
Letters

SCHNITZLER SYNDROME SUCCESSFULLY TREATED WITH METHOTREXATE

Schnitzler syndrome is a rare disorder characterized by a chronic urticarial rash and a monoclonal gammopathy (usually IgM type) accompanied by 2 of the following features: intermittent unexplained fever, arthritis or arthralgia, bone pain, lymphadenopathy, hepatomegaly or splenomegaly, and elevated inflammatory markers.^{1,2} This disease was first described in 1972 by L. Schnitzler, a French dermatologist, and since that time, only 60 cases have been reported in the literature.² The etiology and exact pathogenesis of this disease remain unknown, but cytokines such as interleukin 1 (IL-1) may play an important role.³ Treatment of this disorder has been challenging and has included the use of nonsteroidal anti-inflammatory agents, high-dose glucocorticoids, thalidomide, interferon alfa, colchicine, IL-1 receptor antagonists, and anti-tumor necrosis factor agents, all prescribed with varying success.¹⁻⁴ A definitive treatment remains to be found. We present a case of Schnitzler syndrome successfully treated with weekly methotrexate and low-dose prednisone.

The patient is a 73-year-old white woman with an urticarial rash, an IgM-type monoclonal gammopathy, and inflammatory arthritis with elevated inflammatory markers. She had a 10-year history of rash, which began at the waist and bra line; however, the rash had worsened in the year before presentation. At the time of presentation, the urticarial rash was diffuse, including her palms and soles, but was nonpruritic. Findings from skin biopsy were consistent with urticaria. She also complained of joint pain and swelling, with prolonged morning stiffness. She noted that when her rash was particularly severe, she had more generalized joint pain. She had tried taking ibuprofen and acetaminophen, without relief; however, high-dose glucocorticoids relieved the rash and the arthritis. The remainder of the review of systems was unrevealing.

Physical examination findings were notable only for the joint and skin examinations. There was synovitis of the bilateral wrists, metacarpophalangeal joints, and proximal interphalangeal joints. Skin examination revealed a generalized urticarial rash with oval/circular erythematous wheals approximately 3/4 inches in diameter. Results of a test for dermatographism were negative, and there was no evidence of angioedema.

Laboratory data revealed an elevated erythrocyte sedimentation rate (105 mm/h), an increased C-reactive protein level (8.7 mg/L), and leukocytosis (white blood cell count, $13.5 \times 10^9/L$). Serum protein electrophoresis revealed a large increase in monoclonal IgM levels. Further evaluation revealed no evidence of autoimmune disease or malignancy. A diagnosis of Schnitzler syndrome was made based on the symptoms, physical examination findings, IgM gammopathy, and elevated inflammatory markers.

Previous therapies had included a variety of antihistamines, without relief. Oral glucocorticoids had improved the rash but were difficult to taper without rash recurrence, and their use was complicated by adverse effects, including weight gain, palpitations, symptoms of gastritis, and arthritis flares. To control the patient's symptoms quickly, prednisone, 20 mg/d, was administered. On tapering

the prednisone to 5 mg/d, the rash and joint pain returned. Celecoxib and hydroxyzine were administered, but she continued to have rash and arthritis, and she required assistance with her daily activities due to joint pain. Prednisone was increased to 8 mg/d, and the patient reported a 70% improvement in symptoms. Owing to the anticipation of long-term glucocorticoid treatment, the need for a glucocorticoid-sparing agent was considered. Methotrexate therapy was initiated at 10 mg orally weekly. The patient continued taking prednisone, 8 mg/d. After 4 weeks of therapy with methotrexate, the patient had less joint pain and minimal urticarial rash and tapered the prednisone by 1 mg every 2 weeks.

After 10 weeks of methotrexate therapy, the patient had successfully tapered the prednisone to 5 mg/d. She denied joint pain and could perform daily activities without assistance. Laboratory evaluation after 10 weeks revealed improvement (erythrocyte sedimentation rate, 44 mm/h; C-reactive protein level, 3.8 mg/L). The methotrexate dose was increased to 15 mg weekly because the patient was experiencing soreness before the next dose. Thus, this patient experienced a clinical and serologic response to low-dose glucocorticoids and methotrexate. Methotrexate blocks DNA synthesis, suppresses lymphocyte proliferation, inhibits neutrophil activity and adherence, and decreases IL-1, IL-6, IL-8, and tumor necrosis factor α production.⁴

In summary, we describe a patient with Schnitzler syndrome whose urticarial rash and inflammatory arthritis responded to treatment with methotrexate and low-dose glucocorticoids. Previous reports have shown that high-dose glucocorticoids improve urticarial rash and arthralgia; however, this treatment cannot be maintained for prolonged periods owing to toxic effects. Methotrexate may be an effective treatment for the skin- and joint-related manifestations of Schnitzler syndrome. Further studies to evaluate this are needed.

