The Schnitzler Syndrome

Four New Cases and Review of the Literature

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Introduction

The Schnitzler syndrome is defined by a unique and particular constellation of clinical and biologic signs including chronic urticaria, intermittent fever, bone pain, arthralgia or arthritis, and a monoclonal IgM gammopathy. The syndrome was described by Schnitzler, a French dermatologist, in 1972 (42) and since then more than 40 other patients have been reported. The syndrome is often underdiagnosed, and the delay to diagnosis is more than 5 years in most cases. Because of the variety of clinical signs, this syndrome is of concern to the dermatologist, the internist, the rheumatologist, and the hematologist. Many patients have seen all these specialists before the diagnosis is established. In this study, we report 4 new patients with this syndrome and review all cases in the English, German, and French literature.

Patients and Methods

We report here 4 new cases and the results of a literature review of the Schnitzler syndrome. A MEDLINE (National Library of Medicine, Bethesda, MD) search was performed using the key words "urticaria" and "monoclonal gammopathy"; "urticaria" and "IgM"; "urticaria" and "macroglobulinemia"; and "Schnitzler syndrome." The search period was 1966–2000. Both English and non-English literature were retrieved. Only patients with chronic urticaria and a monoclonal IgM gammopathy, in the absence of any other disease that might explain these findings, were included.

Case Reports

From 1992 to 2000, we investigated 4 patients with the Schnitzler syndrome. None of these patients have been reported previously. Two of these patients were followed in the dermatology department of a university hospital (Patients 1 and 2), 1 in the internal medicine department of a university hospital (Patient 3), and 1 in the dermatology department of a military hospital (Patient 4).

Patient 1

A 67-year-old man had a 6-year history of persistent, antihistamine-resistant urticaria. He had been examined already by 5 physicians, including dermatologists and hematologists, but no diagnosis had been established. Usually, individual lesions resolved within 24–48 hours. They consisted of moderately pruritic rose macules or maculopapules with varying topography (Figures 1 and 2). The face, the soles, and the palms were spared. He never experienced arthralgia affecting the shoulders and recurrent episodes of fever. The fever, which could reach 39 °C, was well tolerated, and was accompanied by an exacerbation of the skin rash. Alcohol ingestion also aggravated the skin rash. He reported occasional night sweats. On examination, he had a widespread, edematous, maculopapular rash, as well as palpable inguinal and axillary lymph nodes.

Histologic examination of a biopsy from an urticarial lesion showed edema and a perivascular infiltrate of neutrophils and eosinophils in the papillary dermis. Fibrinoid deposits were seen around dilated superficial blood vessels. However, fibrinoid necrosis, the hallmark of fully developed leukocytoclastic vasculitis, was not seen. Immunofluorescence studies were negative.

Laboratory investigations showed a moderately increased erythrocyte sedimentation rate (ESR) of 32 mm/h; C reactive protein level was 17.8 mg/dL, Interleukin (IL)-6 level was increased to 97.1 pg/mL (normal < 20 pg/mL), IL-2 receptor level was slightly increased to 230 pg/mL (normal < 180 pg/mL), while tumor necrosis factor (TNF) α and IL-8 levels were within normal range. Serum protein electrophoresis demonstrated a monoclonal IgM component with kappa light chains on immunofixation. No Bence-Jones proteinuria was detectable. Total IgM was 5.4 g/L (normal, 0.4–3.1 g/L); IgG, IgA, IgD, complement hemolytic assay (CH) 50, C3, C4, and C1 inh were in normal range. Hepatitis C was excluded. Creatinine, complete blood count, and serum calcium were in normal range. Skeletal X-rays were normal. Bone marrow aspirates and histology showed no abnormality. The histologic examination of an axillary lymph node showed inflammatory hyperplasia. Cerebral and thoracic scans and abdominal sonography were normal.
His symptoms proved difficult to control. Antihistamines (loratadine, terfenadine, dexchlorpheniramine, hydroxyzine), colchicine (1 mg/d), dapsone (100 mg/d), aspirin (3 g/d), and ibuprofen (1,200 mg/d) were ineffective. Psoralens and ultraviolet A (PUVA) therapy allowed moderate improvement of the rash.

