CASE REPORT

Schnitzler syndrome

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ABSTRACT

The Schnitzler's syndrome is a rare entity characterized by an urticarial rash and recurrent fever in a patient with monoclonal IgM component. Other signs include joint, bone and muscle pain, enlarged spleen, liver and lymph nodes, increased erythrocyte sedimentation rate, elevated leukocyte count and abnormalities on bone morphologic investigations. Treatment of Schnitzler's syndrome is challenging. Various modalities have been employed with often inconsistent or unsatisfactory results. Here we report a patient with this rare condition treated with oral dapsone, resulting in dramatic and sustained improvement response.

INTRODUCTION

The Schnitzler syndrome is a rare and acquired systemic disease which bears in common many features with a group of inherited diseases referred to as autoinflammatory syndromes. Diagnostic criteria for Schnitzler syndrome consist of urticarial skin rash, monoclonal IgM component, and at least 2 of the following: Fever, arthralgia or arthritis, bone pain, palpable lymph nodes, liver or spleen enlargement, elevated erythrocyte sedimentation rate, leukocytosis, abnormal findings on bone morphologic investigation. Conventional therapies including, anti-histamines for the skin rash, as well as anti-inflammatory drugs, steroids and immunosuppressive drugs. However, the IL-1 receptor antagonist anakinra was found to rapidly control all the symptoms of this syndrome. About 15% to 20% of patients with a Schnitzler's will develop a lymphoproliferative disorder.[1] Amyloidosis is a concern in untreated patients.[2,3] Here, we report a patient with this rare condition.

CASE REPORT

A 55-year-old man presented with attacks of mildly itchy skin lesions, fever and bone pain in lower limb since 9 months (one attack per month). The lesion subsided partially with oral antihistamines. Medical and family history was unremarkable.

Clinical examination revealed multiple, bilateral, asymmetrical, well defined, erythematous and edematous urticarial plaques distributed over the trunk and extremities (Fig.1). Mucous membrane, hair and nail were not affected. The patient had a low grade fever (37.8ºC) and complained of pain in lower limbs. Lymph nodes, liver and spleen were not palpable.

A biopsy was taken from plaque on the left forearm. Histopathological examination was consistent with urticarial vasculitis. Perivascular lympho-monocyte with numerous neutrophils, leukocytoclasia and fibriniod degeneration within the dermal blood vessels (Fig. 2).

Laboratory investigation revealed polymorphonuclear leukocytosis (white blood cell count: 17/µl),

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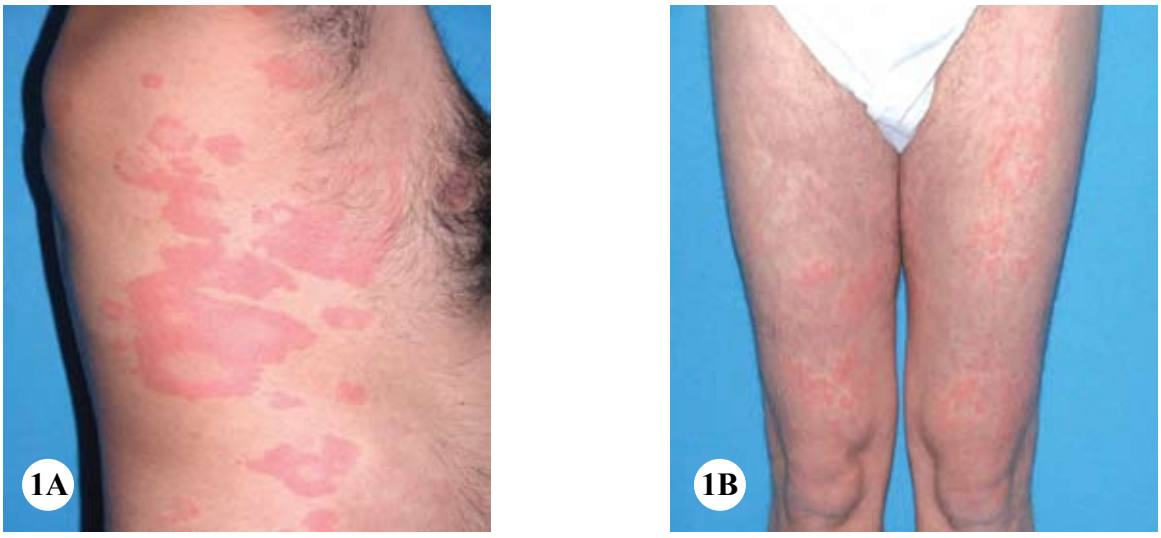

Fig. 1 Multiple, bilateral, asymmetrical, well defined, erythematous and edematous urticarial plaques distributed over the trunk (A) and extremities (B).

