

Schnitzler Syndrome: Clinical Case and Review of The Literature

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Abstract

Schnitzler syndrome is a rare auto-inflammatory disease with a chronic relapsing course, characterized by recurrent urticarial lesions and monoclonal gammopathy. The manifestations of systemic inflammation are complemented by fever, bone and muscle pain, arthralgia/arthritis, lymphadenopathy, hepato- or splenomegaly, increased levels of acute inflammatory markers. A biological marker of the disease is the monoclonal gammopathy. Patients show high risk to develop AA-amyloidosis and lymphoproliferative diseases. A patient with a 5-year delay in diagnosis, who has responded well to systemic corticosteroids is presented. A comprehensive review of the new insights of disease pathogenesis and therapy is also highlighted.

Keywords

schnitzler syndrome; autoinflammatory disease; monoclonal gammopathy; interleukin-1

Introduction

Schnitzler syndrome (SS) was first described in 1972 as a chronic urticaria, accompanied by toxo-infectious syndrome [1]. To date, at about 300 cases have been reported worldwide [2]. The disease onset is usually in the 6 decades of age, rarely before 35 years, and with only one case aged 13 years [3, 4]. The syndrome reflects high male preponderance [2, 5].

SS is a rare autoinflammatory disease, characterized by urticarial rash and monoclonal gammopathy, usually of the IgM type, as a result of pathological dysregulation of interleukin-1 [2, 6-11]. Other less common findings are: recurrent fever, bone or joint pain, lymphadenopathy, headache, myalgia, arthralgia/arthritis, fatigue, weight loss, peripheral neuropathy, leukocytosis and/or elevated C-reactive protein (CRP) [4, 11-14]. The overall prognosis depends on progression to Waldenström macroglobulinemia, lymphomas, leukaemia, myeloma and other lymphoproliferative malignancies [4, 12, 13, 15-18]. Evolution to AA amyloidosis has also been described [4, 19, 20]. Therapeutic options for SS are

extremely limited. In recent years, good results have been reported from the application of the immunobiological agent Anakinra - an inhibitor of IL-1 [4, 10, 12, 18, 20-23].

A case with a delayed diagnosis of Schnitzler syndrome, partially influenced by systemic corticosteroids is herein reported.

Clinical case

We present a 63-year-old patient with a 5-year history of a recurrent, moderately itchy urticarial rash, distributed on the trunk and limbs, sometimes accompanied by fever up to 38.8° C, pain in the knee, ankle and elbow joints, for which he had been repeatedly hospitalized in dermatological, internal, rheumatic and allergological departments. Systemic therapy with non-steroidal anti-inflammatory agents, corticosteroids and antihistamines with a temporary response had been administered. His medical history was complicated with accompanying scoliosis, lumbar disc herniation, right kidney cyst, chronic gastritis, and benign prostatic hyperplasia.



Figure 1: Disseminated urticarial lesions on the trunk and extremities

Physical examination demonstrated disseminated urticarial lesions on the skin of the trunk and extremities (Figure 1). Leukocytosis and elevated CRP proved general inflammatory constellation CRP 62 mg/dl, leukocytosis $14.6 \times 10^9/l$). High levels of alpha 1, alpha 2- and beta 2- micro globulins, and a wide band of Ig M kappa class paraprotein was detected on immune electrophoresis. Numerous studies were conducted, including thyroid hormones, hepatitis B, hepatitis C, Lyme disease, leishmaniosis, Marseilles fever, brucellosis, intestinal helminths, protozoa, toxoplasmosis, echinococcosis, trichinosis, fasciola hepatica, chlamydia trachomatis, which were negative. Normal values of anti-n RNP/Sm, Sm,SS-A, SS-B, Scl-70, Jo-1, PCNA; ds DNA, rheumatoid factor, lupus anticoagulant, and cryoglobulins ruled out connective tissue disease. Thorough neoplastic work-up was negative, including tumor markers and intact positron emission tomography findings. There were no deviations in computer tomography images of the chest, abdomen and small pelvis.

Based on the adapted criteria of the SS experts from Strasbourg, we diagnosed Schnitzler syndrome. Methylprednisolone therapy was started with gradual

dose reduction. At the routine one-month follow up the patient had a partial response.

Discussion

Schnitzler's syndrome is a rare disease, with as yet incompletely elucidated pathogenesis and pathophysiology. One hypothesis suggests that IgM paraprotein synthesis stimulates the immune complexes formation and activates the complement system [7, 10, 24]. Other mechanism suggests uncontrollable activation of IL-1 α [13, 25]. Some authors classify the disease as an autoinflammatory syndrome similar to cryopyrin-related periodic syndrome [3-5, 9, 12, 13, 18, 20, 25], which has been induced by NF- κ B activation [26]. SS is also considered a "paraneoplastic phenomenon" because 15-20% of patients develop lympho-proliferative disorder [4, 12, 13, 15-18]. Genetic predisposition links the disease to NLRP3 mutation [11, 13, 26], which triggers the myeloid cell population to produce abnormally high amounts of IL-1 β . The latter induces chronic stimulation and influence of B cells for IgM expression [27].

Diagnosis of SS is difficult, often delayed [28], as in our patient.