This patient was followed for 7 years and still had a daily rash. IgM levels increased steadily from 2.55 g/L in 1993 to 11 g/L in 2000, but the monoclonal spike remained stable about 7 g/L in the last 3 years.

Patient 2

A 41-year-old woman was admitted for chronic urticaria. The eruption began 3 years earlier and consisted of a daily, mildly pruritic rash involving mainly the trunk (Figure 3), but also the face on occasion. Two years earlier, she had been hospitalized elsewhere to investigate the rash and inflammatory arthralgia of the hands and knees. An extensive workup was negative at that time, except for a slightly increased ESR of 22 mm/h and the presence of traces of a monoclonal IgM gammopathy. No diagnosis was established. Recently, she developed intermittent fever, night sweats, and chills and was therefore referred to us. She was in good general condition, and skin examination revealed numerous red pale macules and maculopapules mainly on the trunk. Individual lesions resolved within 24 hours. Fever reached as high as 40°C. Otherwise, examination was unremarkable except for a single left palpable axillary lymph node.

A skin biopsy showed edema of the upper dermis with an inflammatory infiltrate rich in neutrophils, which was consistent with the diagnosis of neutrophilic urticaria. Direct skin immunofluorescence studies were negative. Laboratory investigations showed an elevated ESR of 121 mm/h. IL-6 level was increased to 50.6 pg/mL (normal < 20 pg/mL), IL-2 receptor level was increased to 240 pmol/L (normal < 190 pmol/L), and TNFα level was within normal range. Blood count revealed leukocytosis of 21.69 × 10⁹/L, eosinophilia of 0.58 × 10⁹/L, thrombocytosis of 559 × 10⁹/L, and anemia (hemoglobin 99 g/L). Serum protein electrophoresis demonstrated a monoclonal IgM component with kappa light chains on immunofixation. No Bence-Jones proteinuria was detectable. The monoclonal component was estimated at 6.1 g/L. Total IgM was 5.35 g/L (normal, 0.4–3.1 g/L); IgG, IgA, IgD, CH 50, C3, C4, and C1-inh were in normal range. There were no antinuclear antibodies, rheumatoid factor, cold agglutinins, cryofibrinogen, or cryoglobulins. Hepatitis C was excluded. Creatinine and serum calcium were in normal range. Skeletal X-rays were normal. Bone marrow aspirates and histology showed slight plasmacytosis (8%). Abdominal and thoracic scans were normal.

Antihistamines (cetirizine, hydroxyzine), aspirin (3 g/d), and diclofenac (150 mg/d) did not alleviate the skin rash. PUVA therapy partly improved the skin rash. Naprosyn (1 g/d) controlled the joint pain but did not prevent the fever or the skin rash. An increase in intensity and duration of the inflammatory symptoms (fever and arthralgia) and a symptomatic inflammatory anemia (6.5 g Hb/dL) necessitated immunosuppressive treatment with chlorambucil (4 mg/d) and dexamethasone 20 mg/d for 5 days every 3 weeks. Although this treatment corrected the anemia, and partially the fever, it did not control skin rash or joint pain. This patient was followed for 6 years and still had a daily rash. IgM levels steadily increased from 5.35 g/L in 1994 to 17.9 g/L in 2000. The monoclonal component increased more slightly during the last 3 years from 6.1 g/L to 8.1 g/L.

Patient 3

A 74-year-old man had an erythematous widespread eruption of 3 years’ duration. Individual lesions resolved within 24–48 hours.
They consisted of rose pale macules or maculopapules with varying topography (Figure 4). The face, the palms, and the soles were not affected by the eruption, which was not pruritic until recently. He never experienced angioedema. The patient concomitantly developed recurrent fever with peaks above 39.5 °C, and he had lost 7 kg in the past 7 months. He complained about morning stiffness affecting the hands and feet. On examination, he had bilateral palpable axillary lymph nodes.

