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Schnitzler's syndrome: A broader clinical spectrum

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Schnitzler's syndrome is characterized by chronic urticaria, recurrent fever, bone pain, and lymphadenopathy in conjunction with a serum IgM M component in a concentration that is usually <10,000 mg/L. Complement activation and cryoprecipitation do not appear to be involved. We report two additional patients who share many of the characteristics of this entity. These patients differ from patients previously reported because of the markedly elevated IgM M-component concentration in one patient and the severity of anemia in the second patient. An increased frequency of IgG autoantibodies to interleukin-1- α has been reported by other investigators; it has been suggested that an antibody-mediated prolongation of the half-life of interleukin-1- α might account for some of the symptoms and signs of this disorder. However, neither the mediators involved in the induction of nonpruritic urticaria nor the role of the IgM M component has been established. (J ALLERGY CLIN IMMUNOL 1991;87:849-54.)

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IgM M components are associated with urticaria and angioedema in several entities. Urticaria may be found in patients whose IgM M component is cryoprecipitable, either alone (type I cryoproteinemia) or together with other immunoglobulins (type II cryoproteinemia).¹ Angioedema, in a pattern resembling hereditary angioedema, may be found in patients in whom the IgM M component and anti-idiotypic antibodies form complexes. These complexes activate and consume early complement components together with the C1 INH, which is thereby depleted, leaving unopposed the actions of the C1 esterase.² An additional, less well-recognized entity is Schnitzler's syndrome, in which an IgM M component is associated with chronic urticaria; complement activation does not appear to be involved. This syndrome was first described by Schnitzler et al. in 1974.³ Since that time, 15 cases have been reported, most of them in the French literature.⁴⁻¹¹ Patients with Schnitzler's syndrome share several distinguishing features. Their urticaria involves primarily the trunk and extremities, sparing the face. They may have recurrent fever, bone pain, and lymphadenopathy. Laboratory features include the presence of an IgM M component, elevated ESR, and leukocytosis. Radiographic examination may reveal hyperostosis of the tibia and pelvic bones. Complement values are normal, and there is an absence of detectable ANA, rheumatoid factor, and cryoprotein.

Schnitzler's syndrome is a rare cause of chronic urticaria. A review of 178 case records of patients with an IgM M component observed at the MGH between 1984 and 1989 disclosed the presence of urticaria or angioedema in six patients. Of the six, two patients had cryoproteinemia. One of these patients had cold urticaria, but the other patient had urticaria most likely caused by a drug reaction. The third patient developed acute urticaria after treatment with an antibiotic, and another patient had urticaria of undetermined etiology. We report on the fifth and sixth patients who share many of the characteristics of the previously reported patients with Schnitzler's syndrome.

RESULTS

Case 1

Patient 1, a 59-year-old white man presented to the MGH in 1980 with a history of low back pain of many years duration and a 13-year history of chronic urticaria. The patient experienced daily episodes of nonpruritic urticarial lesions of the trunk and extremities; the face was not involved. He had recurrent episodes of nocturnal sweating, fever to 103° F, chills, diffuse myalgia, arthralgias, and low back pain. The fever and arthralgias resolved within hours,

Abbreviations used

C1 INH:	C1 esterase inhibitor
ESR:	Erythrocyte sedimentation rate
ANA:	Antinuclear antibody
RF:	Rheumatoid factor
MGH:	Massachusetts General Hospital
SLE:	Systemic lupus erythematosus
IL-1:	Interleukin-1

but the urticaria tended to worsen after these attacks. The frequency of the nocturnal episodes varied from daily to monthly. Initial and subsequent physical examinations revealed no evidence of lymphadenopathy or hepatosplenomegaly. Biopsy specimen of an urticarial lesion revealed superficial and middermal perivascular and interstitial neutrophilic infiltrates together with prominent dermal edema. There was no evidence of vasculitis. Direct immunofluorescence demonstrated deposition of IgM, C3, and fibrin within and around the walls of small dermal blood vessels. These changes were considered to be nonspecific and to reflect a response to vascular injury. Deposition of immunoglobulin or complement at the dermal-epidermal junction was not observed. Overall, the findings were considered to be those of chronic urticaria. Bone marrow biopsy specimens were unremarkable, without signs of granulomas or malignancy.

