5] In recognizing that an increased number of Schnitzler syndrome patients will be identified by clinicians who inevitably will encounter cases which may not meet the diagnostic criteria but have certain features to be considered for Schnitzler syndrome, a group of ex[p4]erts proposed Strasbourg diagnostic criteria [Table 2] to define probable cases.[4] Strasbourg criteria are adopted from the Lipsker criteria and put forth the two essential features, "chronic urticarial rash" and "monoclonal IgM or IgG" as obligate criteria. A definite diagnosis of Schnitzler syndrome will meet the two obligate criteria and at least two minor criteria if the monoclonal is IgM, but three minor criteria if IgG. A probable diagnosis of Schnitzler syndrome is defined as having two obligate criteria and at least one minor criterion if the monoclonal is IgM, but two minor criteria if IgG. The minor criteria require more

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Table 1: Lipsker diagnostic criteria with modifications for Schnitzler syndrome.[*]

Major criteria
    Urticarial skin rash
    Monoclonal IgM component (or IgG: variant type)
Minor criteria
    Intermittent fever
    Arthralgia or arthritis
    Bone pain
    Lymphadenopathy
    Hepato- and/or splenomegaly
    Elevated ESR and/or leukocytosis
    Bone abnormalities (on radiological or histological investigation)

[*] The criteria were first proposed by Lipsker et al[3] and were later modified by de Koning et al.[17] ESR: Erythrocyte sedimentation rate. A patient can be diagnosed with Schnitzler syndrome when there is a combination of both major criteria and two or more minor criteria, after exclusion of other causes.
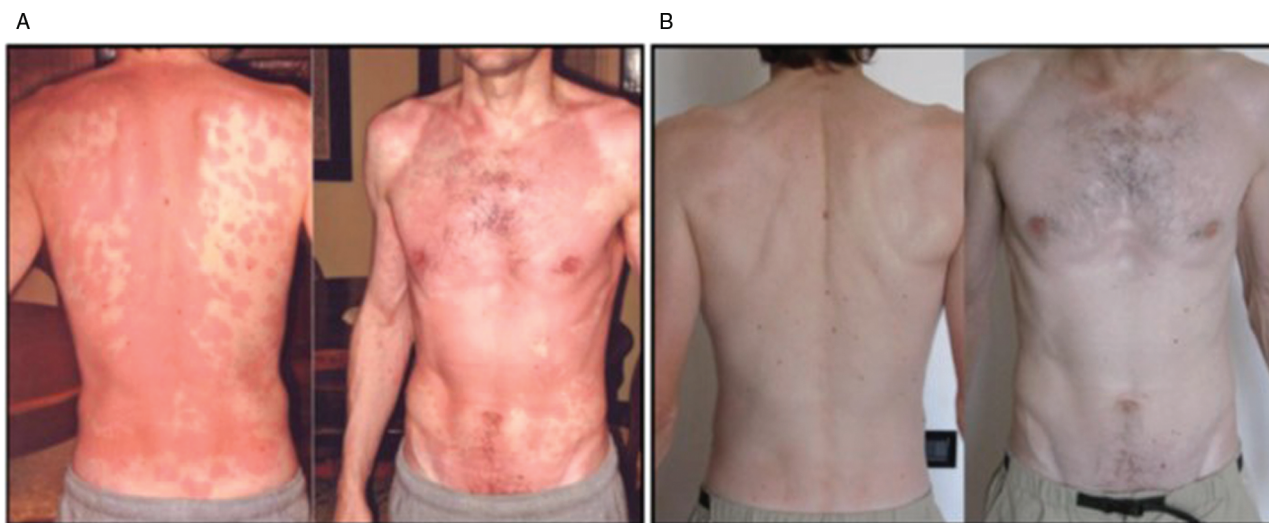
Figure 1: Urticarial skin rash of Schnitzler syndrome. (A) Urticarial skin rash on the trunk of patient with Schnitzler syndrome. (B) Resolution of skin rash after treatment with anakinra (reproduced with permission [license number: 5191401500242] from Figure 1, Tianzzi et al.[78]).

Table 2: Strasbourg diagnostic criteria for Schnitzler syndrome.[4]

Obligate criteria
    Chronic urticarial rash +
    Monoclonal IgM or IgG
Minor criteria
    Recurrent fever[*]
    Objective findings of abnormal bone remodeling with or without bone pain[†]
    A neutrophilic dermal infiltrate on skin biopsy[‡]
    Leukocytosis and/or elevated CRP[§]
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 valid criterion if objectively measured. Must be >38°C, and otherwise unexplained. Occurs usually – but not obligatory – together with the skin rash. [†] As assessed by bone scintigraphy, MRI, or elevation of bone alkaline phosphatase. [‡] Corresponds usually to the entity described as "NUD"[27]; absence of fibrinoid necrosis and significant dermal edema. [§] Neutrophils 6,610,000/mm^3 and/or CRP >30 mg/L. CRP: C-reactive protein; IgM: Immunoglobulin M; IgG: Immunoglobulin G; MRI: Magnetic resonance imaging; NUD: Neutrophilic urticarial dermatosis.

objective findings, that is, including abnormal bone remodeling as assessed by bone scintigraphy, magnetic resonance imaging (MRI), or elevation of bone alkaline phosphatase; skin biopsy showing neutrophilic dermal infiltrate; leukocytosis and/or elevated C-reactive protein level; and recurrent fever must be >38°C. Minor criteria in Lipsker criteria, "Arthralgia or arthritis," "Palpable lymph nodes," "Liver or spleen enlargement," and "Elevated erythrocyte sedimentation rate" are eliminated from Strasbourg criteria. Both sets of diagnostic criteria have been validated in real-life patients.[18] The sensitivity and specificity of the Lipsker criteria were 100% and 97%, respectively, compared with a sensitivity of 81% and specificity of 100% for Strasbourg criteria. The sensitivity and specificity for probable diagnosis using Strasbourg criteria reached 93% and 97%, respectively. Clearly, Strasbourg criteria emphasize subjective findings and are more applicable for insight of pathophysiology, while Lipsker criteria require less subjective findings and are easier to apply in daily practice for making initial diagnoses in suspected cases. Thus, both sets of criteria performed well and are reliable for clinical use. Both diagnostic criteria emphasize that other conditions which may mimic Schnitzler syndrome should be first excluded before the diagnostic criteria can be applied.[3,4]

