

Schnitzler's syndrome associated with pancreatitis: a disease of IL-1 dysregulation

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Abstract Schnitzler's syndrome (SS) is a rare inflammatory disease of unknown origin characterized by chronic urticaria and monoclonal gammopathy (usually IgM) associated with at least two of the following components: fever, arthralgia or arthritis, bone pain, hepato- and/or splenomegaly, lymphadenopathy, elevated erythrocyte sedimentation rate, leukocytosis, and/or abnormal findings on bone morphological investigations. To date, about 100 cases have been described with only 4 being reported in the USA. The mean time to diagnosis from the onset of disease is 5.4 years, given the varied symptoms with which patients may present. The pathogenesis of SS remains unknown but likely involves dysregulation of the IL-1 pathway. We describe here a 48-

year-old woman with a monoclonal IgM gammopathy and a 3-year history of chronic pruritic urticarial dermatosis, unexplained fevers, chronic polyarthritis, lymphadenopathy, leukocytosis, hepatomegaly, and weight loss. She also had a history of chronic pancreatitis as well as a family history of recurrent pancreatitis. The diagnosis of Schnitzler's syndrome was made, and she was successfully treated with the IL-1 receptor antagonist, anakinra.

Keywords IL-1 · Monoclonal gammopathy · Pancreatitis · Schnitzler's syndrome · Urticaria

The case

A 48-year-old woman presented with acute-onset epigastric abdominal pain radiating to her back. She had a 19-year history of recurrent pancreatitis, with evidence of small calcifications within the pancreatic head by CT. Her episodes of pancreatitis were often, but not always, associated with alcohol consumption. She had insulin-dependent diabetes mellitus, associated with peripheral neuropathy of the lower extremities, and fat malabsorption, likely secondary to chronic pancreatitis. She also had a history of hepatitis C infection. She suffered from a polyarthritis involving the knees, ankles, shoulders, elbows, and small joints of the hand, which had been present for the past 3 years. She also experienced frequent episodes of self-limited painless urticaria, which resolved completely within 24 h and were occasionally associated with fevers and sweats. The onset of urticaria preceded the development of arthritis by 1 year.

Her family history was significant for recurrent pancreatitis, present in her mother and son. Her son's episodes of pancreatitis were often associated with alcohol consumption.

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However, the patient's mother, who experienced two episodes of acute pancreatitis in her lifetime, had no history of alcohol use. The patient did not have a personal or family history of autoimmune disease. She had a 20-pack-year history of smoking and reported intermittent alcohol and crack cocaine use. She was not taking any medications.

On physical examination, she was cachectic and ill-appearing with bilateral temporal wasting. On abdominal examination, she had diffuse tenderness without rebound or guarding. Her bowel sounds were normal. Her liver edge was palpable 2 cm below her costal margin. She had diffuse, urticarial papules and plaques on her arms, thighs, and back with scattered excoriations. Her knees were warm with moderate effusions. She had no lower extremity edema. While in the hospital, she was observed to have nightly high-spiking fevers up to 40°C and her urticaria waxed and waned in severity.

Initial laboratory studies were notable for a white blood cell count of 33,720/mm³ with 95% polymorphonuclear cells. Her hemoglobin was 7.9 g/dL with an MCV of 74 and an RDW of 19.9. Her erythrocyte sedimentation rate (ESR) was 57 mm/h and CRP was 3.9 mg/dL. Serial blood and urine cultures were negative for bacterial, fungal, and mycobacterial pathogens. RPR screen, Lyme disease antibody, cryoglobulin screen, CMV quantitative

PCR, HIV antibody and HIV RNA PCR, and PPD testing were all negative. HCV antibodies were positive, but HCV RNA was not detected. Serum protein electrophoresis showed an IgM kappa monoclonal gammopathy with an M-spike of 0.38 g/dL. Immunoglobulin G (IgG) subclasses were as follows: IgG1 1,270 mg/dL, IgG2 201 mg/dL, IgG3 52 mg/dL, and IgG4 61 mg/dL.