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SUCCESSFUL USE OF C1 INHIBITOR DURING MITRAL VALVE REPLACEMENT SURGERY WITH CARDIOPULMONARY BYPASS

Hereditary angioedema (HAE) is a syndrome of deep tissue edema due to an absolute deficiency (type 1) or a functional defect (type 2) of C1 esterase inhibitor (C1 INH). HAE also occurs in patients who have normal complement levels but in whom angioedema may be caused by enhanced factor XII enzymatic plasma activity (type 3).¹ Often these attacks are triggered in times of physiologic stress, tissue trauma, infections, and pregnancy.¹

Current therapy for an acute attack of HAE includes fresh frozen plasma (FFP), which provides replacement of variable amounts of C1 INH. Prophylactic treatment includes anabolic steroids, which increase hepatic production of C1 INH through unknown mechanisms because therapeutic response does not typically correlate with increases in C1 INH levels.¹ Previous case reports have shown the benefit of FFP before oral surgery and cardiac bypass surgery.^{2–4} However, no controlled studies have demonstrated the efficacy of FFP as a prophylactic treatment for HAE. A C1 INH replacement agent is available in Europe, Australia, and Canada, and previous cases using this therapy preoperatively for cardiopulmonary bypass have been reported.^{2–4}

Several C1 INH deficiency therapies are now being developed in the United States for the treatment of this disorder, including plasma-derived C1 INH replacement therapies, recombinant human C1 INH derived from rabbit breast milk, a kallikrein inhibitor, and bradykinin receptor antagonist. Herein, we report the use of C1 INH replacement therapy preoperatively for a patient undergoing mitral valve reconstruction with cardiopulmonary bypass and as an acute rescue therapy for postoperative breakthrough symptoms.

A 51-year-old man with type 2 HAE functional C1 INH abnormality and severe mitral valve regurgitation that required mitral valve reconstruction with cardiopulmonary bypass presented for presurgical management. The patient reported the onset of HAE symptoms at approximately 11 to 12 years of age. Attacks consisted of painful swelling of his abdomen, face, hands, feet, knees, and occasionally genitalia. He also reported 2 previous episodes of uncomplicated laryngeal edema. A consistent trigger for his edema episodes was trauma secondary to previous oral surgical procedures. Maintenance therapy consisted of danazol, 200 mg twice daily; however, he still would have significant breakthrough swelling episodes, including laryngeal edema, while taking this medication in response to physical triggers.

Preoperative laboratory studies revealed a low C4 level (4 mg/dL; reference range, 10–40 mg/dL), a normal C2 level (2.2 mg/dL; reference range, 1.6–3.5 mg/dL), an increased C1 INH quantitative level (50 mg/dL; reference range, 21–39 mg/dL), and a low functional C1 INH level (20%; reference range, >68%), consistent with type 2 HAE. Because of the patient's underlying mitral valve disease, he could not be randomized in a double-blind, placebo-con-

trolled trial. However, compassionate approval was granted by Lev Pharmaceuticals to provide prophylactic open-label C1 INH replacement therapy. An open-label treatment protocol and informed consent were approved by the University of Cincinnati institutional review board, and an informed consent form was signed by the patient before treatment.¹

Cardiac evaluation included a transesophageal echocardiogram that revealed holosystolic mitral valve prolapse that involved the posterior leaflet, resulting in moderate to severe mitral regurgitation. The patient was admitted to the hospital the morning of surgery for complex mitral valve reconstruction and annuloplasty. One hour preoperatively, the patient was administered 1,000 U of C1 INH infused intravenously for more than 15 minutes. Mitral valve reconstruction with annuloplasty and cardiopulmonary bypass was successfully performed without complications. No significant blood loss was recorded during surgery. The total time the patient was attached to the cardiopulmonary bypass pump was 2 hours 22 minutes. The total surgical time was 4 hours 35 minutes. After transfer to the cardiac intensive care unit postoperatively, the patient was extubated on postoperative day 1 and had chest tubes removed on postoperative day 2. On postoperative day 2, he felt the onset of swelling of his lower back and lips, which were rated by the investigator to be mild. However, another treatment of 1,000 U of C1 INH was administered as a precaution, and these symptoms resolved within 2 hours. He was transferred to the surgical unit on postoperative day 3 and discharged home on postoperative day 4 in stable condition.

This case represents the first report of a patient with HAE successfully treated prophylactically with C1 INH replacement therapy in the United States for cardiac valve reconstruction with a cardiopulmonary bypass pump. This study supports the use of C1 INH as a prophylactic treatment for patients with HAE undergoing open-heart surgical procedures that require cardiopulmonary bypass because both are associated with excessive complement activation. It also demonstrates the effectiveness of C1 INH replacement as a rescue therapy for further abrogating breakthrough symptoms postoperatively.

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