Clinical features

The clinical features of Schnitzler syndrome are well described by de Koning[5] based on 281 cases published in the literature. Readers are directed to this comprehensive review article for details. However, a few practical points are worth iterating. The male to female ratio in Schnitzler syndrome is 1.5 and the median age of onset is 51 years. The demographics clearly indicate Schnitzler syndrome is an adult-onset disorder and in older adults. In addition to the two essential features, chronic urticarial skin rash [Figure 1] and monoclonal gammopathy, bone pain (or referred to as bone remodeling) has been a distinctive feature that is present in 55% of Schnitzler syndrome patients.[5] Bone pain can involve the femurs, tibias, and forearms in the extremities; and the pelvis, clavicles, and spine.[19] In a retrospective analysis of bone imaging

studies including plain X-ray, MRI, isotope bone scan, and positron emission tomography (PET)/computed tomography (CT) in 22 patients with classical Schnitzler syndrome, 64% of patients displayed skeletal imaging findings involving 40 bone regions. These include osteosclerosis on plain X-ray which is found in the distal femur, proximal tibia, and iliac bones. The same regions showed increased uptake on bone scan.[20] MRI findings include dense bony sclerosis with various degrees of marrow edema and periostitis.[20]

In Strasbourg diagnostic criteria, it was stated as "Objective findings of abnormal bone remodeling with or without bone pain" as assessed by bone scintigraphy, MRI, or elevation of bone alkaline phosphatase. This criterion may increase the index of recognition of bone abnormalities in those patients who do not complain of bone pain and may be detected by imaging studies when arthralgia or arthritis is being assessed. One advantage of bone imaging studies is that other conditions other than Schnitzler syndrome may be differentiated. A recent study compared PET/CT with ^{99m}Technetium bone scan for diagnostic value in ten patients with Schnitzler syndrome.[21] Increased radiotracer uptake appeared to be more sensitive in detecting lower extremity inflammation than PET/CT. Moreover, radiotracer uptake in bone scan correlated with disease activity, but PET/CT did not appear to be useful for diagnosis or disease activity follow-up.[21] The diagnostic value of bone scan and correlation with disease activity of Schnitzler syndrome were also confirmed by another study of 25 cases.[22] Limited data suggest that MRI with low T1 and high T2 signal abnormalities also correlated with clinical disease activity.[21] On the other hand, since Schnitzler syndrome has a potential risk to evolve to hematological malignancies, PET/CT should be the image of choice if clinical suspicion is indicated.

Peripheral neuropathy is relatively commoner in the Mayo Clinic cohort and is found in up to 56% of the patients,[13] but is as low as 7% reported in de Koning's review.[5] Neuropathy is more likely related to the monoclonal protein as this has been commonly seen in patients with IgM monoclonal protein.[23,24]

Hearing loss is infrequently presented in classical Schnitzler syndrome although it is a common feature in cryopyrin-associated periodic syndrome (CAPS).[10,25,26] Like in CAPS, the hearing loss in Schnitzler syndrome appears to be sensorineural and responsive to IL-1 blocking treatment.[25,26]

The histological features of a skin lesion in Schnitzler syndrome are referred as neutrophilic urticarial dermatosis (NUD), which is included as a minor criterion in the Strasbourg diagnostic criteria.[4,27] NUD is defined as perivascular and interstitial neutrophilic infiltrate [Figure 2]. Intense leukocytoclasia is often present but vascular wall is intact and dermal edema is absent. That is, vasculitis is not present.[27] The absence of signs of vasculitis in NUD is associated with systemic diseases including Schnitzler syndrome, systemic lupus erythematosus, and adult-onset of Still's disease. In reported cases of Schnitzler syndrome with available skin biopsy, over half of them show NUD, but some cases reported vasculitis.[5] It is important to distinguish NUD from common urticaria and urticarial vasculitis. Urticarial vasculitis represents a wide spectrum of diseases varying from mild disease to fetal organ injury. Hypocomplementemia-associated urticarial vasculitis is often manifested with more organ involvement.[28] Bonnekoh et al[29] proposed to use skin biomarkers to distinguish Schnitzler syndrome skin lesions from chronic spontaneous urticaria. Schnitzler syndrome skin lesion expresses IL-1, IL-6, and IL-18 which are produced by neutrophils and mast
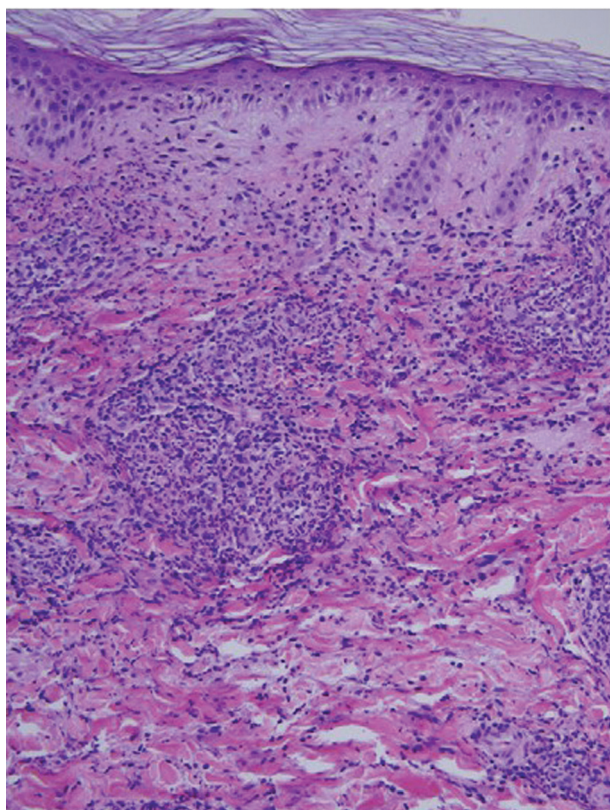
Figure 2: Histopathology of urticarial skin rash of Schnitzler syndrome. Predominantly perivascular infiltrate with neutrophils and interstitial inflammation (Hematoxylin-eosin staining, original magnification ×20, reproduced with permission [License number: 5191400527622] from Figure 1, Sokumbi et al[57]).