Table 1: SS diagnostic criteria (Strasbourg experts' meeting)

| | | | | |
|--------------------|------------------------------|--|---|--|
| Main criteria | Chronic urticarial exanthema | Monoclonal IgM or IgG gammopathy | | |
| Secondary criteria | Recurrent fever > 38°C | Impaired bone remodeling processes with/without pain | Neutrophilic dermal infiltrate in skin biopsy | Leukocytosis > 10000/mm ³ and/or CRP > 30mg/L |

For the purpose of timely and correct diagnosis, D. Lipsker and co-authors [3] introduced diagnostic criteria, which are subsequently modified by H. D. De Koning and co-authors [4] and revised at the SS experts' meeting in Strasbourg (12) (Table 1). Diagnosis is certain for 2 major and at least 2 minor criteria for IgM or 3 minor criteria for IgG and likely for 2 major and at least 1 minor criteria for IgM or 2 minor criteria for IgG [8].

Our patient meets two major and two minor diagnostic criteria: urticarial rash, monoclonal IgM gammopathy, recurrent fever, leukocytosis and increased CRP.

SS is suspected in patients with chronic urticarial rash associated with fever, fatigue, general malaise, pain in the joints, muscles or bones, lymphadenopathy, hepato-/splenomegaly, leukocytosis, increased levels of inflammatory markers. The presence of only one of the above factors may correspond to a monoclonal dyscrasia. The manifestations of the individual symptoms vary: chronic urticaria - 100%, itching - 45-79%, fever - 88-93%, arthralgia / arthritis - 77-94%, bone pain - 68-79%, weight reduction - 64%, lymphadenopathy - 44-85%, hepatosplenomegaly - 29-34%, angioneurotic edema - 5%, leukocytosis - 69-85%, anemia - 56%, increased ESR - 95-98%, monoclonal gammopathy - 100%, IgM - 86-97% [29]. The urticarial rash is usually the first and constant manifestation of the SS. The trunk, limbs, palms and soles, head and neck are affected. It lasts about 12-24 hours, and may disappear or persist. Fever is present in the majority of patients and is ≥ 38.5 °C (88-93% of all patients). The frequency of relapses varies, and may occur daily or several times per year [2, 12-14, 29, 30]. Monoclonal gammopathy (usually IgM, less often IgG) is mandatory, but does not always occur early in the disease, sometimes delays with a few decades [31].

Before making a diagnosis of SS, it is necessary to exclude the following diseases: Still's disease in adults; cryopyrine-associated syndromes (Muckle-Wells syndrome); urticarial vasculitis; cryoglobulinemic vasculitis; systemic lupus erythematosus; hypocomplement-associated vasculitis; chronic idiopathic urticaria; lymphoproliferative diseases; monoclonal gammopathy and monoclonal gammopathy of unknown origin.

The SS is chronic relapsing condition with a variable prognosis. About a quarter of patients develop lymphoproliferative disorders such as Waldenström's macroglobulinaemia, lymphomas, leukemias, multiple

myeloma, etc. [4, 12, 13, 15-18]. In a small series of 20 patients, Socumbi et al [5] reported almost half of the patients evolving into hematological dyscrasia. AA-amyloidosis occurred in 3 cases as a result of the persistent systemic inflammation [4, 19, 20].

SS patients should be strictly monitored by controlling the inflammatory activity and severity of monoclonal gammopathy [2, 12-14]. Markers of inflammation (ESR, leukocytes, CRP) need to be tested every 3 months in active disease, and twice per year - in remission. IgM titers are checked every 3 months. An increase in their levels and / or an onset of peripheral lymphadenopathy serves as an indicator for hematological disorder and necessitates immediate bone marrow puncture and lymph node biopsy.

Therapeutic options for SS are limited. No improvement was found with administration of antihistamines and thalidomide [3, 4]. Arthralgia is well alleviated with short courses of NSAIDs, especially ibuprofen [12]. Methotrexate, azathioprine, cyclosporine, intravenous immunoglobulins and plasmapheresis are ineffective [3, 4, 12]. Therapy with colchicine, dapsone, pefloxacin, hydroxychloroquine, ciclosporin, interferon- α and corticosteroids have partial effect [2, 4, 7, 12, 13].

In patients with significant impairment in quality of life and/or persistence of inflammation, even in the absence of significant symptoms, administration of an IL-1 inhibitor, Anakinra 100 mg/morning, subcutaneously [12, 21-23] is recommended. Neel et al. [20] presented a retrospective analysis of 29 patients receiving Anakinra who experienced complete remission in 83% and partial remission in 17%. No lympho-proliferative malignancy was detected at 9.5 years mean observation time. In the absence of an effect of Anakinra, the diagnosis should be confirmed once again, and subsequently adjust the treatment with an increase in the dose to 200-300 mg and complimentary use of colchicine, as an adjuvant. Alternatively, Tocilizumab may be used [31]. In remission for more than 2 years, stopping treatment or continuing with colchicine for 3 to 6 months is prevented. Long-term inhibitors of IL-1 - Rilonacept [32] and Canakinumab [33-37] have been administered to patients with SS, but there is no long-term experience of their administration. There are single, conflicting reports of Rituximab and phototherapy [18]. IL-6 inhibitor was tried in non-compliance with the IL-1 inhibitor [38].

Conclusion

Schnitzler syndrome is a rare auto inflammatory disease that represents an enormous diagnostic challenge. The nonspecific clinical findings delay its verification for years. The pathogenesis is still obscured with genetic predisposition and defective innate immunity considered the most important triggers. The role of monoclonal gammopathy is not yet fully understood, most likely underlying the development of lymphoproliferative malignancies. IL-1 receptor blockers prove to be the most effective therapeutic modality. Timely diagnosis and appropriate treatment require multidisciplinary approach and deductive insight to further elucidate the scientific research in this widely expanding area of clinical medicine.

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