Background of the Case

Schnitzler’s syndrome is a rare condition characterized by urticarial vasculitis, hyperostosis, lymphadenopathy, fever, and serum IgM monoclonal component. The role of cytokines in the systemic features of this syndrome is not fully understood. The objective of this case report is to present a patient with Schnitzler’s syndrome presenting as fever of unknown origin (FUO) and to discuss the role of cytokines in its systemic features.

Case Presentation

A patient with characteristic features of Schnitzler’s syndrome was admitted to our hospital with fever of unknown origin. Although the patient had all characteristic features of the syndrome, including urticarial vasculitis, hyperostosis, lymphadenopathy, and fever, the diagnosis was delayed. Cytokines were measured to gain insight into the role of cytokines in this syndrome, but only interleukin-6 was elevated.

Discussion

Fever is a common feature of Schnitzler’s syndrome and can lead to misdiagnosis as FUO. However, recognizing this syndrome in patients with FUO is crucial to avoid unnecessary diagnostic procedures. Cytokines, particularly interleukin-6, may play a role in the systemic features of Schnitzler’s syndrome.

Conclusion

Schnitzler’s syndrome should be considered in the differential diagnosis of patients with FUO. Cytokine measurements may provide additional insight into the pathogenesis of this syndrome.

Keywords: Fever of unknown origin; Urticaria; Vasculitis; Macroglobulinaemia; Fever, diagnosis; Cytokines; Interleukin-1
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 TNFα was 80 pg/ml (normal, <120 pg/ml), IL-1β 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 IFNγ 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 TNFα, IL-1β, 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 TNFα and IL-1β. 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-1α (IL-1α) 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.

References