ANA was positive at a titer of 1:40. Rheumatoid factor was negative. Anti-CCP, Ro, La, Sm, and RNP antibodies were not detected; c-ANCA and p-ANCA were negative. Serum C1-esterase inhibitor levels and complement levels were normal. Cold agglutinins were not detected. The patient was HLA-B27 negative. Serum ferritin level was 184 ng/mL. Tests for aminolevulinic acid, porphyrins, porphobilinogen, uric acid, and T3 and T4 levels were normal; thyroglobulin or thyroperoxidase antibodies were absent.

CT of the abdomen revealed periaortic retroperitoneal lymphadenopathy measuring 1.9×2.3 cm on the left and enlarged bilateral inguinal lymph nodes measuring 2.6×1.6 cm on the left and 1.5×1.4 cm on the right. Hyperostosis was not seen on available plain films or CT scans.

An excisional inguinal lymph node biopsy revealed polyclonal plasmacytosis (Fig. 1). IgG staining of the lymph node identified a large proportion of plasma cells

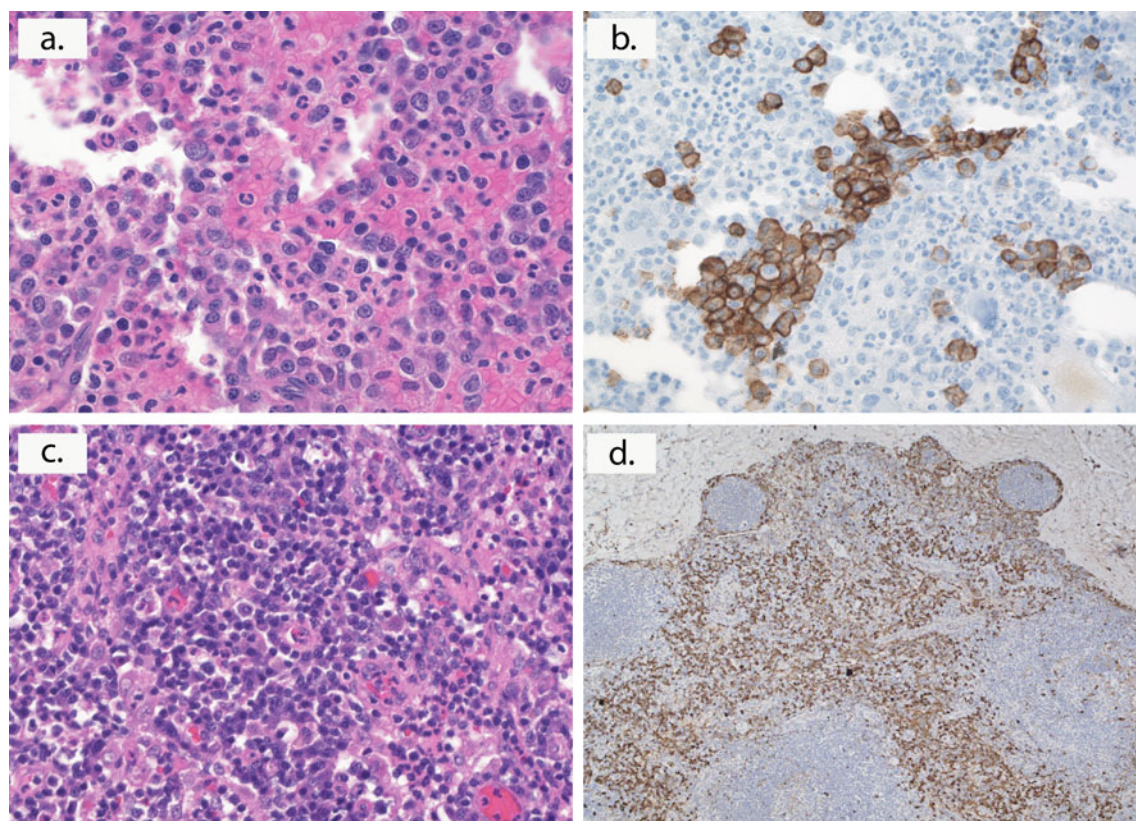


Fig. 1 **a** H&E stain of bone marrow demonstrating plasmacytosis. **b** CD138 immunostain of bone marrow demonstrating plasmacytosis. **c** H&E stain of lymph node showing sheets of plasma cells. **d** IgG immunostain of lymph node demonstrating clusters of IgG positive plasma cells