A cutaneous biopsy showed neutrophilic urticaria rich in eosinophils. Direct cutaneous immunofluorescence studies showed granular IgM deposits in the papillary dermis. Laboratory investigations showed a moderately increased ESR of 40 mm/h; C reactive protein level was 47.7 mg/dL. Serum levels of IL-6, IL-8 and TNFα were in normal range, but the level of the IL-2 receptor was increased to 460 pmol/L (normal < 190 pmol/L). Serum protein electrophoresis demonstrated a monoclonal IgM component with kappa light chains on immunofixation. No Bence-Jones proteinuria was detectable. The monoclonal IgM spike was 2.6 g/L (normal, 0.4–3.1 g/L); IgG and IgA were in normal range. An undosable IgM monoclonal spike had been detected 2 years earlier. CH50, C3, C4, and C1-inh were in normal range. Ferritin level was increased to 424 ng/mL (normal, 28–284 ng/mL), and IgD level was increased to 16.4 g/L and 4.79 g/L respectively. An undosable IgM monoclonal spike had been detected 2 years earlier. CH50, C3, C4, and C1-inh were normal. Ferritin level was increased to 424 ng/mL (normal < 284 ng/mL), and IgD level was in normal range. There were no cold agglutinins, cryofibrinogen, or cryoglobulins. No antinuclear antibodies was positive at 1:320. Hepatitis C was excluded. Creatinine and serum calcium were in normal range. Complete blood count revealed moderate anemia. Bone marrow aspirates and histology showed medullary hypoplasia. Skeletal X-rays were normal. Morphologic studies of the thorax, abdomen, and pelvis revealed no abnormality.

Prednisone (20 mg/d), chlorambucil (4 mg/d), ketoprofen (300 mg/d), cetirizine (10 mg/d), and hydroxyzine (50 mg/d) proved ineffective to control his symptoms.

This patient was followed for 4 years and still had a daily rash. His monoclonal IgM gammopathy slightly increased about 0.5 g/L every 6 months in the last 3 years.

**Patient 4**

A 49-year-old man was referred for a rash of 2 years’ duration. His eruption started 2 years ago and consisted of erythematous, nonpruritic, slightly elevated red plaques. Individual lesions appeared daily, lasted about 12 hours, and resolved without sequel. The eruption involved the whole body, including the face, but the patient never experienced angioedema. The patient noticed that the rash was triggered when he ingested alcohol and spicy food. A few months after the eruption started, other clinical signs appeared. He developed fever about twice a week, up to 39.5 °C, often preceded by chills as well as inflammatory arthralgia of the knees and ankles and pain in both ankles. His examination was otherwise unremarkable except for a xanthelasma at the right eyelid.

A cutaneous biopsy showed neutrophilic urticaria. Direct cutaneous immunofluorescence studies revealed no immunoglobulin or complement deposition. Laboratory investigations showed an increased ESR of 66 mm/h; C reactive protein level was 53 mg/L. Serum level of TNFα was in normal range, but the level of the IL-2 receptor was increased to 514 pmol/L (normal < 190) and IL-6 level was increased to 41 pg/mL (normal < 20 pg/mL). Serum protein electrophoresis demonstrated a monoclonal IgM component with kappa light chains on immunofixation. No Bence-Jones proteinuria was detectable. The monoclonal IgM spike was 5.3 g/L (normal, 0.4–3.1 g/L); IgG and IgA levels were moderately increased to 16.4 g/L and 4.79 g/L respectively. An undosable IgM monoclonal spike had been detected 2 years earlier. CH50, C3, C4, and C1-inh were normal. Ferritin level was increased to 424 ng/mL (normal < 284 ng/mL), and IgD level was in normal range. There were no cold agglutinins, cryofibrinogen, or cryoglobulins. No antinuclear antibodies were detected. Hepatitis C was excluded. Creatinine and serum calcium were in normal range. Complete blood count revealed a moderate anemia (10.5 g Hb/dL) and leucocytosis (11.41 × 10⁹/L neutrophils), and thrombocytosis (442 × 10⁹/L). Bone marrow aspirates and histology were normal. Skeletal X-rays were normal. Morphologic studies of the thorax, abdomen, and pelvis revealed no abnormality.

