Chronic Urticaria and Monoclonal IgM Gammopathy (Schnitzler Syndrome)

Report of 11 Cases Treated With Pefloxacin

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Background: Schnitzler syndrome is characterized by chronic urticarial rash and monoclonal IgM gammopathy and is sometimes associated with periodic fever, arthralgias, and bone pain. Current treatment is unsatisfactory.

Observations: Eleven patients with Schnitzler syndrome were treated with oral pefloxacin mesylate (800 mg/d). In 10 patients, we observed a dramatic and sustained improvement of urticarial and systemic manifestations. Corticosteroid therapy could be stopped or reduced in 6 patients. In 9 patients, pefloxacin was administered for more than 6 months (≤10 years), with a good safety profile.

Conclusions: Pefloxacin therapy can be considered for patients with Schnitzler syndrome because it usually improves chronic urticaria and the systemic symptoms of the disease.

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The features of Schnitzler syndrome include chronic nonpruriginous urticaria and monoclonal IgM gammopathy. Intermittent fever, asthenia, arthralgia, and bone pain with imaging evidence of osteosclerosis also occur frequently. Biological findings usually include an increase in white blood cell count and erythrocyte sedimentation rate, which reflect an inflammatory syndrome and the presence of the monoclonal IgM.

Skin biopsy findings often include mononuclear or neutrophilic perivascular infiltrates. The link between urticaria, systemic symptoms, hyperostosis, and the monoclonal B-cell proliferation is unknown. Current treatment is unsatisfactory. The use of systemic corticosteroids may be effective but is hampered by corticoidpendence, with well-known attendant adverse effects. Chemotherapy may induce myelodysplasia. Many other therapies have been proposed in the context of isolated case reports.

We observed a dramatic and sustained improvement of manifestations of Schnitzler syndrome in a patient who was treated with pefloxacin mesylate for a urinary tract infection. This prompted our study of the efficacy of the antibiotic in 10 other consecutive patients.

Methods

After the first patient, the drug was proposed to all patients who were referred to us and fulfilled the following criteria: (1) recurrent urticarial rash persisting more than 2 months; (2) presence of a serum monoclonal IgM; (3) a serum complement level within the reference range and no detectable cryoglobulinemia; (4) no associated systemic disease; and (5) no contraindication to treatment with quinolone agents. All patients gave informed consent.

Between January 1, 1995, and December 31, 2005, 11 patients (including the index case) were enrolled in the study. Before initiation of treatment and while receiving pefloxacin, patients were asked to note daily any symptom, particularly skin changes, and their temperature. They also had to note changes in dosages of any drug being used. Pefloxacin mesylate was administered orally at an initial dosage of 800 mg/d.

Results

The main characteristics of the 11 patients are summarized in Table 1. Age at diagnosis of Schnitzler syndrome ranged from 44 to 80 years (mean age, 57.5 years). All patients presented with chronic urticaria, with a disease duration of 4 months to 16 years (mean duration, 4.6 years).
Current urticarial wheals usually consisted of sharply demarcated, raised maculopapular erythematous lesions that predominated on the lower limbs and abdomen and were asymptomatic. The wheals lasted from several hours to 1 week and were separated by periods of remission of various durations. Skin biopsy specimens showed few perivascular mononuclear or polymorphonuclear cells with or without mild edema (in 8 patients) and a clear perivascular infiltrate with leukocytoclastic vasculitis but without necrosis (in 2 patients). Skin biopsy results were normal in 1 patient.

In 9 patients, some urticarial wheals were accompanied by spiking fever (≤40°C). In these cases, arthralgias, myalgias (n=11), fatigue (n=7), and weight loss (n=5) were typical. Such symptoms, particularly an unusual fatigue, were also reported by 1 of the nonfebrile patients. Nine patients reported bone pain, usually in the lower back, pelvis, and lower limbs, with radiographic evidence of bone densification and hyperfixation apparent on technetium Tc 99m scan findings in 2 of 7 and 8 of 9 patients, respectively. Increase in the erythrocyte sedimentation rate, hyperfibrinemia, decreased albuminemia, polymorphonuclear hyperleukocytosis, hypochromic anemia, and thrombocytosis were frequent (Table 1). Results of searches for an infectious process or a connective tissue disorder were consistently negative. In all cases, test results for cryoglobulin and antimuclear antibodies were negative, and the serum level of the C3 complement component was within the reference range. Serum C4 level was within the reference range in all but 1 patient, in whom a heterozygous deficiency was documented. In all studied cases, results of searches for antibodies against hepatitis B or C viruses were negative.