cells while these inflammatory cytokines were absent in chronic spontaneous urticaria or healthy skin.[29,30] It is critical to distinguish chronic urticaria from urticarial skin rash in Schnitzler syndrome since chronic urticaria is responsive to antihistamine but not to IL-1 blockade.[31] Conversely, urticarial skin rash in Schnitzler syndrome is not responsive to antihistamine but to IL-1 blockade.[5]

Pathogenesis

Genetics

The clinical phenotype similarity between Schnitzler syndrome and CAPS and dramatic response to IL-1 blocking treatment pointed to activation of inflammasome, NLRP3 (nucleotide-binding oligomerization domain [NOD]-like receptor [NLR] family pyrin domain containing 3) might be responsible for the over-production of IL-1; and a gain-of-function in *NLRP3* gene was expected for Schnitzler syndrome. However, such mutations in *NLRP3* gene have not been identified in patients with classical Schnitzler syndrome.[32,33] In a study of 21 patients with classical Schnitzler syndrome, one patient had p.V198M mutation in *NLRP3* gene.[33,34] p.V198M is a common variant of uncertain significance. Therefore, the significance of the pathogenesis of Schnitzler syndrome is not certain but is likely minimal. In a family study of Schnitzler syndrome, one patient harbors p.V198M mutation, but four other family members spanning three generations also have p.V198M detected but were asymptomatic either for Schnitzler syndrome or CAPS.[34,35] In another study by the same group of investigators expanded the patient population to include nine additional patients with classical Schnitzler syndrome and screened for *MYD88* gene somatic mutation,[32,33] p. L265P, which is considered an independent risk factor for and is present in >90% of patients with Waldenström's macroglobulinemia (WM).[36] Eleven out of 30 patients with classical Schnitzler syndrome carry p.L265P mutation.[32] In two independent case reports, two patients with classical Schnitzler syndrome also carry p.L265P mutation.[10,37] These findings do not explain the profound inflammation is Schnitzler syndrome, but may be useful to guide clinical monitoring since a significant proportion of patients with Schnitzler syndrome might develop lymphoproliferative malignancy.

Intriguingly, somatic NLRP3 mosaicism was found in those patients with non-classical, variant Schnitzler syndrome or Schnitzler-like syndromes [Table 3].[38-41] Two patients with IgGκ variant Schnitzler syndrome and severe clinical phenotype among a cohort of 11 patients showed myeloid lineage restrict somatic NLRP3 mosaicism.[38] Similarly, in two independent single-patient studies and a study of a cohort of eight patients with Schnitzler-like syndromes[39-41] (see below) somatic *NLRP3* mosaicism in myeloid lineage was detected. Among the ten mutations, four were reported previously to cause CAPS, six were novel variants [Table 3].[38-41] Gain-of-function of p.Q636E was confirmed by two classical *in vitro* assays and an *ex vivo* assay for detecting inflammasome activation.[39] Transfection of this mutated *NLRP3* gene (c.1906C >G p.Q636E) resulted in cell

Table 3: Somatic mosaic mutations of NRLP3 in patients with variant Schnitzler syndrome and Schnitzler-like syndromes.

Somatic mosaic mutation	Number of patients	Novel variant	Known association with CAPS	Reference
c.1688A>G p.Y563C	3	Yes		[40]
c.1706 G>T p.G569V	1	Yes		[40]
c.1700G>C p.E567Q	1	Yes		[40]
c.1691G>A p.G564D	1	Yes		[40]
c.1906C>G p.Q636E	1	Yes		[39]
c.1303A>G p.K435E	1	Yes		[38]
c.1054G>A p.A352T	1		Yes	[40]
c.1699G>A p.E567K	1		Yes	[40]
c.1709A>G Y570C	1		Yes	[41]
c.1569C>G F523L	1		Yes	[38]

CAPS: Cryopyrin-associated periodic syndrome.

death in a monocyte cell line, THP-1 cells, and adaptor molecule apoptosis-associated speck-like protein containing a CARD (ASC)-dependent activation of nuclear factor (NF)-κB in human embryonic kidney 293FT cells. After inflammasome activation, ASC assembles into a large protein complex called speck which can be visualized in the plasma of patients with CAPS. The patient with p. Q636E mosaic mutation showed increased levels of ASC speck during disease flares.[39] Increased ASC speck levels in the plasma of patients carrying other novel variants, such as p.Y563C,p.G569V, p.E567Q, and p.G564D, were also detected,[40] suggesting these variants are also gain-of-function mutations. Although not formally tested, the p.K435E variant, localized in exon 3 and in close proximity to known CAPS-causing mutations, is likely another pathogenic mutation.[38]

The absence of mutation in *NLRP3* gene in those patients with classical Schnitzler syndrome is puzzling as the evidence clearly indicates inflammasome activation, that is, plasma levels of ASC speck in these patients are substantially higher than those in healthy individuals and compatible with those in CAPS patients.[40]

Cytokines

Schnitzler syndrome is now considered as an adult-onset autoinflammatory disease driven by IL-1 and related cytokines. This is proven by the dramatic therapeutic efficacy of IL-1 blockade.