Prednisone (20 mg/d) and ibuprofen (300 mg/d) proved ineffective to control his symptoms. This patient was followed for 2 years and still had a daily rash.

**Discussion**

The Schnitzler syndrome is a rare and probably underdiagnosed disorder. Including the 4 patients reported here, 52 patients with this syndrome have been reported to date (1–9, 10–26, 29–32, 35–40, 42–44, 46–50). The mean delay to diagnosis was 5.4 years (SD 4.9 yr). Mean age at diagnosis was 60 years (SD 12 yr) and the male to female ratio is 1.45. Of note, most cases were reported in Europe, mainly in France and Spain. Only 3 North American patients with this syndrome have been reported so far (6, 26).

**Clinical signs**

The nature and frequency of the different clinical signs reported in patients with the Schnitzler syndrome are shown in Table 1. The presence of the skin rash and the monoclonal IgM component, which define this syndrome, are constant, although the possibility of the Schnitzler syndrome without rash has been advocated in a patient with bone pain, bone densification, and a monoclonal IgM component.
Histopathologic examination of the lesions usually reveals neutrophilic urticaria. de Castro et al (11) reviewed 25 skin biopsy specimens from 15 of the originally reported patients and showed that neutrophilic urticaria is the most common histopathologic finding. The 4 patients we followed had neutrophilic urticaria. Fully developed vasculitis is rare (only 2 patients in the review by de Castro et al), and therefore this syndrome should not be classified with the urticarial vasculitides. When immunofluorescence studies were performed, deposition of immunoreactants, mainly IgM, could be found around the superficial dermal vessels in about 30% of patients (1, 6, 8, 9, 32). In a few noteworthy observations, IgM deposits were found along the dermal-epidermal junction (21, 35, 37). We recently demonstrated, by means of immunoelectron microscopic studies and immunoblotting on epidermal and dermal skin extracts, that IgM-skin interactions play a major role in the pathophysiology of the skin lesion (27). Indeed, anti-IgM autoantibodies of the same isotype as their monoclonal gammapathies can be present in the serum of some patients with the Schnitzler syndrome. These IgM autoantibodies seem to deposit in vivo in the epidermis and at the dermal-epidermal junction, in the region of the anchoring fibrils, and they could thus trigger a local inflammatory response that could induce the skin lesions (27).

**TABLE 1. Frequency of clinical findings in 52 patients with the Schnitzler syndrome**

<table>
<thead>
<tr>
<th>Sign</th>
<th>Frequency in % (% of Patients in whom this Information was Reported)</th>
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<tbody>
<tr>
<td>Skin rash</td>
<td>100/100</td>
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<tr>
<td>Pruritus</td>
<td>29/70</td>
</tr>
<tr>
<td>Fever</td>
<td>90/92</td>
</tr>
<tr>
<td>Arthralgia and/or arthritis</td>
<td>50/94</td>
</tr>
<tr>
<td>Bone pain</td>
<td>50/70</td>
</tr>
<tr>
<td>Liver and/or spleen enlarge-</td>
<td>33/83</td>
</tr>
<tr>
<td>Palpable lymph nodes</td>
<td>50/85</td>
</tr>
<tr>
<td>Elevated ESR (≥30 mm/h)</td>
<td>98/87</td>
</tr>
<tr>
<td>Leukocytosis (&gt;10 × 10^9/L)</td>
<td>88/85</td>
</tr>
<tr>
<td>Monoclonal IgM component</td>
<td>100/100</td>
</tr>
<tr>
<td>Kappa light chain</td>
<td>89/87</td>
</tr>
<tr>
<td>Abnormalities in IgG and/or IgA levels</td>
<td>26/67</td>
</tr>
<tr>
<td>Bence-Jones proteinuria</td>
<td>44/62</td>
</tr>
<tr>
<td>IgM &gt;10 g/L</td>
<td>33/87</td>
</tr>
<tr>
<td>IgM deposition in skin</td>
<td>35/71</td>
</tr>
<tr>
<td>Abnormal bone marrow findings</td>
<td>20/70</td>
</tr>
<tr>
<td>Abnormal bone morphology</td>
<td>56/71</td>
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</tbody>
</table>

Abbreviations: ESR = erythrocyte sedimentation rate.

