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Case Report

Delayed diagnosis of Schnitzler syndrome, an autoinflammatory disease

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Abstract. Schnitzler syndrome is an autoinflammatory disorder, associated with significant risk of developing amyloid A amyloidosis and lymphoproliferative diseases, making timely diagnosis crucial. The diagnosis is based on the validated Strasbourg diagnostic criteria. In this case report, we described a patient with a 1-year delayed diagnosis, who also had a hepatitis B virus infection. The treatment of choice in patients with highly active disease is interleukin-1 receptor antagonist Anakinra, but the effect on chronic hepatitis B virus infection reactivation is unknown. Our patient's disease has been well controlled with low doses of systemic corticosteroids.

Key Words: Schnitzler syndrome, autoinflammatory disease, monoclonal gammopathy, interleukin-1, hepatitis B.

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Introduction

Schnitzler syndrome is a rare autoinflammatory disorder characterized by urticarial rash and monoclonal gammopathy, usually of IgM isotype, secondary to dysregulation of the interleukin 1 pathway (Gusdorf et al 2017, Rowczenio et al 2018). Other less frequent findings are: recurrent fever, bone or joint pain, lymphadenopathy, headaches, myalgia, arthralgia, fatigue, weight loss, peripheral neuropathy, neutrophilic dermal infiltrate, leukocytosis and/or elevated plasma C-reactive protein (Rowczenio et al 2018).

The overall prognosis depends on the possible evolution into a Waldenström macroglobulinemia, lymphoplasmacytic lymphoma, chronic lymphocytic leukemia, splenic marginal zone lymphoma, marginal zone B-cell lymphoma and IgM myeloma, reported to occur in 15-45% of patients over median follow-up of 13 years from the time of initial diagnosis (Sokumbi et al 2012, Simon et al 2013). The evolution in AA amyloidosis (amyloid A amyloidosis) was also described (Claes et al 2008).

The pathophysiology of Schnitzler syndrome is unclear. It is associated with monoclonal gammopathies and has clinical similarities with autoinflammatory syndromes such as cryopirin-associated periodic syndromes.

Herein we report a case with delayed diagnosis of Schnitzler syndrome associated with hepatitis B virus infection.

Case report

A 65-year old man presented with one-year history of urticaria and recurrent fever (> 38,5°C). On physical examination, macules and slightly raised papules and plaques were found on the trunk and proximal extremities (Fig. 1). He also described persistent fatigue, arthralgias, muscle pain and pruritus. The patient was initially treated with antihistamines and low doses of corticosteroids (30 mg/d), with partial remission of symptoms. Laboratory tests revealed elevated erythrocyte sedimentation rate of 67 mm/h, C-reactive protein at 6.3 mg/dl (normal range: < 0.5 mg/dl) and white blood cells at 19,000/µl (normal range: 4,000 - 10,000/µl).

The electrophoresis and immunofixation revealed an IgM kappa monoclonal gammopathy (Fig. 2). Increased IgM levels (947 mg/dL; normal range: 40-230 mg/dL) and decreased IgG (647 mg/dL; normal range 700-1,600 mg/dL) were detected. Bone marrow biopsy was negative for myeloproliferative, lymphoproliferative disorders or mastocytosis. Multiple autoimmune investigations were performed in order to exclude a connective tissue disease: anti-nRNP/Sm, Sm, SS-A, SS-B, Scl-70, Jo-1, PCNA, dsDNA, rheumatoid factor, lupus anticoagulant and cryoglobulines. The investigations revealed normal values. Biopsy of affected skin demonstrated perivascular infiltrate of neutrophils, mononuclear cells and leukocytoclasia in upper dermis (Fig. 3a, 3b). There were no abnormalities found on chest/abdominal/pelvis CT scan.

A screening for HIV infection and viral hepatitis revealed HBsAg-positive, HBV DNA-1,800 UI/ML and HBeAg-negative. Alanine aminotransferase, aspartate aminonotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin, serum albumin, full blood count (except white blood cells) were normal. The patient was not considered a candidate for antiviral therapy. The follow-up recommendations for liver disease were alanine aminotransferase determinations at least every 3 months, HBV DNA determinations every 6-12 months and assessment of liver fibrosis every 12 months.