Peripheral blood mononuclear cells (PBMC) isolated from patients with Schnitzler syndrome spontaneously produced higher levels of several inflammatory cytokines including IL-1α, IL-1β, IL-6, and tumor necrosis factor (TNF) compared with those from healthy individuals. The *ex vivo* production of these inflammatory cytokines further increased upon stimulation by bacterial lipopolysaccharide. The trend of overproduction of inflammatory cytokines is not suppressed in patients treated with anakinra – the recombinant IL-1 receptor antagonist (IL-1RA). Interestingly, cytokines with inhibitory properties such as IL-10 and IL-1RA are also overproduced, which may reflect a counterbalance mechanism of the body, but the proinflammatory effect of inflammatory cytokines outweighs that of inhibitory cytokines in Schnitzler syndrome.[42] Another IL-1 family cytokine, IL-18 is also increased in the circulation of Schnitzler syndrome patients.[43] Intriguingly, the production of cytokines, such as IL-4, interferon-g, and IL-17A after stimulation of PBMC by anti-CD3 and anti-CD28 antibodies, was suppressed in untreated Schnitzler syndrome patients and this suppression is reversed in patients treated by anakinra.[42] In contrast, IL-17 is found to be highly expressed along with IL-1 in the lesional skin in one case of Schnitzler syndrome although the cellular source in the skin for IL-17 was not identified.[44] The significance of diminished T cell response to T cell receptor stimulation is not clear. Further investigation is required to determine whether it contributes to the pathogenesis of Schnitzler syndrome or it is an artificial *in vitro* experimental phenomenon. Nevertheless, the overproduction of IL-1 and overwhelming therapeutic effect of IL-1 blockade indicate that autoinflammation in Schnitzler syndrome is mediated by IL-1. It is poorly understood what is the major cellular source of IL-1, but it is reasonable to believe that neutrophils and mast cells in the lesional skin could contribute to the overproduction of IL-1.[29,30] However, the trigger to initiate IL-1 production is still elusive.

Neutrophil extracellular net formation (NETosis)

NETosis is one of the mechanisms that neutrophils execute their antimicrobial function. Dysregulation of

NETosis and impaired clearance of intracellular materials including nucleotides and proteins/peptides have been implicated in several immune-mediated inflammatory diseases such as SLE, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, and rheumatoid arthritis.[45] NET products markedly increased in the lesional skin and blood of patients with Schnitzler syndrome. Moreover, the serum of Schnitzler syndrome patients contains factors that can promote NETosis of neutrophils from healthy donors.[46] NETosis in the skin could be the initial signal for the subsequent skin and systemic inflammation. On the other hand, NETosis can be the result of systemic inflammation. Alternatively, NETosis may be involved in inflammation resolution.[46]

CCL2

In searching for a biomarker for Schnitzler syndrome, Krause *et al*[47] found that serum levels of CC motif chemokine ligand 2 (CCL2) were highly elevated in patients with Schnitzler syndrome compared with those in healthy individuals and patients with psoriasis or hidradenitis suppurativa, two conditions with skin inflammation but without bone remodeling. The levels of CCL2 are correlated with global disease activity and bone pain/bone remodeling. CCL2 is a chemokine mainly attracting monocytes which may differentiate into osteoclast and be involved in bone remodeling in Schnitzler syndrome.

B cell clonality

Monoclonal hypergammaglobulinemia, in particular IgM (seen in up to 94% classical Schnitzler syndrome patients), is one of the two essential components for this condition. However, little to none is known regarding the role of these paraproteins in pathogenesis. Pathak *et al*[48] investigated the B cell clonality in ten patients with Schnitzler syndrome. By analyzing the variable, diversity, and junctional segment composition of the immunoglobulin heavy chain and sequencing the complementarity determining region 3, the authors found evidence of clonality of individual patients but failed to demonstrate shared B cell clonality between these patients. In screening for shared autoantigens which may recognize by IgM of all Schnitzler syndrome patients, dipeptidyl peptidase 10 (DPP10) was reactive to IgM from all patients. Interestingly, DPP10 can modulate type A potassium channels. Efflux of potassium can trigger NLRP3 activation. It could be postulated that IgM binds to DPP10 leading to aberrant activation of NLRP3.[48] These findings are interesting yet to be replicated in independent cohorts of patients.

Dichotomy between inflammation and gammopathy

It is interesting and intriguing to note that gammopathy or B cell compartment[49] is not affected by either IL-1 or IL-6 blocking treatment despite remarkable suppression of inflammation and other clinical manifestations.[33,50,51] This suggests that IL-1 is not responsible for B cell clonal expansion or growth, but another factor(s) may be involved. IL-18, another member of IL-1 family, is also cleaved by caspase-1 to become active, which could be
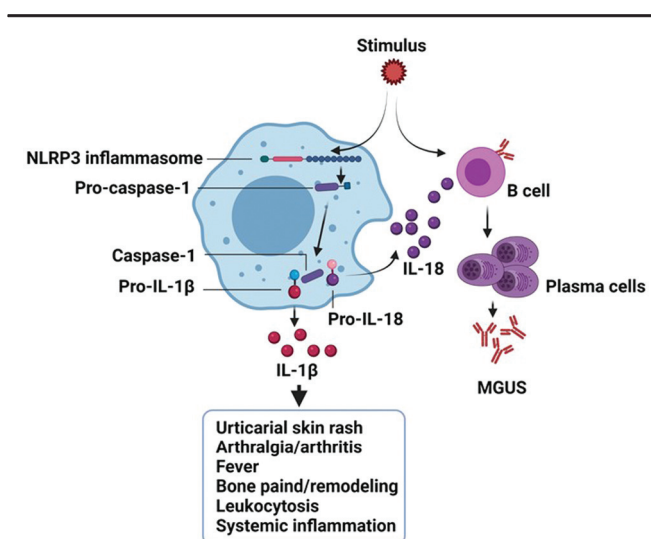
Figure 3: Hypothesis of pathogenesis of Schnitzler syndrome. An unknown stimulus activates NLRP3 and a B cell. The activated NLRP3 cleaves pro-caspase-1 into active caspase-1 which actives inactive IL-1 β and IL-18. IL-1 β causes skin urticarial rash and other clinical manifestations; IL-18 drives expansion of B cell clonality and production of monoclonal antibodies, majority of which is IgM κ. IL: Interleukin; MGUS: Monoclonal gammopathy of undetermined significance; NLRP3: Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family pyrin domain containing 3.