The other 2 most characteristic clinical signs are fever and joint and/or bone pain.

**Fever**

Intermittent fever, with peaks over 40 °C, is present in 90% of patients and is a cardinal feature of the disease. The fever is usually well tolerated and chills are rare. In most patients, there is no relation between the fever and the skin rash. Fever usually responds to NSAIDs or to steroids. The pathophysiology of the fever and of the syndrome in general remain unclear. The presence of anti-IL-1 antibodies was reported with increased frequency in this syndrome by Saurat et al (41), but this finding was not confirmed subsequently by other investigators (19, 31, 32, 37). We found elevated IL-6 and/or IL-2 receptor levels in the 4 patients we followed and then disappear without sequel. The presence of purpura within the plaques was reported in 1 patient (40), but this is an exceptional finding. Short periods ranging from 1 to 2 weeks without eruption are possible. In the beginning of the disease, pruritus is usually absent. After 3 or 4 years, lesions become mildly pruritic in 29% of patients according to 1 patient (40), but this is an exceptional finding.

**Musculoskeletal involvement**

Musculoskeletal involvement is another cardinal feature of the disease, affecting 50% of patients. Bone pain (50% of patients) is the most characteristic finding, but arthralgia and sometimes fully developed...
arthritis are also common (59% of patients). Joint destruction and/or deformities have not been reported so far. Bone pain affects mostly the iliac bone and the tibia. Femur, spine, forearm, and clavicle were less often involved. Lecompte et al (26) reviewed the bone involvement in this syndrome and its differential diagnosis. Bone densification is the most frequent radiologic finding. Lytic lesions were reported in 2 patients (17, 22), and 2 patients had periosteal apposition (18, 26). Radiologic differential diagnosis is broad and includes mastocytosis, POEMS syndrome, Erdheim-Chester disease, Camurati-Englemann or Van Buchem disease, Buschke-Ollendorf syndrome, osteopetrosis, melorheostosis, ribbing disease, and hypertrophic osteoarthropathy. Bone technetium scanning reveals hyperfixation in the areas of radiologic involvement (26). Magnetic resonance imaging was performed in 3 patients (18, 26, 50) and showed medullary bone involvement and marrow infiltration without space-occupying features in the affected areas in 2 patients (26, 50). A bone biopsy was performed in 9 patients (4, 10, 14, 19, 29, 36, 37, 44, 50). It was normal in 3 patients (14, 42, 48) and showed a nonspecific inflammation in 5 patients (4, 10, 19, 29, 36), sometimes associated with hyperactive osteoblasts. One patient had histologic evidence of osteosclerosis (37).

Pallpable lymph nodes and hepatic or splenic enlargement

Palpable lymph nodes are found in 50% of patients and hepatic or splenic enlargement occurs in 35% of patients. Palpable lymph nodes are found in the axilla and inguinal sites and sometimes in the cervical region. Those lymph nodes can be multiple, persistent, and up to 2 or 3 cm large and therefore suggest the diagnosis of lymphoma, but biopsy shows nonspecific inflammation.

Monoclonal IgM component

The monoclonal IgM component is a defining feature of the syndrome. In 89% of patients, it is associated with a kappa light chain. Usually, when diagnosis of the syndrome is made, IgM levels are low (<10 g/L in 67% of patients). IgM levels can remain stable or increase progressively at a rate of about 0.5–1.0 g/L per year. High IgM levels should raise suspicion of Waldenström disease. When patients are seen at the very beginning of the disease, monoclonal IgM component can be present at very low (trace) levels. Nashan et al (33) reported a patient with urticaria, fever, arthralgia, elevated ESR, and a monoclonal IgG component and suggested that their observation could be a variant of the Schnitzler syndrome. We reported a patient in whom urticaria seemed to be related to a myeloma-tous IgA monoclonal spike, but this patient was lacking the other features of the Schnitzler syndrome (28). Bence-Jones proteinuria was reported in 44% of patients. In about 26% of patients, lowered levels of IgG or IgA can be found. At the time of diagnosis, examination of bone marrow is normal in 80% of patients. In the remaining 20%, unspecific, polyclonal, lymphocytic, or plasmocytic infiltrates were reported.