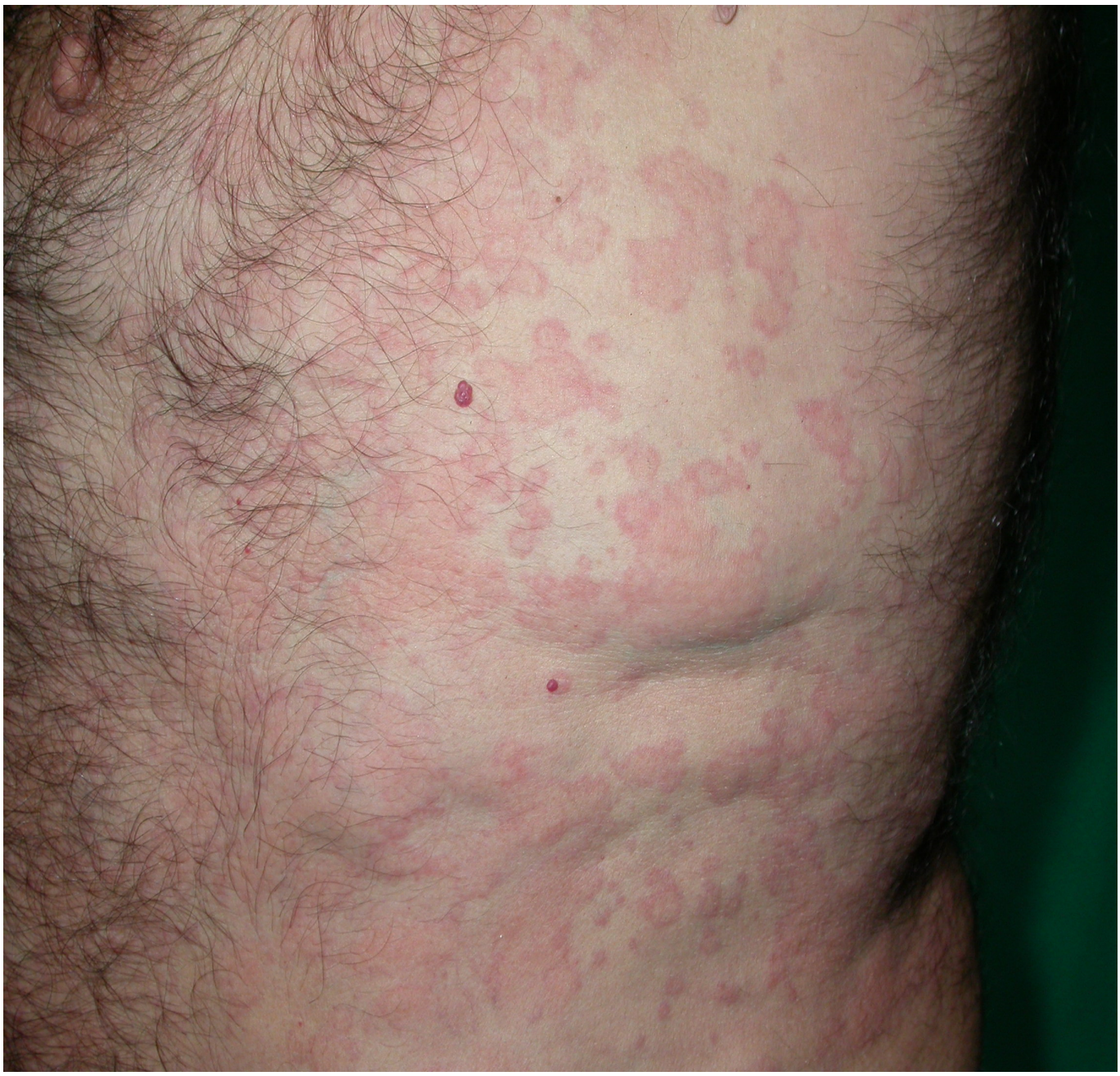

Fig. 1. Erythematous urticarial papules and plaques on the trunk

Based on the Strasbourg criteria (Tabel 1) and exclusion of other causes of systemic inflammation (urticarial vasculitis, systemic lupus erythematosus, cryopyrin-associated periodic syndrome, adult-onset Still's disease, lymphoma, Waldenström's disease, polyclonal gammopathies in viral hepatitis), Schnitzler syndrome was considered to be the diagnosis. A long-term treatment with oral prednisone 20 mg/d was efficient and well tolerated. The liver function and inflammation blood tests were evaluated at three-month intervals in the next year, without significant changes.