such a factor. Indeed, elevated IL-18 level was found in patients with Schnitzler syndrome. Therefore, it can be hypothesized that a stimulus or stimuli activate NLRP3 inflammasome and a B cell at the same time [Figure 3]. When NLRP3 is active, IL-1β and IL-18 are released. While IL-1β drives systemic inflammation, IL-18 acts on the activated B cell and promotes its clonal expansion. Free IL-18 levels were markedly elevated in patients with Schnitzler syndrome while IL-18 binding protein was not altered.[52] Moreover, it has been demonstrated that IL-18 was produced by the monoclonal IgM+ B cells in a patient with Schnitzler syndrome.[53] After treatment with rituximab, levels of both IL-18 and IgM deceased.[53] The role of IL-18 in B cell growth and antibody production has been demonstrated. For example, B cells express functional IL-18 receptors[54]; IL-18 can induce pathogen-specific IgM production[55]; and IL-18 has been implicated in mediating B cell proliferative disorders.[56] It would be interesting to investigate the role of IL-18 in the expansion and growth of monoclonal B cells in patients with Schnitzler syndrome.

Risk in developing hematological malignancy

MGUS in patients with Schnitzler syndrome may evolve to WM or other lymphoproliferative diseases. The risk of developing the lymphoproliferative disease was estimated as 20% within 10 years of diagnosis of Schnitzler syndrome in earlier reported cases.[3,17] In the 281 cases reviewed by de Koning,[5] 35 cases (12.5%) were reported to develop hematological malignancies at a median of 8 years of follow-up after the disease onset. Two-thirds of the malignancies are WM. However, it is difficult to estimate the accurate risk since follow-up data are lacking in 74 cases. In the 20 case retrospective study (collected from 1972 to 2011) reported by Mayo Clinic (USA; included in the 281 cases of de Koning review), nine out of

20 cases developed malignancy in a range of 2 to 13 years since the first onset of symptoms of Schnitzler syndrome.[57] Another independent single-center retrospective observation (Portugal; cases collected from 1988 to 2015, these were not included in de Koning review), five out of nine cases with Schnitzler syndrome developed the lymphoproliferative disease, four with WM and one diffuse large B-cell lymphoma, with a range of duration of 3 to 14 years since first clinical onset.[58] Most recently, a report from the Czech Republic found two out of six patients with a follow-up of 3 to 14 years evolved into WM.[59] These three single-center retrospective observational data demonstrated a rather higher rate of risk (33%,[59] 45%,[57] and 56%,[58] respectively) of lymphoproliferative disease in Schnitzler syndrome. In contrast, in a French multi-centered observational study (France; cases collected from 1998 to 2012, cases were not included in de Koning review),[50] only two out of 42 cases (5%) developed WM at 3 and 9 years, respectively, after initial symptoms onset. In a cohort of 21 patients from two specialist centers of UK, none of the patients developed lymphoproliferative disease within 1.6 to 9.4 years of observation.[33] The reason for the variation in rates of risk for developing lymphoproliferative disease reported in different cohorts is not clear. It is interesting to note that all patients except one (who died of AA amyloidosis in the UK cohort) and 29 out of 42 patients (French cohort) received treatment of anakinra for a duration ranging from 3 to 115 months and a vast majority of patients in clinical remission or partial remission in the two large cohorts.[33,50] The two cases in the French cohort that developed WM were not treated with anakinra.[50] It must be noted that neither anakinra nor canakinumab therapy altered the level of monoclonal components over time.[33,50,60-62] Further study with a large number of patients and long-term observation will be required to assess whether IL-1 blocking treatment will mitigate the risk of lymphoproliferative transformation. Thereby, currently available data underline the importance of long-term follow-up by hematologists to screen for malignancy.

Development of AA amyloidosis

Serum amyloid A (SAA) is an acute-phase protein. Amyloidosis caused by extracellular deposition of the proteolytic cleavage product of SAA, insoluble cross-β-sheet fibrils is called AA amyloidosis. AA amyloidosis is associated with hereditary autoinflammatory diseases. In untreated patients, AA amyloidosis can develop in around 50% of patients with familial Mediterranean fever (FMF) syndrome, 25% with Muckle-Wells syndrome (MWS), 10% to 20% with tumor necrosis factor receptor-associated periodic syndrome (TRAPS).[63] In the 281 cases of Schnitzler syndrome reviewed by de Koning,[5] six cases (2%) developed AA amyloidosis; two cases developed five and ten after disease onset, respectively. No disease duration was reported in other cases. One in the 42 cases of the French multicenter cohort developed AA amyloidosis after 10 years of disease onset.[50] The prevalence of AA amyloidosis is lower compared with that in hereditary autoinflammatory diseases. Nevertheless, since AA amyloidosis is a potential life threatening complication, close monitoring is warranted. Therapy with IL-1 blockers controlling inflamma-tion is likely to reduce the risk of progression to AA Amyloidosis. Interestingly, AL (immunoglobulin light chain) amyloidosis which is associated with multiple myeloma, lymphoma, or WM has not been reported in patients with Schnitzler syndrome despite the persistence of monoclonal gammopathy.[5]

Treatment

Before the availability of IL-1 blocking agents, patients with Schnitzler syndrome had been treated with over 30 various drugs or other therapies. These were summarized in detail in de Koning's review article.[5] The majority of these therapies are ineffective. Table 4 lists the drugs and therapies that have been tried (excluding these discussed below). Corticosteroids and H1 antihistamine drugs had been tried in a larger number of patients. Corticosteroids had a moderate effect in some patients but required a high dose. Antihistamine therapy had literally no effect. Here the discussion is focused on targeted therapies concerning IL-1 blockers, in particular.