Laboratory findings and differential diagnosis

During the course of the disease, elevated ESR is a constant feature. Complement levels are normal or increased in patients with this syndrome. When complement levels are lowered, another diagnosis must be considered and the possibility of a genetic deficiency of C4 should be addressed, since 2 patients with the Schnitzler syndrome had a C4a deficiency (39). Thrombocytosis and an inflammatory anemia are present in about 10% of patients. In 2 patients, inflammatory anemia was severe and symptomatic (6). One of these 2 patients is reported here (Patient 2), and anemia was so severe that this patient had to be treated with steroids and an alkylating agent, to which the anemia responded well. It is noteworthy that persistent leukocytosis (>10 × 10^9/L), in the absence of any treatment, occurred in 80% of patients. In this regard, both adult-onset Still disease and the Schnitzler syndrome can be associated with a skin rash, fever, palpable lymph nodes, spleen and liver enlargement, arthralgia, and leukocytosis (46). However, ferritin levels are usually more elevated in the former while a monoclonal IgM component is present in the latter.

Other diseases that should be considered in the differential diagnosis of this syndrome are shown in Table 2. There is no biologic marker for this disease. Thus, diagnosis requires a combination of clinical, biologic, and radiologic findings as well as exclusion of other diseases. In Table 3, we suggest a combination of criteria that can be used to diagnose the Schnitzler syndrome. Although the criteria are useful for the positive diagnosis of the syndrome, they are not intended to distinguish the Schnitzler syndrome from other diseases that can closely mimic this syndrome. Therefore, exclusion of other diseases, mainly cryoglobulinemia, hypocomplementic urticarial vasculitis, acquired C1 inhibitor deficiency, hyper IgD syndrome, and adult-onset Still disease, remains essential.

Associated findings included pseudoxanthum elasticum in 2 patients (29, 49), peripheral neuropathy with the presence of monoclonal IgM with anti-MAG (myelin-associated glycoprotein) in 1 patient (25), C4 deficiency in 2 patients (39), and nodular regenerative hyperplasia of the liver in 1 patient (24).

Course and treatment

The disease pursues a chronic course. Spontaneous or treatment-induced remissions have not
been reported. Although the disease features chronic inflammation and a monoclonal component, to our knowledge no patient has developed systemic amyloidosis. Nevertheless, amyloidosis should be considered as a possible complication of the syndrome. The prognosis of the Schnitzler syndrome depends on the possible evolution into a lymphoproliferative disorder, either a lymphoma, including lymphoplasmacytic lymphoma, lymphoma of the Richter type, IgM myeloma, or Waldenström disease. Fifteen percent of the patients reported with this syndrome developed lymphoproliferative disorders (1, 9, 20, 30, 38, 39, 47, 48). However, the number of patients with the syndrome who will eventually develop lymphoproliferative disorder is probably much higher, since the reports of most patients were published shortly after diagnosis, and therefore follow-up was too short to draw any conclusion about long-term outcome. Lymphoma or Waldenström disease appears more than 10–20 years after the beginning of the first signs of the disease in most cases. Schnitzler’s original patient died from diffuse lymphoplasmacytic infiltration of the liver and bone marrow 23 years after the first signs of the disease (47). However, in rare cases, Waldenström disease was revealed by the Schnitzler syndrome (9). There is no specific predictive factor of the development of a lymphoproliferative disorder. Thus, initial workup of a patient with this syndrome should include an examination of bone marrow, immunoelectrophoresis of serum and urinary proteins, and dosage of immunoglobulin subtypes. The 2 latter examinations can then be used to follow-up those patients on a biannual basis. Lymph nodes should be biopsied when they enlarge.