Agarose gel electrophoresis revealed an M component in the gamma globulin zone. By immunofixation, the M component was identified as an IgM kappa protein. Initially, the IgM concentration was 4900 mg/L; however, repeated determinations demonstrated a progressive elevation to 32,500 mg/L.

The ESR was persistently elevated at 52 to 117 mm/hr, and there was a microcytic anemia (hemoglobin, 100 gm/L; hematocrit, 0.33; mean cell volume, 70 fL). Serum iron was 156 µg/dL (50 to 150), and total iron-binding capacity was 424 µg/dL (250 to 410). Before prednisone therapy there was a leukocytosis with white blood cells, $14.5 \times 10^9/L$, and an elevated platelet count, $480,000 \times 10^9/L$. Complement values were normal: total hemolytic complement, 287 U/ml (180 to 250); C3, 1060 mg/L (830 to 1070); C4, 340 mg/L (150 to 450); C1 INH, 280 mg/L (126 to 246); C1q, 475 µg/ml (349 to 561). Tests for ANA, RF, and cryoproteins were negative. There was no hyperostosis revealed by bone radiographs.

His systemic symptoms have required daily prednisone (10 mg) for control. Attempts to omit prednisone or to switch to an alternate-day treatment regimen led to worsening of urticaria and more frequent episodes of nocturnal fever, chills, and myalgia. Separate trials of chlorambucil, plasmapheresis, and hydroxychloroquine sulfate did not lead to an improvement. For several years, the patient has been main-

tained with prednisone, colchicine, and diflunisal. This regimen partially controls his symptoms, reducing the intensity and extent of urticaria and diminishing his low back and shoulder pain. Complications of steroid treatment include osteoporosis and diabetes mellitus.

This patient's illness has many features of Schnitzler's syndrome; an unusual feature of this case is the large amount of IgM M component.

Case 2

Patient 2, a 59-year-old white woman presented to the MGH in 1989 with a 9-year history of daily urticarial lesions occurring on her trunk and extremities, sparing her face. Initially, the lesions were nonpruritic, with new lesions appearing at night. After several years, the urticarial lesions became pruritic. She also complains of swelling of the buccal lining and the soles of her feet, but these changes have not been confirmed by examination. The urticarial lesions were associated with recurrent fever to 101° F, chills, night sweats, pain along the anterior surface of her legs, and arthralgias of her hands and feet. Attacks, lasting for hours, occurred at irregular intervals (but averaged about 1 per week). On physical examination, there have been intermittent lymphadenopathy and hepatosplenomegaly. A biopsy specimen of an urticarial lesion demonstrated edema of the dermis and a prominent perivascular infiltrate consisting of lymphocytes and a few neutrophils. There was no evidence of vasculitis. Direct immunofluorescence demonstrated focal deposits of C3 in blood vessels and extensive staining for fibrin throughout the reticular dermis. It was suggested that these changes may have resulted from leakage of plasma proteins secondary to injury of blood vessels. The findings were interpreted to be those of chronic urticaria. A lymph node biopsy specimen demonstrated no evidence of malignancy. Two bone marrow biopsy specimens revealed the absence of myeloproliferative or lymphoproliferative disease; the positive findings were those of hyperplasia of mature granulocytes.

Agarose gel electrophoresis demonstrated an M component in the gammaglobulin zone. By immunofixation, the M component was identified as an IgM kappa protein. The initial amount was 1000 mg/L; subsequently, this concentration has increased to 5000 mg/L. The ESR was elevated to 50 to 100 mm/hr. There was a microcytic anemia (hemoglobin, 70 gm/L; hematocrit, 0.24; mean cell volume, 66 fL) and leukocytosis (white blood cells, $21 \times 10^9/L$), and the differential count demonstrated 89% polymorphonuclear neutrophils, 10% lymphocytes, and 1% monocytes. The platelet count was normal. Complement values were normal: total hemolytic complement, 262 U/ml; C3, 1200 mg/L; C4, 342 mg/L; C1 INH 310 mg/L. There was no hyperostosis on bone radiographs. There was no detectable ANA, RF, or cryoprotein. Treatment with ibuprofen, cyproheptadine, clemastine fumarate, and astemizole has partially controlled her symptoms but has not eliminated the daily episodes of urticaria. The pruritus has worsened. Her course

has been complicated by progressive anemia. Treatment with erythropoietin (200 mg/kg) for 2 months was accompanied by a slight increase in the hematocrit. Treatment with cyclophosphamide is planned.