IL-1 inhibition has dramatically changed the management of Schnitzler syndrome. Among the three IL-1 blocking medications, anakinra is the most commonly prescribed, followed by canakinumab and rilonacept.[5]

Table 4: Therapies used for treatment of Schnitzler syndrome but less or not effective.[*]

Moderately or partially effective
    Corticosteroids
    Interferon-a
    Thalidomide
    Colchicine
    Pefloxacin
    Cyclosporin
Little or not effective
    UVB or UVA phototherapy
    PUVA (combination treatment with psoralens and UVA)
    Plasmapheresis
    Extracorporeal immunoadsorption
    Intravenous immunoglobulins
    Alkylating agents
    Cyclooxygenase inhibitors
    Hydroxychloroquine
    Dapsone
    Histone deacetylase inhibitor (ITF2357)
    Doxepin
    Bisphosphonates
    Psoralen
    H1 antihistamine
    Bortezomib
    Dihydroergotamine
    Azathioprine
    Chloroquine
    Sulfasalazine
    Fludarabine
    Sulphones
    Leflunomide

[*] Modified from de Koning.[5] UV: Ultraviolet.

Anakinra

Anakinra is a recombinant version of naturally existing IL-1RA. IL-1RA binds to IL-1 receptor with high affinity but does not trigger signal transduction. By occupying the binding site of IL-1 receptor, IL-RA blocks the binding of IL-1α and IL-1β to IL-1 receptor. Anakinra is first approved for treating rheumatoid arthritis, later for neonatal-onset multisystem inflammatory disease and deficiency of IL-1 receptor antagonist. The first case of successful treatment by anakinra for Schnitzler syndrome was reported by Martinez-Toboada et al.[64] The dramatic response in this case encouraged numerous subsequent cases reported in the literature on successful treatment of anakinra in Schnitzler syndrome with high efficacy rate up to 94% and indicate the pivotal role of IL-1 in the pathogenesis.[5] For this reason, some authors proposed using treatment response to anakinra as a criterion for Schnitzler syndrome.[65] However, individual case and a small number of case reports inevitably suffer from publication bias. Indeed, several cases of refractory to anakinra have been reported.[57,66] Nevertheless, it is advised that revisit of diagnosis of Schnitzler syndrome is needed if a patient is not responsive to IL-1 blocking treatment. Despite the lack of randomized clinical trials, results from an observational study confirmed the high efficacy of anakinra in the treatment of Schnitzler syndrome. This study followed 29 patients treated with anakinra in comparison to 13 patients treated with other agents excluding IL-1 blockers. All the patients treated with anakinra had a dramatic response within 48 h after initiation of anakinra. In a median of 36 months follow-up, 83% of patients sustained in complete remission and 17% with partial remission.[50] Clinical information was available for analyzing 12 of the 13 patients who were treated with other medications. All of the patients had active disease with elevation of C-reactive protein.[50] In another cohort of 21 patients with Schnitzler syndrome, all except one patient (who died of AA amyloidosis before starting anakinra) received anakinra treatment, 19 achieved complete remission, and 1 achieved partial remission in a duration ranging from 15 to 115 months.[33] All these patients treated with anakinra had sustained long-term efficacy.

Canakinumab

Canakinumab is a human monoclonal antibody (IgG1, k) against IL-1β. Canakinumab has been indicated for CAPS in adults and children of 4 years and older for familial cold auto-inflammatory syndrome, MWS, TRAPS in adults and children; hyperimmunoglobulin D syndrome/mevalonate kinase deficiency in adults and children; FMF in adults and children; adult-onset Still's disease and systemic juvenile idiopathic arthritis in patients aged 2 years and older. As summarized by Betrains et al,[67] up to date, a total of 34 patients with Schnitzler syndrome were treated in reports with one or two cases and in two large cohorts ($n = 8$ and $n = 20$, respectively). Overall, a complete response was reported in 58.6% of patients and all the other patients had a partial response. In an open-labeled, 9 months observation, the sustained therapeutic effect was demonstrated in eight patients treated with canakinumab at 150 mg monthly.[60] In a randomized placebo-controlled study, Krause et al[62] demonstrated that on day 7, five out of seven patients treated with canakinumab had a complete response, whereas none of the 13 patients treated with placebo showed a response. In the open-label phase of the trial, all the patients received canakinumab and were observed for 16 weeks, 15 patients had complete response and five had partial response as determined by global physician assessment (GPA) score (range 0–20). The total GPA decreased from baseline of 14.5 to 3.5.[62] In the 4 years extension of the study, 17 patients were included and 15 completed the study, all showed sustained response to canakinumab with normalization of C-reactive protein and SAA levels.[61] Thus, in addition to cases in reported cases, sustained therapeutic efficacy of canakinumab for Schnitzler syndrome is confirmed in clinical trials.

Rilonacept

Rilonacept is a recombinant fusion protein comprising the extracellular domain of human IL-1 receptor type 1 and IL-1 receptor accessory protein and the Fc fragment of human IgG1.[68] Rilonacept acts as a decoy receptor trapping IL-1a and IL-1β with high affinity and prevents their binding to cell membrane IL-1 receptor. Rilonacept has been approved by US Food and Drug Administration and European Medicines Agency for the treatment of CAPS. In an open-labeled clinical trial including eight patients[69] who met Lipsker diagnostic criteria.[3] Rilonacept was administered with a loading dose of 320 mg, then followed by 160 mg weekly subcutaneous injection. Clinical outcome was measured by a patient-reported Schnitzler activity score (ranging from 0 to 50, 50 being the highest disease activity) based on a Daily Health Assessment Form that was previously validated for CAPS[70] and GPA (ranging from 0 to 10, 10 being the maximum disease activity). Overall, rilonacept is well tolerated. During the 1 year follow-up, four patients (50%) achieved complete or nearly complete remission; three patients were judged as partial response; and one patient failed to respond to rilonacept. In those responsive patients, the onset of therapeutic effects occurred within 24 h after the first dose of rilonacept injection and the effects remained for 1 year.[69]

Currently, anakinra remains the most popular prescription among the three IL-1 blockers. The major adverse effect of anakinra is injection site reaction which is well tolerated. Infections have been associated with IL-1 blockade, but they do not seem to be exceeding other conditions treated by IL-1 blockers. Infections were associated with other comorbidities in Schnitzler syndrome patients.[50]