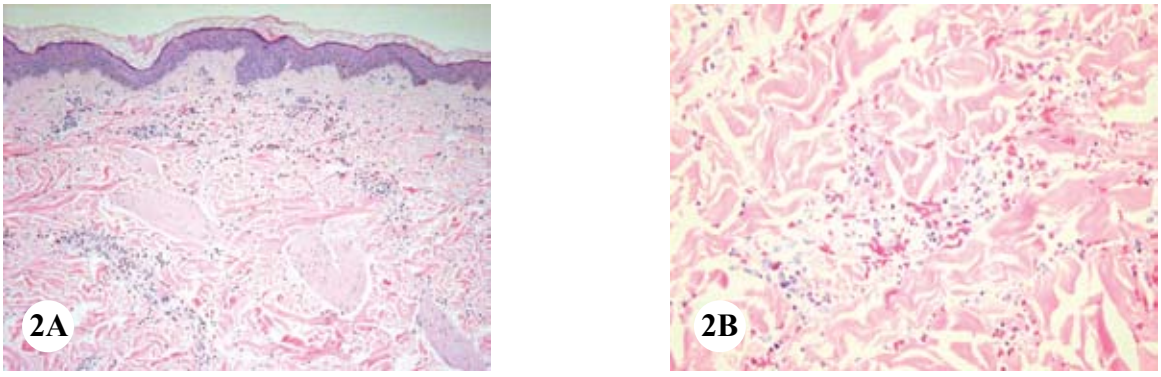

Fig. 2 Perivascular lympho- monocyte (A) with numerous neutrophils, leukocytoclasia and fibriniod degeneration within the dermal blood vessels (B).

increased erythrocyte sedimentation rate (92mm/l/h) and C-reactive protein was normal. On serum protein immunoelectrophoresis, an elevated serum IgM with IgM-kappa-monoclonal immunoglobulin was detected at a level of 1050mg/l. Serum complement studies showed no abnormalities. Serum ferritin was normal. Results of search for cryglobulin, antinuclear antibodies and antibodies against hepatitis B or C were negative. Liver and kidney profiles, as well as urine were normal. X-rays of lower limb bones showed no abnormal findings. Bone marrow biopsy was normal, also CT of mediastinum and abdomen showed no abnormal findings.

From history, clinical, histological and laboratory findings, the diagnosis of Schnitzler syndrome was made.

There was no contraindication for the treatment of the patient with dapsone, as the serum level of G-6PD was normal. Oral dapsone 100mg/day resulted in marked (within 7 days) control of both the urticarial rash and the systemic symptoms. The dose of dapsone was reduced from 100 mg to 50mg/day after 15 days and the patient continued on 50 mg for two months. No significant adverse reaction were reported. During follow up, serum IgM level remained unchanged but leukocytes count returned to the normal level. Currently, the patient is in good health, with no recurrence noted during the 4-months follow-up period.

DISCUSSION

The Schnitzler's syndrome was described in 1974 and it typically presents with chronic nonpruritic urticaria, bone pain, fever and monoclonal IgM gammopathy.[1,2] Diagnostic criteria for Schnitzler syndrome[1] are summarized in (Table 1). Shnitzler's syndrome is a differential diagnosis to consider in patient with chronic urticaria and fever of unknown origin[3] (Table 2).

Table 1 Diagnostic criteria of Schnitzler's syndrome

Major criteria • Urticarial skin rash • Monoclonal IgM component or IgG by variant type **Minor criteria** • Intermittent fever or subfebrile fever eposodes • Arthralgia or arthritis or bone pain • Palpable lymph nodes • Liver or spleen enlargement • Elevated erythrocyte sedimentation rate • Leukocytosis • Abnormal finding on bone morphologic investigation
Diagnosis of schnitzler's syndrome requires the presence of two major criteria and at least two minor criteria

The hallmark of Schnitzler syndrome is a chronic, recurrent urticarial rash, most often affecting the trunk and the extremities. Pruritus is an inconstant feature. Recurrent spiking fever is the second most common symptom. The fever and rash usually appear simultaneously. About 80% of patients complain of relapsing arthralgia, commonly of the large joints. Frank arthritis is uncommon. Bone pain has been reported in 72% of cases, typically in the tibia and ilium. Immunoelectrophoretic analysis documents an IgM kappa monoclonal gammopathy. Monoclonal IgG kappa type gammopathy represents a very rare variant of Schnitzler syndrome. In the vast majority of cases, light chains are of the κ-type. IgM levels can either remain stable or show a progressive increase.[1] A very high concentration of IgM may be an indication of Waldenström macroglobulinemia (WM).[4] Skin biopsy commonly shows features of urticarial vasculitis or neutrophilic urticaria. Findings often include a mononuclear or neutrophilic perivascular infiltrate.[5]

