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Hyperimmunoglobulinemia E and efficacy of elimination diet in two patients with Schnitzler syndrome

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Summary
Background. *Schnitzler syndrome (SS) is a rare clinical entity characterized by chronic recurrent urticarial rash, monoclonal IgM gammopathy, intermittent fever and other symptoms. In this report, we present the cases of two patients with SS: a male and a female aged 50 and 49 years, respectively. Both patients had hyperimmunoglobulinemia E and showed good response to elimination diet.* ***Methods.*** *The patients had chronic urticaria, IgM gammopathy and an elevation of the serum levels of inflammation markers. Total IgE levels were found to be high (2000 U/ml and 540 U/ml, respectively). No underlying causes for hyperimmunoglobulinemia E (allergy, parasites, etc.) were revealed. The first patient did not respond to the treatment with antihistamines, while the second one responded only to high doses. The response to prednisolone in the second patient was incomplete.* ***Results.*** *Following a strict elimination diet resulted in marked improvement in skin lesions in both patients. In one of our patients we observed a decrease in IgE and IgM levels after a 3 week diet. The systemic symptoms persisted and improved only after adding pefloxacin, followed by a 3-day empirical course of intravenous prednisone in the first patient and a course of plasmapheresis in the second one.* ***Conclusion.*** *The high serum levels of total IgE may be associated with chronic urticaria activity, severe disease course and a poor response to treatment with antihistamines, and may be considered a possible marker of a subset of patients with SS showing a good response to the restriction diet. In general, we can assume that elimination diet can have an influence on the skin lesions and other symptoms of SS as well as on total IgE and IgM levels, but such association, the underlying mechanisms and the reasons for excessive IgE synthesis should be investigated in further studies.*

Introduction

Schnitzler syndrome is a rare clinical entity which associates urticarial rash, enlarged lymph nodes, bone pain, fever, arthralgia or arthritis, hepato- or splenomegaly, leukocytosis, elevated erythrocyte sedimentation rate (ESR), and a monoclonal IgM gammopathy (1).

Case 1

A Russian 50 year-old male was diagnosed with SS in February 2013. Since the end of 2007, he complained of itchy urticarial rash (**figure 1 a**, **b**), general malaise, abdominal pain, bone pain in extremities, sweating, and fever. He had enlarged lymph nodes. High serum levels of total IgE persisted from 2011 till 2013,

Figure 1 a, b *- Multiple urticarial lesions on trunk of the first patient with SS.*

Figure 1a

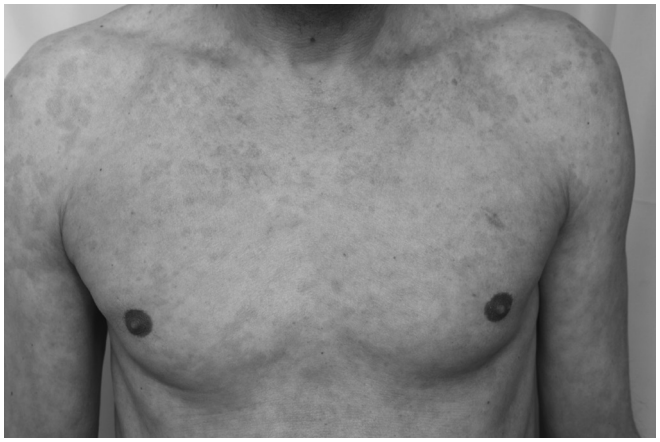
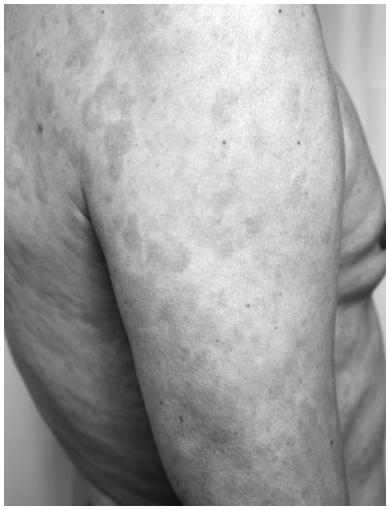
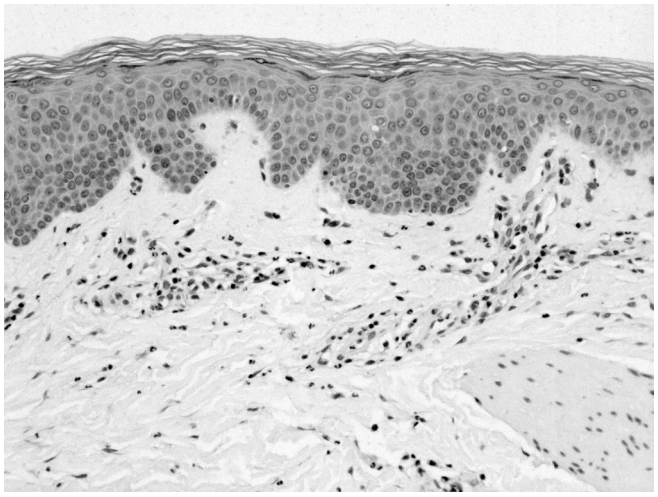