Anti-IL-6 treatment

Tocilizumab is a humanized monoclonal antibody against IL-6 receptor and has been indicated for various inflammatory diseases. Mixed results were reported on the effect of treatment with tocilizumab in Schnitzler syndrome. Krause et al[66] first reported a remarkable efficacy in 2012 in three patients who failed IL-1 blockade. Tocilizumab at 8 mg/kg intravenous infusion monthly achieved a rapid and complete remission, and the remission was sustained for 10 months.[66] In another

report, one case of a Chinese patient also achieved complete remission on treatment with tocilizumab 8 mg/kg monthly infusion in combination with methylprednisolone and methotrexate.[10] Claus and Vanderschueren[71] reported experience with four cases of Schnitzler syndrome treated with tocilizumab at 8 mg/kg infusion; two patients showed effectiveness; and two had no effect. Patient 1 achieved complete remission on anakinra but symptoms relapsed after 4 months. Treatment was switched to tocilizumab monotherapy but failed. Patient 2 was treated for 7 weeks with anakinra and had no benefit. Tocilizumab in combination with glucocorticoids and colchicine achieved complete and sustained remission for 2.5 years. Patient 3 was in remission for 21 months on combination therapy with tocilizumab, methylprednisolone, colchicines, and azathioprine. Patient 4 failed combination of methyl-prednisolone and tocilizumab but responded to anakinra. In an open-labeled prospective clinical trial,[72] eight patients who met Strasbourg criteria[4] for Schnitzler syndrome were treated with weekly subcutaneous injections of tocilizumab at 162 mg monotherapy. After initial response to tocilizumab, half of the patients lost benefit after 16 weeks and discontinued treatment, and at the end of 52 weeks of observation, three out of four patients also showed relapse of the clinical symptoms although C-reactive protein remained normal. Loss of benefit from tocilizumab is also seen in cases reported in Japan recently.[51]

In summary, tocilizumab monotherapy in Schnitzler syndrome showed initial effect but benefit lost over time. Tocilizumab may be considered in non-responders to IL-1 blockers and may be used in combination with other immunosuppressants.

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20 which is expressed by B lymphocytes. Rituximab is indicated in treating B cell lymphoma, rheumatoid arthritis, and ANCA-associated vasculitis. Because of monoclonal gammopathy in Schnitzler syndrome, it is logical for rituximab to be tried. There are no clinical trials of rituximab in the treatment of Schnitzler syndrome conducted. Published case reports demonstrated about 20% cases highly and 16% partially responsive to rituximab.[5,53,73-78] Cases were responsive to rituximab included those who were in combination therapy of rituximab with chemotherapy or radiation for malignancy.[75,79] There are cases who failed rituximab but were responsive to anakinra, and vice versa.[76-78]

Anti-TNF

TNF inhibitors including etanercept, adalimumab, and infliximab have been tried to treat Schnitzler syndrome.[5,80,81] Only one report showed adalimumab is beneficial to one patient[80], but the rest of the cases showed no benefit or even exacerbated the symptoms.[81]

Anti-IL-17 therapy

IL-17A is found in the lesional skin of patients with Schnitzler syndrome.[30,44] The cellular source in the skin

is neutrophils.[30] IL-17A is a potent neutrophil chemo-attractant. Neutrophil infiltrate in dermis is a hallmark of skin lesion in Schnitzler syndrome. It is reasonable to consider that IL-17A plays an important role in recruiting neutrophils to the lesional skin in Schnitzler syndrome patients. Anti-IL-17A therapy might be beneficial in Schnitzler syndrome and could be tried in patients who fail IL-1 blockers or in the region there is no access to IL-1 blockers.

As mentioned above, despite clinical remission can be achieved by IL-1 or IL-6 blockade, the elevated gamma globuline levels are hardly improved.[33,50,51] Thereby, long-term clinical monitoring of the progression of MGUS is still required even in those patients in clinical remission.

Schnitzler-like syndromes

Cases have been reported in the literature that clinical features are similar to Schnitzler syndrome but do not meet the diagnostic criteria for Schnitzler syndrome.[3,4] Here these conditions are collectively referred to as Schnitzler-like syndromes.

Chronic urticarial rash without monoclonal gammopathy

The first group of cases is collected from published cases in the literature. These patients present all features of classical Schnitzler syndrome except monoclonal gamm-opathy which is one of the two essential criteria for Schnitzler syndrome [Table 5]. It is relatively easier to recognize this group of patients because of their urticarial skin rash and other clinical features. They either have normal immunoglobulin levels or have polyclonal IgM, IgG, or IgA. One case shows biclonal IgM.[82] It is interesting to note that three cases were absent in monoclonal gammopathy at the initial presentation but a monoclonal IgM was developed later[83-85] and could meet the diagnostic criteria of classical Schnitzler syndrome. These cases highlight that urticarial skin rash and other clinical phenotypes can precede the develop-ment of monoclonal gammopathy. A long-term follow-up and periodic testing for gammopathy in those highly suspected for Schnitzler syndrome are warrant.

Another group of patients with chronic urticarial rash but without monoclonal gammopathy were reported from a single tertiary referral center [Table 6].[40] In the UK National Amyloidosis Center, eight patients presented with CAPS in mid to late adulthood and absence of monogenic mutations. The median age at disease onset was 50 years and the diagnosis of CAPS was 65 years. These late-onset CAPS patients had urticarial rash accompanied by fevers and exacerbated by exposure to cold. The major distinctive feature from other reported cases of Schnitzler-like syndromes is that all of these eight patients had progressive bilateral sensorineural deafness. Moreover, the deafness does not have a good response to IL-1 blockade. In this group of eight patients, only two patients showed improvement of deafness as measured by audiometric test. In addition to arthralgia and myalgia and lymphadenopathy, other clinical features which are not reported in Schnitzler syndrome include headache,

Table 5: Schnitzler-like cases without monoclonal gammopathy.