This patient's illness also has many of the characteristics of Schnitzler's syndrome; the unusual feature of this case is the severity of the anemia.

DISCUSSION

These two patients share many of the characteristics of the cases of Schnitzler's syndrome previously reported (Table I). Both patients experienced chronic, nonpruritic urticaria of the trunk and extremities, recurrent fever, and arthralgias lasting many years. Several years after the onset, urticaria became pruritic in one patient who also had intermittently palpable lymphadenopathy and hepatosplenomegaly. Laboratory findings included an IgM kappa M component, elevated ESR, and leukocytosis, and in one patient, thrombocytosis. Both patients had normal complement values including a normal concentration of C1 INH, and the absence of RF, ANA, and cryoprotein. Additionally, both patients had a microcytic anemia without evidence of iron deficiency, unlike the normochromic, normocytic anemia previously reported.^{4-6, 11} The two patients differ from patients previously described in that one patient has a large amount of IgM M component (whereas previous cases, with two exceptions, had levels of 10,000 mg/L or less) and that the other patient has a profound microcytic anemia.

Other diagnostic entities were considered in our patients. Adult Still's disease was considered in our first patient because of fever, rash, arthralgias of his shoulders, and back pain.¹² Earlier, the diagnosis of ankylosing spondylitis had been made on the basis of his chronic low back pain, but confirmatory radiographic evidence was lacking. Whether his low back pain is, indeed, a manifestation of Schnitzler's syndrome is uncertain. In the second patient, the severe progressive anemia has led to a search for malignancy of the lymph nodes, bone marrow, or gastrointestinal tract. To date, there is no explanation for the anemia other than Schnitzler's syndrome. Although for most patients with Schnitzler's syndrome the course is benign, the development of lymphoplasmacytic lymphoma in two patients⁶ underscores the importance of periodic reevaluation of the bone marrow and lymph nodes of the second patient.

Chronic urticaria or angioedema associated with an M component appears in disorders that are readily distinguishable from Schnitzler's syndrome. Acquired C1 INH deficiency and angioedema have been described in association with various B cell lymphopro-

TABLE I. Characteristics of patients with Schnitzler's syndrome

Manifestations	Previously reported cases*	Patient 1	Patient 2
Clinical course			
Chronic urticaria	15/15	+	+
Recurrent fever	11/15	+	+
Arthralgias	4/5	+	+
Bone pain	8/15	?	+
Angioedema	4/15	-	-
Physical examination			
Hepatomegaly	4/15	-	±
Splenomegaly	1/15	-	±
Lymphadenopathy	7/15	-	±
Laboratory data			
Serum IgM M component	14/15†	+	+
IgM >10,000 mg/L	2/11	+	-
ESR >60 mm/hr	14/15†	+	-
Anemia	7/12‡	+	+
Leukocytosis >10 × 10 ⁹ /L	5/5	+	+
Thrombocytosis >400 × 10 ⁹ /L	4/5	+	-
Normal complement level	9/9	+	+
Normal CI INH level	7/7	+	+
Presence of rheumatoid factor	0/9	-	-
Presence of ANA antibodies	0/9	-	-
Presence of cryoprotein	1/12	-	-
Hyperostosis on bone radiographs	5/12	-	-
Absence of abnormal lymphoproliferation in			
Bone marrow	13/13	+	+
Lymph nodes	6/7	+	+

+, Present; -, absent; ±, intermittently present.

*References 3 to 11.

†In one patient the ESR and results of immunoelectrophoresis were not reported.

‡Type and severity not specified in most studies.

liferative disorders, such as lymphosarcoma, chronic lymphocytic leukemia, and multiple myeloma.^{2, 13} Systemic capillary leak syndrome, in which angioedema is associated with an IgG M component, is characterized by its dramatic presentation with acute, profound hypotension, hemoconcentration, and hypoalbuminemia.¹⁴ Appearance of daily urticaria, fever, and arthralgia is not a feature. In contrast to the cold urticaria of cryoproteinemia, Schnitzler's syndrome is not linked to any known physical stimulus.¹⁵