The patient signed an informed consent form, that gives the permission for the use of medical data and pictures.

Discussion

The diagnostic criteria of Schnitzler syndrome suggested in 2001 were revised by an expert meeting in Strasbourg and validated in a multicentric study (Lipsker et al 2001, Simon et al 2013, Gusdorf et al 2017). Sensitivity and specificity of the Strasbourg criteria for definite diagnosis were 81% and 100% respectively (Gusdorf et al 2017). Our patient fulfilled the criteria for a definite diagnosis of Schnitzler syndrome: chronic urticarial rash, monoclonal IgM, recurrent fever, neutrophilic dermal infiltrate on skin biopsy and leukocytosis.

Schnitzler syndrome shares many clinical and biological features with genetically determined autoinflammatory syndromes: recurrent fever of unknown cause; urticarial rash characterized by a neutrophilic infiltrate very similar to the one observed in the auto-inflammatory cryopyrinopathies (CINCA/MOMID syndrome, Muckle-Wells syndrome and familial cold-urticaria); a significant increase of neutrophils in blood and tissue, not otherwise explained; an increase IL-1beta production by LPS (lipopolysaccharide) - stimulated peripheral blood monocytes (Rowczenio et al 2018); IL-6 and IL-18 level are increased in

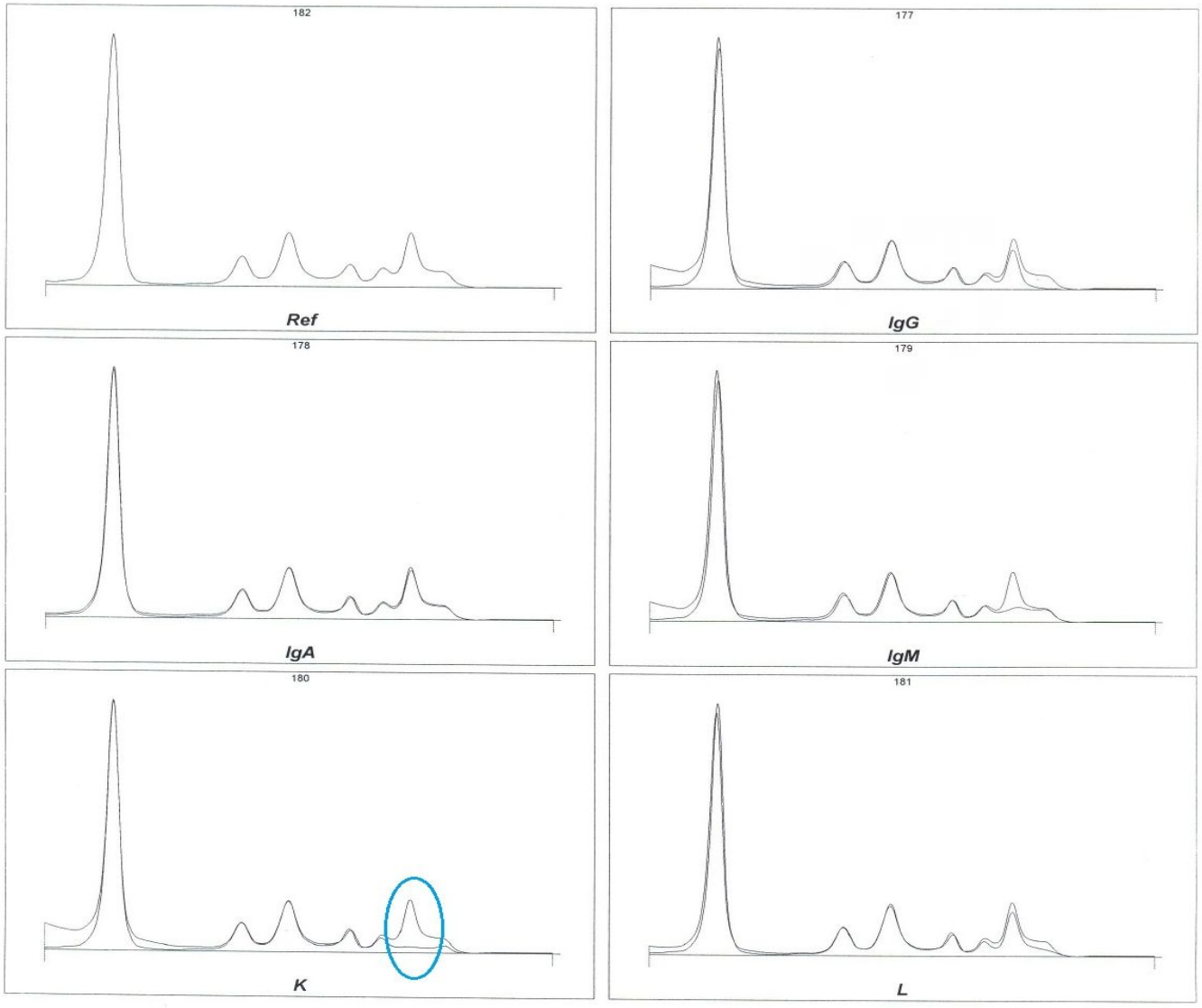

Fig. 2. Immunofixation analysis with immunoglobulin IgM, kappa light chain, monoclonal peak