Case	Age/sex	Urticarial rash	Skin neutrophil infiltrate	Hypergamma-globulinemia	Response to IL-1 blockade	Reference
1	58/F	Yes	Yes	Polyclonal IgA and polyclonal IgG	Excellent to anakinra	[87]
2	54/F	Yes	Not done	Polyclonal IgA	Excellent to anakinra	[88]
3	36/M	Yes	Yes	Polyclonal IgM	Unknown	[89]
4	64/M	Yes	Not done	Polyclonal IgA	Excellent to anakinra	[39]
5	21/F	Yes	Not done	Polyclonal IgM	Excellent to anakinra	[90]
6	57/M	Yes	Not done	Polyclonal IgM and polyclonal IgE	Unknown	[91]
7	63/M	Yes	Yes†	Biclonal IgM, κ and λ	Unknown	[82]
8	71/M	Yes	Not done	Absent at presentation, monoclonal IgM, κ developed later‡	Excellent to anakinra	[85]
9	58/M	Yes	Yes	Absent at presentation, monoclonal IgM developed 20 months later‡	Partially to canakinumab§	[83]
10	51/M	Yes	Not done	Absent at presentation, monoclonal IgM developed 4 years later‡	Excellent to anakinra	[84]
11	44/F	Yes	Yes	Absent	Excellent to anakinra, but injection site reaction; excellent to canakinumab	[83]
12	62/M	Yes	Yes	Absent	Excellent to anakinra	[92]
13	52/F	Yes	Yes	Absent	Excellent to anakinra	[41]
14	69/M	Yes	Not done	Absent	Excellent to anakinra	[93]

* Sensorineural hearing loss was not improved. † Had hypocomplementemia. ‡ Case 8: Monoclonal IgM, κ developed >2 years after initial presentation of urticarial skin rash; Case 9: Monoclonal IgM developed during intermittent treatment with anakinra, one dose of infliximab and prednisone; and Case 10: Monoclonal IgM developed 4 years after initial presentation and being treated with anakinra. § He had improvement in his fevers and arthralgia, but inflammation markers remained unchanged. He died of ventricular tachycardia arrest after the fourth dose of canakinumab. IL-1: Interleukin.

conjunctivitis, clubbing, papilledema, iritis, and optical neuritis. Two out of eight patients developed AA amyloidosis with nephrotic syndrome. All patients have markedly elevated AA amyloid and C-reactive protein. All patients have remarkable clinical responses to anakinra with resolution of skin rash, fever, and joint symptoms. Two patients with AA amyloidosis have resolution of proteinuria and improvement of renal function.

Table 6: Schnitzler-like cases without monoclonal gammopathy, but with sensorineural deafness.[40]

Clinical features	Frequency
Urticarial rash	8/8
High-grade fever	8/8
Bilateral sensorineural deafness	8/8
Headache	5/8
Conjunctivitis	4/8
Arthralgia	3/8
Papilledema	3/8
Lymphadenopathy	2/8
Myalgia	2/8
AA amyloidosis and nephrotic syndrome	2/8
Bilateral clubbing	2/8
Weight loss	2/8
Abdominal pain	1/8
Diarrhea	1/8
Iritis	1/8
Optical neuritis	1/8

An isolated case reported (included in Table 5, Case 4)[39] also shows bilateral sensorineural hearing loss, which is not responsive to anakinra, consisting with findings in these patients of the UK National Amyloidosis Center.

Monoclonal gammopathy without chronic urticarial skin rash

In contrast to the cases with urticarial rash without monoclonal gammopathy, a series of patients with monoclonal gammopathy and other features of autoinflammatory diseases but the absence of urticarial rash was reported by investigators of the French Network of Dysimmune Disorders Associated with Hemopathies.[86] Terré and colleagues identified 16 patients with monoclonal gammopathy and recurrent fever among 751 with autoinflammatory disease. Five out of these 16 patients with monoclonal gammopathy (1 IgM λ, 1 IgMκ, 2 IgG λ, 1 IgGκ, and IgMκ) displayed recurrent fevers with a frequency of 3 to 12 attacks per year and a duration of 2 to 12 days per episode, myalgia (100%) and polyarthralgia (80%). Three out of five patients were men. The age at onset of symptoms ranged from 30 to 71 years. All had leukocytosis and elevated C-reactive protein (range 84–250 mg/L) during fever attacks. No monogenic mutations were identified by Sanger sequencing. Two patients were treated with anakinra with good response. The authors proposed to name this gammopathy-related autoinflam-matory syndrome as monoclonal gammopathy, arthralgias, and recurrent fever syndrome or MGARF.[86] Clearly more cases are to be expected by

independent investigators to validate this newly described autoinflammatory syndrome.

Concluding remarks

Schnitzler syndrome is an adult-onset autoinflammatory disease with two prominent features, chronic urticarial skin rash and MGUS with marked systemic inflammation. It is rare but is under diagnosed. Recognition of this condition is important since IL-1 blockade can induce almost all patients in clinical remission and lead to a favorable prognosis. Because of the diverse clinical manifestations, patients may present to dermatologists or allergists for urticarial lesion or hematologists for MGUS or rheumatologists for arthritis or bone pain. Awareness is the key to derive a correct diagnosis. The two sets of diagnostic criteria, Lipsker and Strasbourg criteria both perform well in the real world of practice. MGUS in a significant proportion of Schnitzler syndrome patients have a risk to evolve into lymphoproliferative malignancy, and it is not known if long-term of IL-1 blocking treatment will alter the risk, and hence close monitoring is required. Schnitzler-like syndromes with systemic inflammation have been reported: Cases presented with chronic urticarial skin lesion but without MGUS and yet display an equally dramatic response to IL-1 blockade; others with MGUS, but without urticarial skin lesion. The latter group is infrequently reported and response to IL-1 blockade is not as remarkable as those with classical Schnitzler syndrome.

Clinically, classical Schnitzler syndrome and Schnitzler-like syndromes represent groups of patients in the spectrum of late-onset CAPS. Intriguingly, there is no genetic mutations of *NLRP3* have been identified in classical Schnitzler syndrome patients despite evidence of inflammasome activation, whereas somatic mosaicism of *NLRP3* genes is frequently detected. Nevertheless, recognition of IL-1 as the common pathway mediating these conditions is important for proper management.

Conflicts of interest

None.

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