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Successful use of anakinra to treat refractory Schnitzler's syndrome

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ABSTRACT

Schnitzler's syndrome is a rather rare disease which may appear in a rheumatologist's office because patients often report rheumatic symptoms with joint, bone and muscle pain. However, it is characterized by chronic urticaria, recurrent fever, liver and spleen enlargement, osteosclerosis, and lymphadenopathy, in conjunction with a serum IgM M component. A patient who had been treated with relatively high doses of corticosteroids for 10 years with insufficient response was treated with the IL-1 receptor antagonist anakinra, this led to a complete resolution of symptoms.

Introduction

Schnitzler's syndrome, first described by the French rheumatologist in 1974, is characterized by chronic urticaria, recurrent fever, enlarged liver and/or spleen, bone pain, and lymphadenopathy, usually in conjunction with a serum IgM M component – in a concentration mostly below 10,000 mg/L (1, 2), but some cases without gammopathy have been described (3, 4). An elevated erythrocyte sedimentation rate and leukocytosis are often present. The rheumatic symptoms, joint and bone pain are frequently associated with radiologic evidence of osteosclerosis (5, 6). Schnitzler's syndrome is a diagnostic challenge also for rheumatologists but it is rare and the mean delay to diagnosis has been estimated at more than 5 years (2).

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 lymphoplasmacytic malignancy which occurs in at least 15% of patients (7). This hematologic transformation can occur more than 20 years after the first signs of the disease, and 9 patients were reported to have developed lymphoplasmacytic neoplasias, particularly Waldenstrom's macroglobulinemia. Therefore, there is need for periodic long-term clinical assessments.

In this report, we describe a case of a 42-year-old female who had skin lesions diagnosed as remitting urticaria for over 10 years, arthalgia and intermitting fever and fatigue for about 5 years. Corticosteroid therapy had to be given in a dosage not less than 20mg/day with only limited efficacy over years. Treatment with the IL-1 receptor antagonist anakinra led to complete relief of all symptoms.

Case report

A 42-year-old female had skin lesions diagnosed as remitting urticaria for over 10 years. About 5 years ago, she also experienced intermitting fever, polyarthralgia and fatigue. The patient came to our hospital for the first time in September 2006.

She had been treated with 20 mg of prednisolone with some efficacy but incomplete resolution of symptoms. The addition of oral methotrexate 15 mg/week helped to decrease the frequency of the fever episodes to some degree. However, it had been impossible to reduce the glucocorticoid dosage below 20mg because of severe flares of urticaria and arthralgia.

In the physical examination, we saw a 42-year-old woman in a good state of health with a body weight of 58.7 kg and a height 171 cm. Rectal temperature and blood pressure were normal. All over the body, small, not elevated, not scaling erythemata prevalently on the upper extremities were seen (Fig. 1).

The examination of the heart, the lungs, the abdomen and the kidneys was normal. There was no lymphadenopathy, no synovitis, no swollen or tender joints.

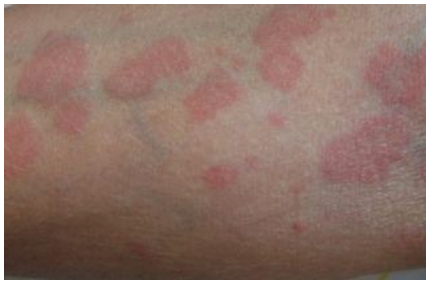

Fig.1. Urticaria lesions on the right forearm before therapy with anakinra.

The laboratory tests revealed normocytic anemia with an hemoglobine of 10.9 g/dl (normal <12g/dl), leucocytosis (23,400/µl) and thrombocytosis (514,000/µl), and an elevated erythrocyte sedimentation rate (ESR): 57mm/1. hour and an elevated C-reactive protein 7.6mg/dl (normal <1mg/dl). All other parameters were within the normal range including rheumatoid factor, antinuclear antibodies, total protein, electrophoresis, immune electrophoresis, immunoglobuline levels, and ferritine. Her medical history contained one report of a low serum level of κ-light chains in 2003.

The chest x-ray and the sonography of the abdomen were normal. A bone scan showed periarticular enhancement at the metacarpal and the proximal interphalangeal joints, the knees and the shoulders, indicative of polyarthritis. A pelvic radiograph showed localized sclerosis near the left sacroiliac joint (Fig. 2).