Figure 1 b



with an average level of 2000 U/ml. The level of specific IgE to different allergens was within normal limits, and the patient had no history of allergy. Laboratory analyses showed leukocytosis, accelerated ESR (25 mm/h), increased levels of CRP (25 mg/l), total IgM (5.1 g/l), total IgA (277 U/ml), rheumatoid factor (436 U/ml) and fibrinogen (7.85 g/l). IgM-κ paraprotein (5.7 g/l) was found. Tests for cryoglobulins and autoantibodies were negative. A skin biopsy was performed (**figure 2**). A bone marrow biopsy revealed no specific involvement of the bone marrow. The patient was initially treated with antihistamines and antibiotics, without any positive effect. His past medical history was remarkable for the significant improvement in skin symptoms when he was put on elimination diet. In June 2013, we administered him a 3-week course of elimination diet accompanied by pefloxacin (800 mg/d), followed by a 3-day empirical course of intravenous prednisone (500 mg/d), that resulted in a nearly complete resolution of cutaneous symptoms, a significant decrease in bone pain, and disappearance of fever. Interestingly, total IgE and IgM levels decreased at the end of the 3-week diet (from 2156 to 500 U/ml and 5.1 to 3.56 g/l, respectively).

Figure 2 *- Hyperkeratosis, irregular acanthosis. Loose lymphocytic perivascular infiltrate with admixture of plasma cells, macrophages, neutrophils in the upper dermis. Morphological signs of neutrophilic dermatosis (hematoxylin and eosin X100).*



Case 2

A Russian 49 year-old female was diagnosed with SS in November 2013. Since the end of 2000, she complained of itchy urticarial rash (**figure 3**), swelling of lips, eyelids, throat and pain in the small joints of hands and feet. The last exacerbation of the disease began in April 2013. The urticarial lesions occurred daily after exposure to pressure (from shoulder strap of bags, tight-fitting shoes, etc.) and the symptoms of angioedema worsened. Since 2002, the patient had high serum levels of total IgE (540 U/ml in 2013) and IgM (10.6 g/l in 2013). The patient had no history of allergy. Laboratory analyses showed increased serum levels of rheumatoid factor (27.7 U/ml), D-dimer (3.36 μg/ml), CRP (18.4 mg/l), fibrinogen (6.7 g/l), beta-2 microglobulin (3.16 mg/l), IgM-κ paraprotein (4 g/l). A bone marrow biopsy enabled to rule out multiple myeloma. A skin biopsy was performed (**figure 4**).