with relatively few IgG4-positive cells. An HHV-8 stain of the lymph node was negative. Bone marrow biopsy showed a hypercellular marrow with a myeloid predominance, but no evidence of a lymphoproliferative disorder (Fig. 1). Flow cytometry, cytogenetic analysis, and karyotype of bone marrow and lymph node biopsy specimens were negative for a malignant process.

Skin biopsy was notable for lipoatrophy, as well as a mild superficial perivascular and interstitial infiltrate with a neutrophil predominance (Fig. 2). There were also some admixed eosinophils. There was no evidence of urticarial vasculitis; direct immunofluorescence for IgG, IgA, IgM, C3, and fibrinogen was negative.

The right knee synovial fluid had a WBC count of 2,520/cu mm with 87% polymorphonuclear leukocytes and 13% mononuclear cells. Cultures of the fluid were sterile. A diagnosis of Schnitzler's syndrome was made based on the presence of urticaria, monoclonal gammopathy, and her other systemic complaints.

Discussion of diagnosis

The diagnosis of Schnitzler's syndrome (SS) requires the presence of two major criteria—chronic urticaria and monoclonal IgM gammopathy—and two or more minor criteria—intermittent fever, bone pain, arthritis, lymphadenopathy, hepatomegaly, leukocytosis, elevated ESR, radiologic bone abnormalities, or splenomegaly. Other diagnoses such as lymphoproliferative disorders must be excluded [1].

Epidemiology

More than 100 cases of SS have been reported with the largest case series including 94 patients [1]. Males are affected 1.6 times as often as females. The mean age of onset is 52 years.

The onset of symptoms before the age of 40 is rare. Almost all cases are Caucasian. No familial cases have been observed and no clear risk factors have been identified [2].

Etiology/pathogenesis

The pathophysiology of Schnitzler's syndrome is unknown. However, there is mounting evidence that the IL-1 pathway is important in the pathogenesis of the disease. Interleukin-1 β , a proinflammatory cytokine, may cause fever, leukocytosis, anorexia, joint destruction, tissue remodeling, and elevated markers of systemic inflammation [3]. There are several regulatory pathways that control interleukin-1 β (IL-1 β) activity including IL-1 β gene transcription, pro-IL-1 β cleavage, secretion of the mature cytokine, and inhibition of IL-1 function by circulating IL-1 receptor antagonists [4]. The dysregulation of IL-1 β via an imbalance between interleukin-1 and interleukin-1 antagonist activity is observed in several autoinflammatory diseases with symptoms similar to those of Schnitzler's syndrome including familial Mediterranean fever, adult and juvenile Still's disease, hyper-IgD syndrome, and Behcet's syndrome. Infants with deficiency of interleukin-1 receptor antagonist, caused by mutations in interleukin-1 antagonist, develop neutrophilic pustular skin eruptions and bone abnormalities. The severity of the disease is directly associated with the levels of IL-1 β activity [5]. The uncontrolled activity of IL-1 β may explain some of the clinical features of Schnitzler's syndrome, namely, fever, systemic inflammation, weight loss, bone pain, and arthritis.