Table 1. Strasbourg diagnostic criteria of Schnitzler syndrome

Obligate criteria
Chronic urticarial rash and
Monoclonal IgM or IgG
Minor criteria
Recurrent fever[a]
Objective findings of abnormal bone remodeling with or without bone pain[b]
A neutrophilic dermal infiltrate on skin biopsy[c]
Leukocytosis and/or elevated CRP[d]
Definite diagnosis if
Two obligate criteria and at least two minor criteria if IgM and three minor criteria if IgG
Probable diagnosis if
Two obligate criteria and at least one minor criteria if IgM and two minor criteria if IgG
[a]Must be > 38°C and otherwise unexplained. Occurs usually - but not obligatory - together with the skin rash
[b]As assessed by bone scintigraphy, MRI, or elevation of bone alkaline phosphatase
[c]Corresponds usually to entity described as "neutrophilic urticarial dermatosis"; absence of fibrinoid necrosis and significant dermal edema
[d]Neutrophils > 10,000/mm^3 and/or CRP > 30 mg/l

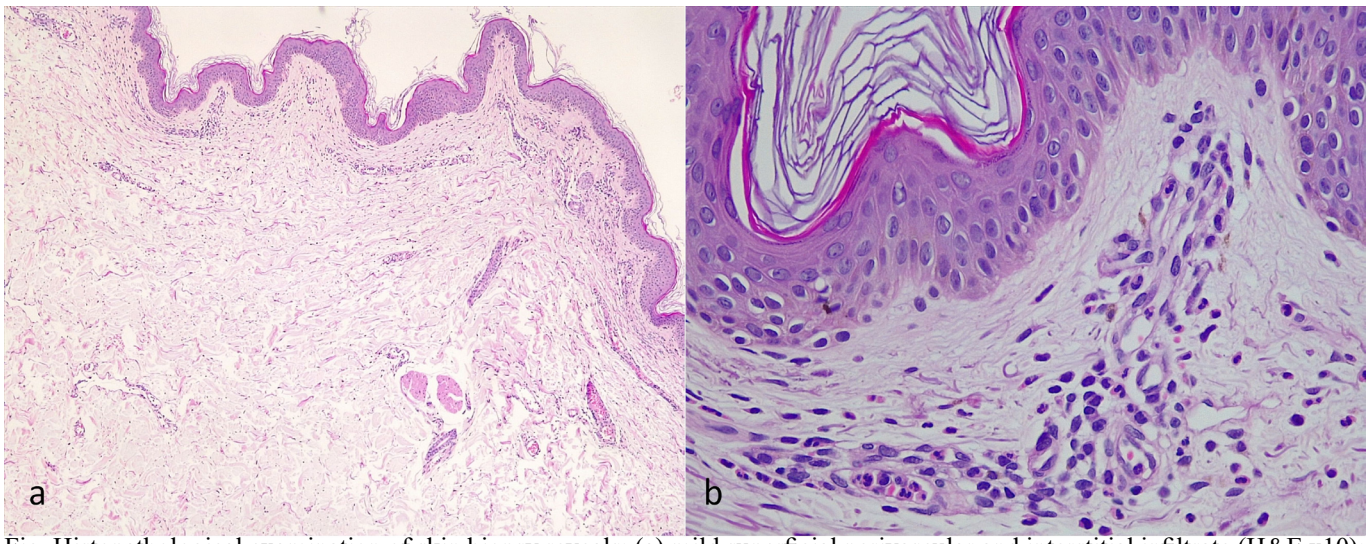

Fig. Histopathological examination of skin biopsy reveals: (a) mild superficial perivascular and interstitial infiltrate (H&E x10); (b) perivascular infiltrate of neutrophils, mononuclear cells and leukocytoclasia (H&E x40)

the serum of Schnitzler syndrome patients, and can be used as a sensitive marker of disease severity; a genetic predisposition involving an activating NLRP3 mutation; IL-1 blocking agents are the most effective therapies (Lipsker 2010).

