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Brief report

Schnitzler's syndrome presenting as fever of unknown origin (FUO)

The role of cytokines in its systemic features

E.M.H.A. de Kleijn^{a,*}, D. Telgt^a, R. Laan^b

^a Department of General Internal Medicine 541, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, Netherlands

^b Department of Rheumatology, University hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, Netherlands

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Abstract

A patient with Schnitzler's syndrome is described presenting with fever of unknown origin. Although he had all characteristic features of the syndrome (urticarial vasculitis, hyperostosis, lymphadenopathy, fever and serum IgM monoclonal component), it was recognized very late in the diagnostic process. Cytokines were measured to get more insight into the role of cytokines in this syndrome, but only interleukin-6 was elevated. It is important for internists and rheumatologist to recognize this entity in order to prevent unnecessary diagnostic procedures. © 1997 Elsevier Science B.V.

Keywords: Fever of unknown origin; Urticaria; Vasculitis; Macroglobulinaemia; Fever, diagnosis; Cytokines; Interleukin-1

1. Introduction

Urticarial vasculitis can be secondary to many diseases causing fever of unknown origin (FUO, i.e., systemic lupus erythematosus and other connective tissue diseases, helminthic infections, hepatitis B, infectious mononucleosis, malignancies, thyroid diseases and hypocomplementaemia with renal diseases [1].

In 1974 Schnitzler et al. [2] reported 5 patients with urticarial vasculitis together with hyperostosis,

lymphadenopathy, fever and serum IgM monoclonal component. Even after extensive diagnostic workup no underlying cause was found and it appeared to be a specific entity. Schnitzler's syndrome has since been described in 28 cases, mostly in French [3–7]. Fever is an important feature of the syndrome and cases can be wrongly labeled as FUO. In computer-aided literature databases like MEDLINE (Medline National Library of Medicine, Bethesda, MD) this entity cannot be found using 'fever of unknown origin' as a key word. However, it is important to recognize this syndrome as a cause of FUO, in order to prevent unnecessary diagnostic procedures.

In this case report, we present a patient with Schnitzler's syndrome, with fever as a prominent symptom leading to many unnecessary investigations in several hospitals, before recognition of the syndrome.

Abbreviations: FUO = fever of unknown origin; IL-1 = interleukin-1; TNF α = tumour necrosis factor- α ; IL-6 = interleukin-6; IFN γ = interferon-gamma; IL-1ra = interleukin-1 receptor antagonist

* Corresponding author. Tel.: +31 24 3614782; fax: +31 24 3541734.

2. Case report

A 72-year-old man was referred to our department for a second opinion because of fever of 1 year duration. Despite extensive diagnostic workup in two other university hospitals no diagnosis had been established. His medical history revealed bronchial asthma and eczema. The patient also had urticaria for approximately 1 year, which became pruritic 3 months before referral to our hospital. Body temperatures were remittent and hectic with a difference of 3–4°C between peak and trough, and he complained about night sweating, fatigue and pain in both upper legs. He had received up to 40 mg of prednisone until a few months before, without any improvement. At the time of referral, only slightly swollen cervical lymph nodes were present. The urticarial lesions were located on trunk and extremities. No arthritis or splenomegaly was evident. Laboratory data were significant for elevated erythrocyte sedimentation rate (79 mm/h), C-reactive protein (84 mg/l), microcytic anaemia of chronic disease (5.2 mmol/l) and hypoalbuminaemia. Cryoglobulin and circulating immune complexes were absent, serology for hepatitis C was negative and complement profile was normal. Immunoelectrophoretic analysis identified a serum monoclonal IgM (6.5 mg/l). Blood for cytokine measurement was drawn once during fever. Circulating TNF α was 80 pg/ml (normal, < 120 pg/ml), IL-1 β 70 pg/ml (normal, < 65 pg/ml) and IL-1ra 330 pg/ml (normal, < 490 pg/ml), measured by RIA as described elsewhere [8]. Circulating IFN γ was < 6 pg/ml (normal, < 6 pg/ml) and IL-6 74 pg/ml (normal, < 3 pg/ml), measured by ELISA as described elsewhere [8]. Whole blood in-vitro stimulation assays were performed on TNF α , IL-1 β , IL-6 and IL-1ra as described elsewhere and were all normal. Biopsy of an urticarial lesion showed urticarial vasculitis without depositions in the immunofluorescence. Bone marrow biopsy and lymph node biopsy were unremarkable, showing polyclonal plasmacytosis, with normal distribution of immunoglobulin and light chains, without domination of IgM-positive cells. An X-ray of the right femur showed hyperostosis of the right femur, whereas scintigraphic imaging was unremarkable. Multiple cultures of blood, urine and sputum were all negative. Because of these symptoms, we concluded that

the patient suffered from Schnitzler's syndrome and started colchicine therapy. The fever and urticaria became less but did not disappear. Remission of symptoms was obtained only after addition of prednisone (15 mg) and naproxen (500 mg twice a day). Our patient has now had a free follow-up of 24 months.

3. Discussion

Our patient presented for a second opinion because of FUO. Schnitzler's syndrome was not diagnosed by many previously consulted internists. A review of the literature on Schnitzler's syndrome showed that most patients appear to share the presence of chronic, usually non-pruritic urticaria, recurrent fever, lymphadenopathy, monoclonal serum IgM and hyperostosis with bone pain. The prognosis is generally good, but long-term follow-up is advisable since 3 of the 28 reported cases developed a malignancy: Waldenström's macroglobulinaemia, lymphoplasmocytic lymphoma and angio-immunoblastic lymphadenopathy (AILD) [6]. Our patient was examined in several hospitals and underwent an extensive diagnostic program, which could have been prevented by the recognition of the syndrome. Because of the presence of monoclonal IgM it will still be necessary to perform a bone marrow biopsy in this category of patients. A possible pitfall remains the fact that AILD was found after a long follow-up in one patient with Schnitzler's syndrome. It is sometimes difficult to establish this diagnosis and several lymph node biopsies may be necessary.

To get more insight into the role of cytokines in the systemic features of Schnitzler's syndrome we measured cytokines in our patient. Despite the fever there were no increased circulating concentrations of known endogenous pyrogens such as TNF α and IL-1 β . IL-6 was slightly elevated in our patient, which would imply that IL-6 plays a role in some of the systemic features of the syndrome. Indeed, IL-6 is a major modulator of the acute phase reaction characterized by fever, leukocytosis, increased vascular permeability and elevation of acute phase protein [9].

To date, the pathophysiological mechanism of this syndrome has not yet been clarified. IgM and IgG

antibodies against interleukin-1 α (IL-1 α) have been shown in serum and human epidermis [10], which would imply a pathophysiological role for IL-1 in the systemic features of this syndrome. However, the physiological role of circulating auto-antibodies is not clear at all, because auto-antibodies (mostly of the IgG but sometimes also IgM) are detectable in 24% of apparently normal adults [11].

No specific therapy for patients with Schnitzler's syndrome is available. Systemic corticosteroids are first choice in therapy, NSAID's are also used successfully [4]. Colchicine also appears to be effective [12] and often, as in our patient, a combination is necessary to suppress symptoms.

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