As part of our diagnostic work up, we observed the patient after reduction of the corticosteroid dose from 10 to 5 mg per day. The next day, the patient developed fever >38°C. No microbes were grown in blood cultures. A skin biopsy was performed, the histologic result was consistent with urticaria but showed no signs of vasculitis.

Schnitzler's syndrome was considered as the most probable diagnosis because of urticaria, fever, arthralgia, leukocytosis, elevated ESR and the characteristic sclerotic bone lesion.

On the basis of positive reports about successful therapies of periodic fever syndromes (8) and because of the insufficient response to relatively high doses of corticosteroids we started treatment with the IL-1 receptor antagonist anakinra in a dosage of 100 s.c. daily. After 12 hours the urticaria and the fever had completely resolved. After one week of therapy the patient felt good, the ESR was reduced to 37 mm n.W./1h, the CRP had dropped to 1.6 mg/dl and the leucocyte count normalized.

When, after 2 weeks of successful therapy without fever or skin lesions, anakinra was discontinued, all symptoms recurred within a few hours. Thereafter, we started to stretch the intervals of injection from an application every day to every 2nd day. After 36 hours the urticaria remitted (Fig. 3), the leucocyte count rose to 17.3/nl and the CRP level increased to 5.9 mg/dl.

After this experience we went back to the regimen with daily dosage of anakinra. After 6 months of therapy, the patient has now been in ongoing remission. For the first time in 10 years, the patient has not taken any more corticosteroids.

Discussion

This case is interesting because of (i) the rarely reported differential diagnosis, also for rheumatologists, and because of (ii) the impressive efficacy of treatment with the IL-1 receptor antagonist anakinra. Schnitzler's syndrome is usually listed among the periodic fever syndromes but a clear genetic trait has not been established as yet. A systematic literature search revealed that no more than 56 cases of Schnitzler's syndrome had been reported until 2001 (7). Patients with Schnitzler's syndrome are often initially considered to have lymphoma or adult-onset Still disease, which are the main differential diagnoses. However, hypocomplementic urticarial vasculitis, systemic lupus, cryoglobulinemia, acquired C1 inhibitor deficiency, hyper IgD syndrome, chronic infantile neurologic cutaneous and articular syndrome (CINCA), and Muckle-Wells syndrome (8) also need to be considered, because the diagnosis relies on a combination of clinical and biologic signs and there is no specific marker for the disease (1, 2). Besides fever, the condition is characterized by chronic urticaria and joint, bone and muscle pain. In addition spleen organ enlargement, lymphadenopathy and a serum IgM M component often occurs (1, 2). Of special interest for rheumatologists are not only the rheumatic symptoms but also the often described osteosclerosis (5, 6) which was rather impressive in the case described here. The appearance of this bone lesion is unlike what we usually see in ankylosing spondylitis but has some similarity to osteitis condensans ilii (9) which, however, has sharper borders.

Schnitzler's syndrome usually comprises a monoclonal gammopathy in addition to urticaria and other signs of inflammation but several cases without gammopathy have been described (3, 4). Our patient had a medical record of a low serum level of κ-light chains. On this basis, no definite diagnosis had been made for the last 10 years – in part because the proposed diagnostic criteria were not fulfilled (10). However, especially because of the combination of the localized sclerosis and the skin manifestations but also the disabling joint pain, Schnitzler's syndrome is the most likely diagnosis in our patient. In

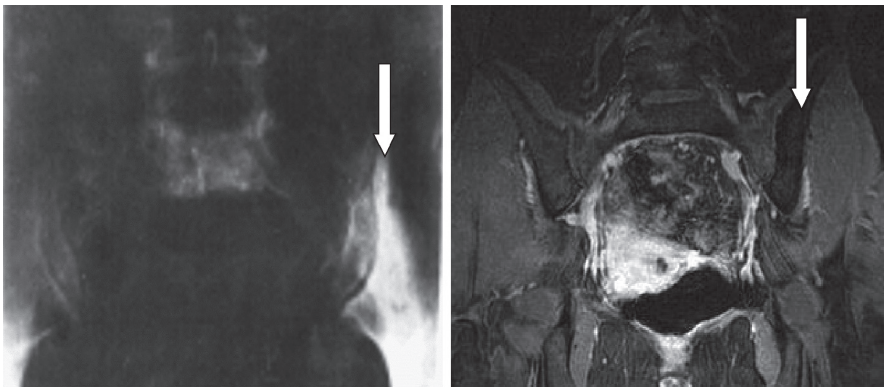

Fig. 2. Pelvic radiograph a.p. showing an area of localized osteosclerosis in the left iliac bone and the corresponding MRI T1 with gadolinium (arrows)