Treatment of the Schnitzler syndrome is difficult and disappointing. No treatment is constantly effective in treating the skin rash. NSAIDs, most notably ibuprofen (3 × 400 mg/d), should be tried first (15), but in most patients those drugs will ameliorate the skin rash only briefly or not at all (3, 7, 21, 29, 32, 36, 50). Antihistamines do not control the skin rash (5, 7, 6, 21, 26), and, as the rash is not pruritic in most patients, they are not indicated. The use of inhibitors of neutrophil migration like colchicine or dapsone appears to be logical in this syndrome characterized by leukocytosis and neutrophilic urticaria, but results were inconstant (7, 8, 18, 21, 29, 32, 35, 40). Hydroxychloroquine and chloroquine also proved ineffective (6, 21, 36). Steroids and immunosuppressive drugs are not indicated to treat the rash and they are not effective at acceptable dosages (3, 5, 6, 8, 13, 14, 17, 18, 22, 31, 32, 35, 36, 37); plasmapheresis (6, 31, 35) and intravenous immunoglobulins (25) also are not effective. Even chemotherapeutic regimens that were prescribed to treat the associated hematologic disorders did not relieve the skin rash. PUVA therapy did reduce the intensity of the skin rash in 2 of the patients reported here, and this has been reported (31). Fever, although intermittent, can be disabling. NSAIDs, and

<table>
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<th>TABLE 2. Differential diagnosis of the Schnitzler syndrome</th>
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<tr>
<td>Disease</td>
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<tr>
<td>Adult-onset Still disease</td>
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<tr>
<td>Hypocomplementemenet urticarial vasculitis</td>
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<tr>
<td>Acquired C1 esterase inhibitor deficiency, especially in the setting of lymphoma and/or paraproteinemia</td>
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<tr>
<td>Cryoglobulinemia</td>
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<tr>
<td>Hyper IgD syndrome</td>
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<tr>
<td>Erythema marginatum</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>CINCA syndrome*</td>
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<tr>
<td>Muckle-Wells syndrome</td>
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<td>Lymphoma, Waldenström disease</td>
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*CINCA (chronic infantile neurologic cutaneous and articular syndrome) is also called NOMID (neonatal onset multisystem inflammatory disease).

<table>
<thead>
<tr>
<th>TABLE 3. Diagnostic criteria for the Schnitzler syndrome*</th>
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<tr>
<td>Urticarial skin rash, monoclonal IgM component, and at least 2 of the following criteria:</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Arthralgia or arthritis</td>
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<tr>
<td>Bone pain</td>
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<tr>
<td>Palpable lymph nodes</td>
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<tr>
<td>Liver or spleen enlargement</td>
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<tr>
<td>Elevated erythrocyte sedimentation rate</td>
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<tr>
<td>Leukocytosis</td>
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<td>Abnormal findings on bone morphologic investigations</td>
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</table>

*Another cause must be eliminated in all cases (see Table 2 for differential diagnosis), most notably hyper IgD syndrome, adult-onset Still disease, hypocomplementemic urticarial vasculitis, acquired C1 inhibitor deficiency, and cryoglobulinemia.
sometimes steroids or immunosuppressive agents (3, 7, 13, 14, 17, 21, 29, 32, 35, 36, 37, 50), alleviate it. Bone pain and arthralgia most often respond well to short treatments with NSAIDs (3, 7, 21, 23, 29, 32, 36, 50). Pagemidor was reported to be an effective treatment of bone pain in 1 patient (34). Thus, treatment depends on the nature and intensity of symptoms. NSAIDs are the first choice in most patients and can be associated with colchicine or dapsone. Steroids and immunosuppressive agents are only indicated when systemic symptoms like fever or arthralgia are disabling and do not respond to the first-line treatments. (When symptoms do not respond to first-line treatments but are tolerable, those agents should not be used.) In rare cases, disabling inflammatory anemia can necessitate introduction of steroids and alkylating agents (6).