Somatic mosaic of NLRP3 mutations exclusively in the myeloid lineage have been reported in 2 cases with Schnitzler syndrome. Furthermore, the authors speculated that a population of myeloid cells with an acquired NLRP3 mutation produces abnormally high quantities of IL-1beta, inducing chronic stimulation and clonal expansion of local B cells expressing IgM (de Koning et al 2015).

However, these results were not confirmed in recent larger series. A genetic analysis on 32 autoinflammatory genes that explores genetic susceptibility factors to Schnitzler syndrome failed to reveal neither germ line nor somatic NLRP3, TNFRSF1A, NLRC4, or NOD2 mutations, apart from one patient with a germ line NLRP30.V198M (Rowczenio et al 2018).

The role of IL-1beta in the pathogenesis of Schnitzler syndrome is well established and the treatment with IL-1 receptor antagonists ameliorates the symptoms. Elevated levels of ASC (apoptosis-associated speck-like protein containing caspase recruitment domain), IL-6, and IL-18 in patients' serum with cryopyrin-associated periodic syndrome were also reported in Schnitzler syndrome (Rowczenio et al 2018).

The most common histopathologic pattern found in skin biopsy was neutrophilic perivascular and interstitial infiltrate with variable leukocytoclasia. Nearly one-quarter of patients also had a mononuclear cell perivascular infiltrate, with or without eosinophils (Sokumbi et al 2012).

The treatment of choice is anakinra, an IL-1 receptor antagonist. The clinical findings resolve within hours after the first dose, in more than 80% of patients. Moreover, the lack of response to anakinra should lead to reconsider the diagnosis. The long-term efficacy and safety of interleukin-1 receptor antagonist was confirmed by a multicentric retrospective cohort study. The median follow-up was three years, with no loss of effectiveness (Neel et al 2014). The treatment required 100 mg subcutaneous daily injections. The only adverse effects were injection site reactions and neutropenia. Anakinra reduces the risk of developing AA amyloidosis, a known complication of any inflammatory disease. On the other hand, the impact of IL-1 receptor antagonist on the clonal B-cell disorder is unknown. Conventional therapies, such as colchicine, pefloxacine, hydroxychloroquine, cyclosporine and corticosteroids had only partial improvement of the symptoms. Our patient also had a hepatitis B virus infection. A systematic review of observational studies involving adult patients diagnosed with rheumatoid arthritis and who used anakinra revealed severe infections in 129 (5.1%) of 2896 patients (Cabral et al 2016). The most frequent infections were pneumonia and cellulitis. No reports of chronic hepatitis B virus infection reactivation have been published in patients being treated with IL-1 receptor antagonist. On the other hand, no clear guidelines are available in terms of safety for anakinra in patients with hepatitis B virus infection. Recently, Jennings et al reported a hepatitis B carrier (only with antibody to HBcAg) with pyoderma gangrenosum, acne, suppurative hidradenitis treated with anakinra. The patient has also commenced entecavir to prevent viral reactivation. For this reason, we decided to continue the treatment with low doses of prednison (20 mg daily), until anakinra associated with antiviral treatment will be started. During prednison treatment a near-complete resolution of cutaneous lesions was obtained. However, long-term systemic corticosteroids may cause serious side effects.

Follow-up with patients with Schnitzler syndrome should include clinical evaluation and looking for modified biological markers of inflammation, as serum CRP and leukocyte count, every 3 months. The overall prognosis depends on the potential evolution into a lymphoproliferative disorder or AA amyloidosis.

Conclusions

Many patients with Schnitzler syndrome have a diagnostic delay of years due to unspecific symptoms. Even today, the patients with Schnitzler syndrome are still underdiagnosed. The management of Schnitzler syndrome could be difficult if hepatitis B virus infection is associated.

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