Several other disease entities have features of Schnitzler's syndrome, but if they are accompanied by a serum M component, the latter is likely to be a coincidental finding. Urticaria, fever, arthralgias, elevated ESR, and anemia with or without an altered complement profile may occur in patients with SLE. The urticarial lesions may be pruritic, generalized, persistent, and difficult to control.¹⁶ In contrast to the leukocytosis and thrombocytosis of Schnitzler's syndrome, leukopenia and neutropenia appear more commonly in SLE. The diagnosis of SLE is unlikely in

our patients because of the consistently negative tests for ANAs during active disease. Patients with cutaneous vasculitis experience urticaria, myalgia, arthralgias, fever, elevated ESR, and leukocytosis.¹⁷⁻¹⁹ The complement profile may be normal or demonstrate activation of the complement pathways. Urticarial lesions may be generalized, nonpruritic, occur daily with few lesions lasting more than 72 hours, reoccur indefinitely, and respond poorly to treatment. Biopsy specimens of lesional skin reveal the presence of neutrophilic perivascular infiltrate and fibrinoid necrosis. Perivascular infiltrates have been reported commonly in the skin biopsy specimens of patients with Schnitzler's syndrome,^{4-7, 10, 11} and these infiltrates were also observed in our patients; fibrinoid necrosis, however, has been observed in only one case.⁸ Urticaria has been described in hepatitis B infection associated with prolonged hepatitis B antigenemia and a necrotizing vasculitis.²⁰ The hives, which may be generalized, appear with fever and arthralgia. Other prominent features of this vasculitis, mononeuritis multiplex, ab-

dominal pain, and renal disease, have not been reported in Schnitzler's syndrome. In surviving patients, the symptoms, once resolved, do not reappear. An additional etiology for urticaria, fever, arthralgias, and myalgia is delayed-pressure urticaria, occurring alone or together with a chronic idiopathic urticaria. In delayed-pressure urticaria, the urticaria may be nonpruritic and spare the face, but it is not associated with an elevated ESR, anemia, leukocytosis, or thrombocytosis.²¹

The role of the IgM M component in the pathogenesis of the urticaria and other systemic manifestations of Schnitzler's syndrome has yet to be elucidated. M components exert their biologic effects based on the physicochemical properties of the molecules (cryoprecipitation or hyperviscosity), the antibody activity of the molecules (anti-IgG), or by unknown processes.¹ Immunofluorescent studies on patients with Schnitzler's syndrome have revealed the presence of IgM deposits at the basement membrane zone of the skin, but this finding was limited to one of seven cases.^{6, 8} Olsen et al.²² demonstrated the presence of IgM, with the identical idiotype as the circulating IgM M component, at the dermal-epidermal junction of lesional skin in a patient with chronic urticaria, fever, and an IgM M component. Hauser et al.²³ demonstrated that human epidermis contains IL-1 activity. In a preliminary study, Saurat et al.²⁴ tested the ability of serum and its purified IgM fraction from a patient with Schnitzler's syndrome to react with epidermal extracts in a Western blot assay. Reactivity appeared to be directed against the IL-1 fraction of the extracts. On testing with recombinant human IL-1- α and IL-1- β , the binding activity appeared to be specific for IL-1- α .²⁴ IL-1 binding by the IgM M component has not been confirmed, and in a subsequent study,²⁵ these authors found IgG antibodies to IL-1- α in 29 of 167 (15%) normal serums and in seven of 11 (64%) serums from patients with the syndrome of urticaria, fever, and macroglobulinemia. IgG anti-IL-1 antibodies enhanced fourfold the circulating half-life of radiolabeled IL-1- α in the rat.²⁵ IL-1- α binding activity was not found in serum from our two patients (Saurat J.-H. Personal communication).

We propose that the spectrum of Schnitzler's syndrome be expanded to include our two patients who share important features with patients previously reported. Each patient differs from patients previously described in that one patient has a large amount of circulating M component and the other patient has a profound progressive anemia. In reviewing these data on all patients previously described, it appears that most patients share the presence of chronic urticaria, recurrent fever, bone pain, and lymphadenopathy, as

well as a circulating IgM M component, markedly elevated ESR, normal complement values, leukocytosis, and possibly an anemia. Perhaps anemia should be included among the diagnostic criteria of the syndrome.

Schnitzler's syndrome is sufficiently well demarcated from other entities so that patients presenting with chronic urticaria, particularly if it is nonpruritic and spares the face and in whom there is a leukocytosis, thrombocytosis, anemia, and elevated ESR, merit further evaluation to probe for the presence of an IgM M component. The pathogenesis of Schnitzler's syndrome is still undefined; preliminary studies suggest that IL-1- α binding activity of the patient's serum may have a role in some cases.

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Announcement

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