A monoclonal serum IgM was detected in all patients. At diagnosis, the IgM level was low (≤0.5 g/dL), intermediate (>0.5 to <2 g/dL), and high (≥2 g/dL) in 4, 6, and 1 patient, respectively. During follow-up, the serum IgM level was higher than 2 g/dL in the 3 patients who developed an overt Waldenström macroglobulinemia (WM). The monoclonal IgM bore k light chains in 10 patients and λ light chains in 1. Results of bone marrow aspirate and/or biopsy, available in 10 of the 11 patients, were normal in 7 and disclosed a lymphoplasmacytic infiltrate typical of WM in 3. At the first examination, small superficial lymph nodes were noted in the 3 patients with WM, 2 of whom also had splenomegaly. Chest radiogram, ultrasound examination results, or computed tomography did not disclose enlarged mediastinal or abdominal lymph nodes in any patient.

**TREATMENT**

As reported in Table 2, before enrollment in the study, patients had received a wide class of medications, including nonsteroidal anti-inflammatory drugs, antihistamines, colchicine, dapsone, and hydroxychloroquine or chloroquine hydrochloride. Although questionable and transient improvement was sometimes observed, these drugs were globally ineffective, particularly for controlling the rash. The only patient who received thalidomide experienced a clear improvement, but the therapy was stopped because of peripheral neuropathy. Corticosteroids were active against urticaria and systemic symptoms in all 7 treated patients when a precise threshold dosage was used; this threshold dosage varied from one patient to the next. The required mean daily dose of prednisone equivalent was 11.5 mg/d (range, 5-30 mg/d). Despite this treatment, persisting flares usually occurred, requiring a transient increase of the corticosteroid dose. Chlorambucil or cyclophosphamide was given to 4 patients without a corticosteroid-sparing effect or any improvement, including in the 3 patients with overt MW. Two of these patients achieved a partial remission, as assessed by decreases of 60% and 75% in the serum IgM level, whereas the last patient had a resistant disease. In one patient, repeated plasma exchanges were ineffective. In another, psoralen–UV-A therapy was ineffective as well.

In all cases, oral pefloxacin mesylate therapy, 400 mg twice a day, was begun during an urticarial flare and was added to the patient's previous treatment. The antibiotic significantly reduced urticarial wheals, with a concomitant sensation of improved condition, in all but patient 7. The improvement occurred within 24 hours of taking the first tablet for 6 patients and within 48 to 72 hours for the others. Fever, when present, disappeared or decreased before the subsequent progressive clearing of the urticarial lesions.

In all but patient 7, pefloxacin mesylate was used as a maintenance treatment, initially at a dose of 800 mg/d. In all cases, it significantly reduced the frequency and intensity of the disease manifestations. This was exempli-
The increased white blood cell counts, erythrocyte sedimentation rates, and serum levels of C-reactive protein and fibrin that were features of the urticarial flares usually decreased during spontaneous or drug-induced remission. For most patients, the periods when C-reactive protein values were within the reference range were longer during pefloxacin therapy than during periods without this treatment, suggesting the efficacy of the drug on the flare frequency.