Saurat et al. found polyclonal IgG-type autoantibodies directed against IL-1 in the sera of SS patients [6]. These autoantibodies increase the half-life of IL-1, change its tissue distribution, and enhance its effects. IL-1 induces the production of interleukin-6 by endothelial cells; elevated serum IL-6 levels have been identified in SS patients,

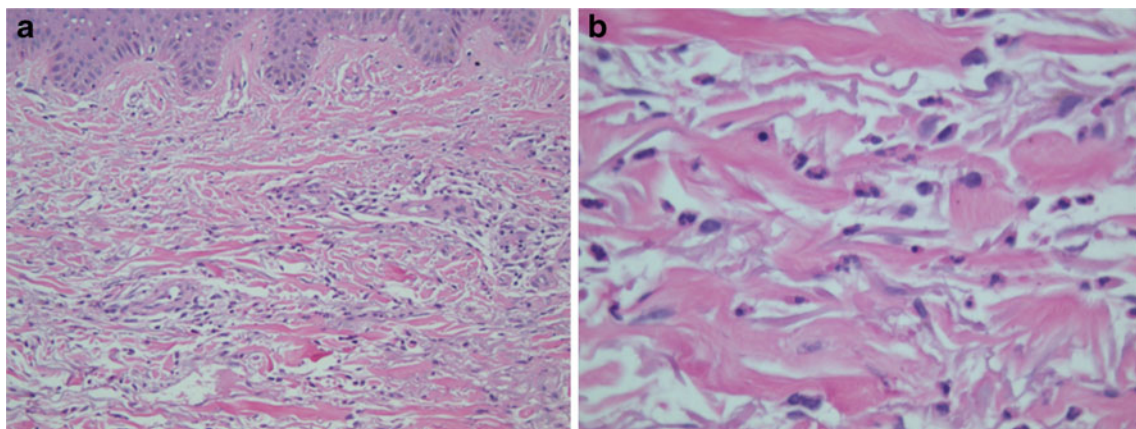


Fig. 2 **a** H&E stain of skin biopsy showing mild superficial perivascular and interstitial infiltrate with a neutrophil predominance. **b** Higher magnification of skin biopsy showing eosinophils

possibly as a consequence of increased IL-1 signaling [7, 8]. In addition, elevated levels of interleukin-18, a cytokine of the IL-1 family, have been found in some SS patients [9].

Although the levels of IL-1 β in SS patients are not consistently elevated, dysregulation of the inflammasome leading to increased synthesis and secretion of IL-1 β may play a key role in the pathogenesis of the disease. Pizzirani et al. showed that peripheral mononuclear cells (PBMCs) from patients with SS have a higher spontaneous secretion of IL-1 β . IL-18 was also released in greater amounts from PBMCs from SS patients [10]. Ryan et al. showed that PBMCs from SS patients stimulated with LPS had greater IL-1, IL-6, and TNF α release compared to controls [7]. Looock et al. has identified a gain of function mutation in the gene nucleotide-binding domain protein and leucine-rich repeat containing gene family, pyrin domain containing 3 [NLRP3] in one of three patients with SS. NLRP3, a component of the inflammasome, leads to IL-1 secretion. The gain of function mutations in NLRP3 is one of the causes of cryopyrin-associated periodic syndromes (cryopyrinopathies) in infants [11].

Deposition of the monoclonal paraprotein (IgM) leading to the formation of immune complexes and the activation of the complement cascade may contribute to the cutaneous manifestations of the disease. Lipsker et al. identified IgM- κ autoantibodies that recognize proteins from epidermal extracts of SS patients. In addition, IgM deposits in the skin have been identified by immunoelectron microscopy in some patients with SS [12].

Clinical presentation

The most common symptom is recurrent urticaria. Pruritus is usually absent, but lesions may become mildly pruritic in 40% of cases [2]. The rash affects primarily the trunk and the extremities sparing the palms, soles, head, and neck areas. New lesions usually appear daily, lasting 12–24 h, and resolve without sequelae. The frequency of urticarial eruptions can differ greatly among patients.

Periodic fever is the second most common symptom affecting approximately 90% of patients [2]. The frequency of febrile episodes can also differ greatly among patients. Episodes usually resolve within a few hours but can persist for up to 48 h. Peaks over 40°C are common. The fever and skin rash do not necessarily coincide. Lymphadenopathy is seen in 50% of cases. Otherwise, nonspecific systemic symptoms are commonplace including malaise, fatigue, and weight loss in 65%. Hepatomegaly and splenomegaly are also recognized.