Figure 3 *- Isolated urticarial rash on left shoulder in the second case.*

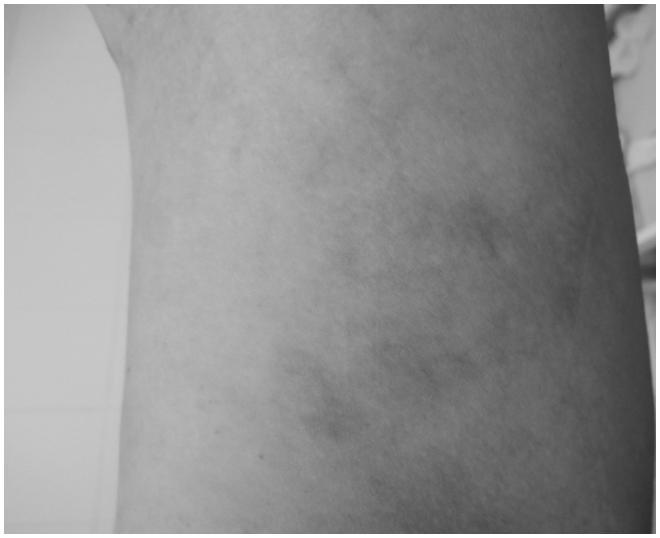
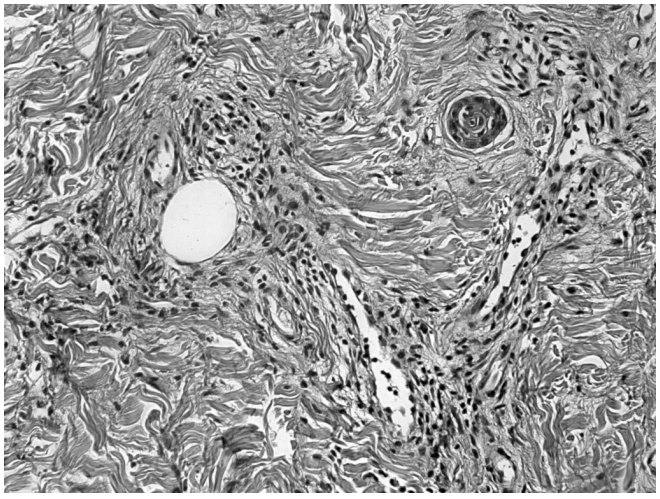


Figure 4 *- Perivascular infiltrates consisting of lymphocytes, macrophages, plasma and mast cells in the dermis. Sclerosis of dermal collagen fibers. Morphological signs of chronic dermatitis (hematoxylin and eosin X100).*



The response to high-dose antihistamines was initially good, but became insufficient. Prednisolone and dexamethasone intramuscular injections had only temporary effects. As in the first case, following strict elimination diet resulted in an almost complete resolution of cutaneous symptoms and in a considerable decrease in bone pain. The patient took several courses of plasmapheresis with positive effect.

In this patient, IgE and IgM serum levels fluctuated, regardless of the diet and the therapy.

Discussion

In our study we used a 3-week elimination diet suggested by Metz M. and Magerl M. (2). Patients could only take bread without any additives, potatoes, rise, raw cereals, wheat pasta (made without eggs), butter, vegetable oil, fresh milk, cream without food stabilizers, natural yoghurt, cottage cheese, some Gouda cheese, fresh meat without spices, any vegetables, salt, onion, spring onion, mineral water, coffee, black and green tea (without flavorings). In both patients, the foods were excluded on the basis of the presence of pseudoallergens like biogenic amines and food additives (preservatives, colorings, etc.). We initially assumed that it is pseudoallergen-low diet that might have helped to reduce the urticarial activity (2). But having conducted a 3-week diet, we observed a considerable decrease in total IgE level in the first case. We found this phenomenon quite interesting. It is unknown if such effects of elimination diet on urticarial activity are based on allergic, non-allergic, mixed mechanisms (3) or associated with altered gastroduodenal permeability (4).

In both our patients, IgE levels were significantly elevated without any underlying reasons (allergy, parasites etc). To our knowledge, the occurrence of IgE hyperimmunoglobulinemia and the efficacy of elimination diet in SS has not been described in literature so far. The high serum level of total IgE may be associated with chronic urticaria activity, severe disease course and a poor response to treatment with antihistamines (5) and may be considered a possible marker of a subset of patients with SS showing a good response to the restriction diet. As we have mentioned before, in one of our patients we observed a decrease in IgE and IgM levels after a 3-week diet. But it is still difficult to say whether it was a spontaneous decrease or if this decline was associated with the diet, pharmacotherapy or both.

In general, we can assume that elimination diet can have an influence on the skin lesions and other symptoms of SS (like bone pain in the second patient) as well as on total IgE and IgM levels, but such association and the underlying mechanisms require further investigation.

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