A 88-year-old woman attributed insomnia to the drug and interrupted the treatment after a few days, although her skin lesions had improved. In the 10 other patients, the pefloxacin dose was maintained during a median time of 32 months (range 2-128 months). Within this follow-up, the treatment had to be stopped in 2 patients after 2 and 6 months because of sexual impotence (that reversed after treatment interruption) and tendon pain. An additional patient who had persistent moderate urticarial lesions and intermittent bone pain during an 8-month period of pefloxacin and nonsteroidal anti-inflammatory drug therapy decided to use the drug only in case of frank flare. In the remaining patients, the benefit on tolerance ratio of the treatment was persistently considered as positive. Achilles tendon pain occurred in 2 patients, and photosensitization with some face hyperpigmentation occurred in 3, without being troublesome enough to interrupt treatment. With the exception of 1 patient who experienced a nonfebrile urinary tract in-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Previous Therapy</th>
<th>Clinical Response to Pefloxacina</th>
<th>Response Delay, h</th>
<th>Relapse Preventionb</th>
<th>Response Duration</th>
<th>Decrease in Corticosteroid Dose</th>
<th>Pefloxacin Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prednisone, 20 mg; antihistamine, colchicine</td>
<td>+</td>
<td>72</td>
<td>+</td>
<td>32 mo (Follow-up)</td>
<td>Interrupted</td>
<td>Face hyperpigmentation</td>
</tr>
<tr>
<td>2</td>
<td>Thalidomide; betamethasone; cyclophosphamide; antihistamine; dapsone; colchicine; plasmapheresis</td>
<td>+ (Less for bone pain)</td>
<td>24</td>
<td>++</td>
<td>10 y (Death)</td>
<td>Interrupted</td>
<td>Partial rupture of Achilles tendon</td>
</tr>
<tr>
<td>3</td>
<td>Antihistamine; NSAID; bisphosphonates</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>6 mo (Poor tolerance)</td>
<td>Not administered</td>
<td>Achilles tendon pain</td>
</tr>
<tr>
<td>4</td>
<td>Prednisone, 15 mg; antihistamine; psoralen–UV-A</td>
<td>+</td>
<td>&lt;6</td>
<td>++</td>
<td>2 mo (Poor tolerance)</td>
<td>50% Decrease</td>
<td>Sexual impotence</td>
</tr>
<tr>
<td>5</td>
<td>NSAID</td>
<td>+ (Less for bone pain)</td>
<td>&gt;48</td>
<td>+</td>
<td>15 mo (Episodic)</td>
<td>Not administered</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NSAID; antihistamine</td>
<td>+ (Less for urticaria)</td>
<td>24</td>
<td>+/-</td>
<td>42 mo (Stop owing to inefficacy)</td>
<td>Not administered</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Prednisone, 10 mg; antihistamine</td>
<td>+</td>
<td>24</td>
<td>+</td>
<td>&lt;5 d (Poor tolerance)</td>
<td>0</td>
<td>Insomnia, vertigo, diarrhea</td>
</tr>
<tr>
<td>8</td>
<td>Prednisone, 30 mg; chlorambucil</td>
<td>+</td>
<td>&lt;24</td>
<td>+</td>
<td>88 mo (Follow-up)</td>
<td>Interrupted</td>
<td>Face hyperpigmentation</td>
</tr>
<tr>
<td>9</td>
<td>Chlorambucil; colchicine; dapsone and ferrous oxalate (Disuloned); prednisone, 20 mg</td>
<td>+</td>
<td>24</td>
<td>++ (2 y), then +/-</td>
<td>51 mo (Death)</td>
<td>Interrupted</td>
<td>Face hyperpigmentation</td>
</tr>
<tr>
<td>10</td>
<td>Prednisone, 25 mg; colchicine; dapsone, 50 mg; cyclophosphamide</td>
<td>+ (Less for urticaria)</td>
<td>72</td>
<td>++ (4 y), then +/-</td>
<td>10 y (Death)</td>
<td>80% Decrease</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Antihistamine</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>24 mo (Follow-up)</td>
<td>Not administered</td>
<td>Achilles tendon pain</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; NSAID, nonsteroidal anti-inflammatory drugs.

a Indicates efficacy for cutaneous eruption, bone pain, and fever (when present).
b Relapse prevention was assessed by evaluating flare frequency as follow: + (++) if reduced by at least 50% (75%) during at least 3 months; +/- if reduced without achieving previous criteria. All patients experienced relapse when therapy was stopped.

c Added during follow-up, shortly after initiation of pefloxacin therapy, because of evidence of overt Waldenström macroglobulinemia.
d Manufactured by Sanofi-Aventis, Paris, France.
Schnitzler syndrome is a rare clinical entity first described in 1972.1 So far, about 50 cases have been reported in the literature. The mean delay to diagnosis is more than 5 years, suggesting that the syndrome may be underdiagnosed.1 The diagnosis should be evoked in the case of any chronic urticaria, particularly when that urticaria is atypical because of persistent and nonpruritic lesions or because of associated arthralgia, bone pain, or systemic symptoms, including recurrent fever. Laboratory findings of an elevated erythrocyte sedimentation rate and leukocytosis or thrombocytosis, sometimes associated with inflammatory anemia, should also suggest this diagnosis. Histopathologic findings usually show a mild perivascular monoclonal or neutrophilic infiltrate.2 In all cases, the diagnosis must be corroborated by the presence of a serum monoclonal IgM, which is, in addition to the urticarial lesions, the key feature of the syndrome,1 although cases of a variant-type Schnitzler syndrome characterized by a monoclonal IgG have been reported.3 Serum protein electrophoresis should be recommended for all patients presenting with chronic urticaria.

We herein report a series of 11 patients who presented with most of the characteristic features of Schnitzler syndrome (Table 1). In particular, all had chronic urticarial lesions and a serum monoclonal IgM. Most of the patients received various therapies (Table 2) that had no clear efficacy. Whereas nonsteroidal anti-inflammatory drugs usually alleviated articular and bone pain,1 corticosteroids represented the only treatment that continued to influence the course of the urticarial, systemic, and osteoarticular symptoms.5 Corticosteroid therapy improved urticarial manifestations only when used at a precise threshold dosage, which varied from one patient to another but was most often about 10 mg/d (range, 5-30 mg). Even when an appropriate dose was taken, some patients still presented with flares requiring transient increases of the corticosteroid dose, and dose-related adverse effects consecutive to long-term treatment were frequent.