About 80% of patients complain of relapsing arthralgias, mainly involving large joints. Joint destruction has not been noted. Bone pain has also been reported in 75%, typically affecting the tibia and iliac bone. Hyperostosis is revealed

by radiologic examination in 40–50% of cases, mostly at the sites of bone pain.

The hallmark on laboratory testing is a monoclonal gammopathy, most frequently of the IgM type, with kappa light chains in 95% of patients. An IgG variant type has been identified [13]. The ESR is almost invariably elevated; in about 60% of cases, it is accompanied by leukocytosis and/or anemia.

Histologic findings

The histopathologic features of skin biopsies are heterogeneous. Neutrophilic urticaria is the most common finding consisting of a superficial dermal and perivascular infiltrate of polymorphonuclear leukocytes. In some patients, a superficial perivascular mononuclear infiltrate suggestive of chronic urticaria and lymphocytic inflammation is found [12]. The perivascular lymphocytic infiltrates in acute lesions consist of both CD4+ and CD8+ T lymphocytes [14]. Urticarial vasculitis has also been reported [15].

Differential diagnosis

The differential for SS is broad and best grouped by the common presenting symptoms (see Table 1).

Clinical course

Our knowledge regarding the natural history of this disease is limited. The largest cohort to date consists of 94 cases followed for 9.5 years after the onset of symptoms [2]. Spontaneous remission is unlikely to occur. Disabling skin rash, fever, and musculoskeletal involvement are the most frequent complications. Anemia of chronic disease occurs in about half of patients. The most feared complication is evolution to a lymphoplasmacytic malignancy (notably Waldenstrom's), which occurred in 15% of patients in one large series [2]. Interestingly, this complication has a similar frequency to that found in a cohort of patients with IgM MGUS (18% in 10 years) [16]. This hematologic transformation can occur more than 20 years after the first signs of the disease [17]. Three cases of AA-amyloid have been reported as a sequelae of chronic SS. Rarely, chronic inflammatory demyelinating polyneuropathy has been noted [18]. In addition, a sensorimotor neuropathy has been reported with the presence of IgM anti-myelin-associated glycoprotein antibodies [19]. Mortality does not seem to differ significantly from that of the general population with 90% survival after 15 years. However, the morbidity of SS has a profound impact on patients' lives necessitating treatment in many cases [2].

Table 1 Differential diagnosis of Schnitzler's syndrome

Urticaria	Arthralgia/arthritis
Hypocomplementic urticarial vasculitis	Erdheim–Chester disease
Systemic lupus erythematosus	Camurati-Englemann/Van Buchem disease
Cryoglobulinemia	Buschke–Ollendorf syndrome
Acquired C1 inhibitor deficiency	Osteopetrosis
Hyper-IgD syndrome	Melorheostosis
Periodic fever syndrome (HIDS)	Ribbing disease
Cryopyrin-associated periodic syndromes	Hypertrophic osteoarthropathy
Familial cold urticaria	
Chronic infantile neurologic cutaneous and articular syndrome (CINCA)	
Muckle-Wells syndrome	
Idiopathic chronic urticaria	
Delayed pressure urticaria	
Behçet's disease	
Mastocytosis	
Periodic fever	Monoclonal Gammopathy
Lymphoma	POEMS syndrome
Adult-onset Still's disease	Waldenström's macroglobulinemia
Hepatitis B and C	Lymphoma
Chronic meningococcemia	Multiplemyeloma
Familial Mediterranean fever	Monoclonal gammopathy of unknown significance (MGUS)
Castleman's disease	Gleich syndrome
TNF-associated periodic syndrome	