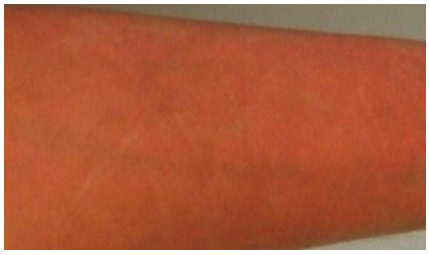

Fig. 3. Erythema of the right forearm 36 h after the last injection of anakinra 100 mg s.c.

addition, the elevated ESR, the leukocytosis and finally the history of κ-light chains serum levels, argue strongly in favour of this diagnosis – in the absence of another suggestive differential diagnosis.

The histopathologic findings in Schnitzler's syndrome are not uniform although most cases have demonstrated neutrophilic urticaria (11). Neutrophils in Schnitzler's syndrome are not usually related to immune complex vasculitis. The histopathologic changes in the urticarial lesions of 25 original biopsies from 15 cases of Schnitzler's syndrome were that 13 specimens showed neutrophilic urticaria and 5 lymphocytic urticaria, while necrotizing leukocytoclastic vasculitis was only found in one patient who was C4 deficient. In 4 biopsies a spongiotic dermatitis and in 2 an eosinophilic spongiosis was seen, one patient later developed pemphigus vulgaris, epidermal changes were seen in 10 patients. Our case showed a more neutrophilic urticaria.

Complement activation and cryoprecipitation are usually not involved in Schnitzler's syndrome. Screening of normal sera with high-affinity binding IgG autoantibodies (Abs) against interleukin-1 alpha (IL-1 α) revealed a positive result in almost 20% of 98 normal subjects and this prevalence was not more frequent in several control groups of patients, except in 6 out of 9 patients with Schnitzler's syndrome (12). Although the pathologic significance of these autoantibodies remains to be determined there is some evidence for an important role of IL-1 in this disease that is categorized under the periodic fever syndromes.

Treatment of Schnitzler's syndrome has been generally symptomatic and largely not really satisfactory so far (1, 2). The skin rash is largely unresponsive to treatment, and nonsteroidal antiinflammatory drugs, antihistamines, dapsone, colchicine, and psoralens and ultraviolet A (PUVA) therapy give inconstant results. Fever, arthralgia, and bone pain often respond to nonsteroidal antiinflammatory drugs. In some patients, these symptoms and/or the presence of severe inflammatory anemia require steroids (13), dapsone, colchicine (2) and/or immunosuppressive treatment with cyclophosphamide (14) or cyclosporine (15), which usually ameliorate inflammatory symptoms but do not change the course of the skin rash. Thalidomide was reported to induce complete remission of patients with Schnitzler's syndrome but therapy often has to be stopped because of polyneuropathy (16).

Treatment of Schnitzler's syndrome with interferon alpha (2b) therapy (IFN-α) has been reported to relieve patients from urticaria and bone pain (17). When this therapy was stopped a relapse of the urticaria occured but the cutaneous lesions disappeared when IFN-α was reintroduced (17). This observation supports the idea of an IL-1-mediated pathogenesis of Schnitzler's syndrome since IFN-α is known to induce an increase of IL-1 receptor antagonist levels. This further backs the classification of this rare disease as an autoinflammatory disorder (10). Indeed, the IL-1 receptor antagonist anakinra in a dosage of 100 mg daily has very recently been successfully used in 3 patients with Schnitzler's syndrome: fever and skin lesions disappeared within 24 hours. After a follow up of >6 months all patients had remained in a symptom free state (16).

Since the treatment of our patient had been with systemic corticosteroids at a dose of about 20mg/day for the last years, we decided to treat the patient with anakinra. The improvement was substantial, and complete remission was induced. For the first time within several years, the patient did not need to take corticosteroids to function normally. The remission is currently ongoing but no reduction of the usual dosage of 100mg s.c. daily was possible. This treatment success is consistent with the hypothesis that IL-1 is of central importance in the pathogenesis of Schnitzler's syndrome – similar to other periodic fever syndromes (8).

Key message

In adult patients with refractory bone, joint and muscle pain, the rheumatologist should think of rare rheumatic conditions such as Schnitzler's syndrome and other periodic fever syndromes. Since therapy with DMARDS and corticosteroids is often not sufficient in these patients, new treatment options with biologicals such as anakinra are appreciated.

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