In our series, as in the literature, therapeutic attempts to reduce the serum IgM level by means of plasma exchanges (patient 1)1 or chemotherapy3 were most often ineffective. This remained true in the 3 patients with WM who achieved a significant but partial remission while receiving chlorambucil (patients 8 and 9) or no remission while receiving cyclophosphamide (patient 10). One of the patients who received alkylating agents died of myelodysplasia, emphasizing that chemotherapeutic drugs should be used only in patients with symptomatic WM.

Thalidomide, which was used in patient 2 and in 3 patients in the literature,3,7 also carries long-term toxic risks, in particular because of its neurotoxic effects. Other innovative therapeutic approaches, such as interferon alpha, interleukin 1 (IL-1) receptor antagonist (anakinra), and cyclosporine, were recently reported to be effective on the basis of isolated case reports3,8,9 and warrant further evaluation.

As illustrated by our data, pefloxacin rapidly improves urticarial and systemic symptoms of the Schnitzler syndrome. It reduces the frequency and intensity of disease flares, resulting in a significant corticosteroid-sparing effect. When used as a preventive treatment, pefloxacin remains active and has a relatively good safety profile, despite associated tendinopathy, the incidence of which is low.10 However, its efficacy is only symptomatic and often incomplete. In addition, pefloxacin usually reduces the cutaneous and systemic symptoms of the syndrome while being less active on its osteoarticular component. Pefloxacin appears to reduce the duration of the biological inflammatory syndrome that features disease flares. We did not observe AA amyloidosis in any patient in the present series and found no reports of it in the literature.

The role of IgM gammopathy in the pathogenesis of urticaria and the other manifestations of the Schnitzler syndrome is poorly understood. It likely does not depend on whether the underlying lymphoid disorder is an overt WM or a monoclonal gammopathy of undetermined significance.1 In our patients, as in the literature, immunofluorescence studies did not document a pathogenic role for monoclonal IgM because the studies showed cutaneous IgM deposits in only some cases with, in addition, different localizations from one case to another.1 Similarly, antiskin autoantibody activity of the IgM could be documented by Western blotting in only few patients.11 Conflicting data were also reported on potential anti–IL-1α autoantibody activity of the monoclonal immunoglobulin.12,13 An alternative hypothesis would not implicate the monoclonal IgM by itself but rather the production of 1 or several cytokines or chemokines by clonal B-cell proliferation or by its cellular environment.13 This hypothesis might be more in accordance with the effect of pefloxacin we noted, which occurred without modifying the level of the monoclonal IgM in any case. As with all fluorinated 4-quinolones, pefloxacin, a nalidixic acid analogue, exerts its bactericidal effect by inhibiting DNA gyrase (a type II topoisomerase), most probably by binding to DNA.14 In addition to their antibacterial properties, fluoroquinolones have been shown to modify immune and inflammatory responses implicating T cells and macrophages, by mechanisms that may involve regulation of messenger RNA for cytokines such as IL-1, IL-2 and its receptors, interferon-γ, granulocyte-macrophage colony-stimulating factor, and IL-3.15 Modulation of the production of other cytokines, including IL-8 and IL-6, were also observed in experimental models.15 Although other antibiotic classes such as macrolides may have immunomodulatory effects,16 only quinolone appears to be effective in the treatment of Schnitzler syndrome. Within the quinolone class, pefloxacin appears to be the most efficient (B.A. and J.-P.F., unpublished data, March 2006). It is ineffective in classical chronic urticaria (data not
shown), whereas we did not have the opportunity to assess its efficacy in urticarial vasculitis without monoclonal IgM gammopathy.

In conclusion, pefloxacin must be added to the small list of drugs that are active in the treatment of Schnitzler syndrome. Because of its efficacy and good safety profile, we propose that this drug be the first-line treatment for Schnitzler syndrome. If too-frequent flare-ups persist despite treatment and if the patient feels uncomfortable, we recommend adding low-dose corticosteroid therapy, eventually continuing pefloxacin therapy for the benefit of its corticosteroid-sparing effect.

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Author Contributions: Dr Fermand had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Fermand. Acquisition of data: Asli, Bienvenu, Cordoliani, Brouet, Uzunhan, Arnulf, Malphettes, Rybojad, and Fermand. Analysis and interpretation of data: Asli, Bienvenu, and Fermand. Drafting of the manuscript: Asli, Bienvenu, and Fermand. Critical revision of the manuscript for important intellectual content: Asli, Bienvenu, Cordoliani, Brouet, Arnulf, Malphettes, and Rybojad.

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