Discussion of treatment and management

A number of therapies have been used to treat Schnitzler's syndrome with inconsistent and disappointing results. High-dose corticosteroids, immunosuppressive drugs (azathioprine, cyclosporine), antihistamines, inhibitors of neutrophilic migration (dapsone, colchicine), cyclooxygenase inhibitors, alkylating agents, thalidomide, plasmapheresis, IV immunoglobulin, IFN- α , psoralene, PUVA, UVB/UVA phototherapy, bisphosphonates, anti-TNF α agents, chloroquine, hydroxychloroquine, immunoadsorption, and sulfasalazine have all been used with varied success. Antihistamines classically have no effect on either the urticaria or pruritus. Corticosteroids help in up to 40% of patients but high doses are usually required. Cyclophosphamide, methotrexate, and nonsteroidal anti-inflammatories are ineffective [2]. Thalidomide has had some success, but results are inconsistent [20]. Only four patients with Schnitzler's syndrome have been treated with rituximab, with sustained response in only two patients [21, 22].

To date, the most promising treatment for SS is the IL-1 receptor antagonist anakinra (Kineret; Biovitrum, Stock-

holm, Sweden). Anakinra is a recombinant human IL-1 receptor antagonist, which competitively inhibits IL-1 β from binding to the IL-1 receptor. The benefit of anakinra in treating Schnitzler's syndrome provides further evidence that IL-1 β is an important mediator in the pathophysiology of the disease.

Several case reports have described the successful use of anakinra in the treatment of the urticaria, arthralgia, and bone pain associated with SS. Besada et al. described a remission of symptoms in all 24 SS patients who were treated with anakinra [23]. However, the short half-life of anakinra requires daily injection with a high incidence of significant injection site reactions that may prompt cessation of therapy [24]. Moreover, a quick flare-up of the disease is observed if the patient misses an injection.

Anakinra alone does not affect the IgM gammopathy [7, 25]. As a result, several investigators have postulated that IL-1 dysregulation may represent a downstream event from the plasmacytosis and IgM gammopathy. In patients with myeloma, IL-1 is known to stimulate the release of IL-6 from marrow stromal cells, which stimulates the survival and proliferation of plasma cells [26]. The inhibition of IL-1 with anakinra reduces IL-6 levels in myeloma patients but does not reduce the number of myeloma cells. However, combining anakinra with apoptosis-inducing dexamethasone was able to induce myeloma cell death raising speculation that treating SS patients with anakinra and dexamethasone may clear the plasmacytosis and monoclonal gammopathy [27].

Our patient's symptoms were difficult to control. She was initially treated with antihistamines and H-2 blockers with minimal relief of her pruritus. Hydroxychloroquine, aspirin, and ibuprofen did not provide symptomatic relief of arthralgia or fever. She was started on 40 mg of prednisone daily but this was subsequently discontinued because of difficulty controlling her diabetes. Unfortunately, she only experienced a mild decrease in the frequency and severity of urticaria and arthralgias with prednisone. Ultimately, she was started on anakinra after several months of failed outpatient therapy. Within 12 h of her first dose, her urticaria resolved and her fatigue, malaise, and arthralgias improved. She is currently being treated as an outpatient with daily injections of anakinra and is clinically doing well. She has had no further episodes of pancreatitis.

Recurrent pancreatitis has not previously been described in patients with SS. However, IL-1 and other members of the IL-1 family have been implicated in the pathogenesis of both acute and recurrent pancreatitis [28, 29]. Furthermore, treatment with IL-1 receptor antagonists has been shown to reduce the severity of acute pancreatitis in experimental models [30]. It is possible that our patient's recurrent acute-on-chronic

pancreatitis was exacerbated by her SS. The fact that she has not had further episodes after starting anakinra provides additional support for this hypothesis.

Conclusions

Schnitzler's syndrome is a rare disorder characterized by monoclonal gammopathy, urticaria, and a number of other systemic inflammatory complaints. The diagnosis of SS is often delayed given the low incidence of disease and the variation in clinical symptoms at presentation. While the pathogenesis of SS is not fully understood, there is compelling evidence that the IL-1 inflammatory pathway plays an important role in the development of the disease. The successful use of anakinra in our patient provides further support for the role of IL-1 in the development of SS and may help to shed light on the role of IL-1 in other inflammatory syndromes.

Disclosures None.

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