In some patients, these symptoms and/or the presence of severe inflammatory anemia require steroids and/or immunosuppressive treatment, which ameliorate inflammatory symptoms but do not change the course of the skin rash.

**References**

6. Barriere H, Schnitzler M, Moulin G, Grolleau Y. Lesioni urtiariennes delanson et/or bone spleen, elevated erythrocyte sedimentation rate, and leukocytosis. The mean delay to diagnosis is more than 5 years, and this syndrome is of concern to internists and many medical specialists. Patients with this syndrome are often initially considered to have lymphoma or adult-onset Still disease, which are the main differential diagnoses. However, hypocomplementemic urtiariael vasculitis, systemic lupus erythematosus, cryoglobulinemia, acquired C1 inhibitor deficiency, hyper IgD syndrome, chronic infantile neurologic cutaneous and articular (CINCA) syndrome, and Muckle-Wells syndrome should also be excluded, because diagnosis relies on a combination of clinical and biologic signs and there is no specific marker of the disease. The disease pursues a chronic course, and no remissions have yet been reported. Disabling skin rash, fever, and musculoskeletal involvement are the most frequent complications. Severe anemia of chronic disease is another serious complication. The most harmful complication, however, is evolution to an authentic lymphoplastic malignant, which occurs in at least 15% of patients. This hematologic transformation can occur more than 20 years after the first signs of the disease, thus patients deserve long-term follow-up. Treatment is symptomatic and unsatisfactory. The skin rash is unresponsive to treatment, and nonsteroidal antiinflammatory drugs, antihistamines, dapsone, colchicine, and psoralens and ultraviolet A (PUVA) therapy give inconsistent results. Fever, arthralgia, and bone pain often respond to nonsteroidal antiinflammatory drugs.

**Summary**

The Schnitzler syndrome is characterized by a chronic urtiariael eruption with a monoclonal IgM gammapathy. The other signs of the syndrome include intermittent elevated fever, joint and/or bone pain with radiologic evidence of osteosclerosis, palpable lymph nodes, enlarged liver and/or spleen, elevated erythrocyte sedimentation rate, and leukocytosis. The mean delay to diagnosis is more than 5 years, and this syndrome is of concern to internists and many medical specialists. Patients with this syndrome are often initially considered to have lymphoma or adult-onset Still disease, which are the main differential diagnoses. However, hypocomplementemic urtiariael vasculitis, systemic lupus erythematosus, cryoglobulinemia, acquired C1 inhibitor deficiency, hyper IgD syndrome, chronic infantile neurologic cutaneous and articular (CINCA) syndrome, and Muckle-Wells syndrome should also be excluded, because diagnosis relies on a combination of clinical and biologic signs and there is no specific marker of the disease. The disease pursues a chronic course, and no remissions have yet been reported. Disabling skin rash, fever, and musculoskeletal involvement are the most frequent complications. Severe anemia of chronic disease is another serious complication. The most harmful complication, however, is evolution to an authentic lymphoplastic malignant, which occurs in at least 15% of patients. This hematologic transformation can occur more than 20 years after the first signs of the disease, thus patients deserve long-term follow-up. Treatment is symptomatic and unsatisfactory. The skin rash is unresponsive to treatment, and nonsteroidal antiinflammatory drugs, antihistamines, dapsone, colchicine, and psoralens and ultraviolet A (PUVA) therapy give inconsistent results. Fever, arthralgia, and bone pain often respond to nonsteroidal antiinflammatory drugs.
7. Schnitzler L. Lesions urticariennes chroniques permanentes (erythème pétaloïde?) Cas cliniques, no. 46 B. Journee Dermatologique d’Angers, 28 octobre 1972.
2. Schnitzler L. Lesions urticariennes chroniques permanentes (erythème pétaloïde?) Cas cliniques, no. 46 B. Journee Dermatologique d’Angers, 28 octobre 1972.
1. Schnitzler L. Lesions urticariennes chroniques permanentes (erythème pétaloïde?) Cas cliniques, no. 46 B. Journee Dermatologique d’Angers, 28 octobre 1972.