The etiology of Schnitzler syndrome remains unknown. Several hypotheses have been proposed, most of which suggest the involvement of autoantibodies. The role of IgM gammapathy in the pathogenesis of urticaria is also unclear. Monoclonal IgM and C3 deposits have been shown in

Table 2 Differential diagnosis of Schnitzler's syndrome

Disease	Distinguishing features
Adult-onset Still's disease	Absence of monoclonal IgM Elevated Serum ferritin level
Hypocomplementemic urticarial vasculitis	Cutaneous biopsy shows vasculitis Low complement level Lupus erythematosus is often associated
Acquired C1 esterase inhibitor deficiency especially in the setting of lymphoma and/or paraproteinemia	Usually angioedema Low C4 levels Low functional C1 inhibitor levels
Cryoglobulinemia	Temperature dependency of clinical signs Presence of cryoglobulins
Hyper IgD syndrome	Elevated IgD levels
Erythema marginatum	Preceding streptococcal infection Elevated antistreptococcal antibodies
Systemic lupus erythematosus	Clinical findings suggestive of lupus erythematosus Presence of antinuclear antibodies
C-INCA	Begins in childhood Neurological involvement Joint deformities
Muckle-Wells syndrome	Deafness and amyloidosis Absence of monoclonal component Family history
Lymphoma	Lymph node biopsy
Waldenström disease	Bone marrow biopsy

the skin of patients in the epidermis and along basement membrane in the region of the anchoring fibrils, or in dermal blood vessels. It has been suggested that the in situ IgM-mediated complement activation and subsequent tissue damage might play a part in the pathophysiology of the skin rash. However, these IgM skin deposits were only detected in approximately 25% of patients with Schnitzler syndrome and were also found in patients with WM without urticaria. Anti-skin IgM autoantibodies of the same isotype as their monoclonal gammopathies can be present in the serum of some patients with Schnitzler syndrome.[6-8]

Saurat et al[9] reported the detection of IgG autoantibodies directed against interleukin (IL)-1α in 6 of 9 patients with Schnitzler syndrome. An autoantibody-mediated prolongation of IL-1α activity and changes in its tissue distribution may account for some of the symptoms. However, other groups could not confirm these findings in their patients.[4,7] The recent success of treatment with the IL-1β inhibitor, Anakinra,[10] seems to indicate that IL-1β may be an important mediator in the pathophysiology of Schnitzler syndrome. IL-1β can cause both systemic inflammation and inflammation of the skin and is also a potent stimulator of bone resorption.[4] An alternative hypothesis could not implicate the monoclonal IgM by itself but rather the production of one or several cytokines or chemokines by clonal B-cell proliferation or by its cellular environment.[11] This hypothesis might be more in accordance with the observation that successful control of the syndrome usually occurs without modifying the level of the monoclonal IgM.[12]

Development into lymphoproliferative disorders occurs in 15% of patient including lympho plasmocytic lymphoma, IgM myeloma and marginal zone B-cell lymphoma. Therefore, patients deserve long-term follow-up with periodic assessment of bone marrow and lymph nodes.[13-15]

Several treatment approaches for Schnitzler syndrome including steroids, azathioprine, cyclophosphamide, cyclosporine, chlorambucil, mycophenolate mofetil, peflacin, hydroxychloroquine, dapsone, colchcine, plasmapheresis and PUVA therapy.[16-20]

Interferon-α (IFN-α2b) caused a major regression in urticarial lesions and bone pain during an 18-month follow-up.[21] Later, it proved ineffective in 5 of 11 patients, and was only partly effective in other 2 patients. Furthermore, in view of the potential side effects, it must be used with caution.[4] Thalidomide appeared to be very effective as it induced remission in 3 of 3 cases. Although it had to be stopped in 2 patients because of polyneuropathy.[10,22] However, 2 patients did not improve on thalidomide and other improved only temporarily. In addition, the potential serious side effects of thalidomide make it a less preferable option.[4]

Rituximab, a chimeric monoclonal antibody directed against the B-cell marker CD20, did not improve clinical symptoms after 8 weeks of treatment, although B-cell counts decreased to zero accompanied by a reduction of paraprotein.[23]

Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist. Until today, 8 cases of successful treatment of Schnitzler syndrome with anakinra (100 mg daily s.c.) have been reported in the literature. Improvement was observed in 24-48 hours and patients were still in remission 6-18 months after the initiation of treatment. The longest follow-up is now 3 years, with persistent remission. Painful erythematous lesions at the sites of injections during the first weeks of

treatment, were the only side effects.[10]

In conclusion, diagnosis of Schnitzler syndrome can be suspected in each patient presented with urticarial rash and constitutional symptoms such as fever and bone pain. Dapsone represents a useful and safe treatment for Schnitzler syndrome. Long term follow up is necessary to evaluate the recurrence of Schnitzler syndrome and progression to malignancy.

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