Schnitzler Syndrome: Chronic Urticaria, Fever and Immunoglobulin M Monoclonal Gammopathy

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Key words: Schnitzler syndrome, urticaria, fever, monoclonal gammopathy

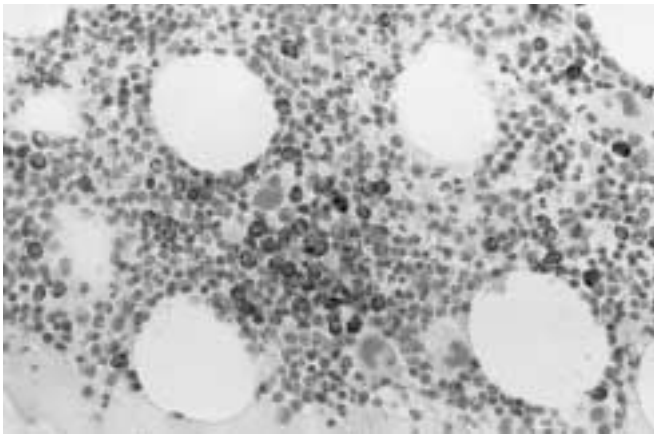
IMAJ 2002;4:466–467

In 1974 Schintzler described a combination of clinical symptoms – including chronic urticaria, intermittent fever, osteosclerotic bone lesions and monoclonal gammopathy – as a syndrome that now bears his name [1]. This is a rare syndrome and only a few dozen cases have been reported thus far. We report a case of Schnitzler syndrome diagnosed in our hospital.

Patient Description

A 46 year old man who recently immigrated to Israel from Iran was hospitalized due to pruritic urticarial rash, fever of 39.5°C, and arthralgia. He had been suffering from bouts of fever, rash and arthralgia for the preceding 4 years. Each episode lasted for 3–4 days and recurred every 3–4 weeks. He did not have abdominal pain, pleuritic chest pain, or oral and genital ulcers. He was not exposed to any known allergens, neither did he drink alcohol or ingest drugs. He was previously treated with short courses of corticosteroids and non-steroidal anti-inflammatory drugs with no apparent improvement.

On physical examination he was oriented and in no obvious distress. His blood pressure was normal at 110/65, tachycardia was 102 beats/minute, and his body temperature was 39.3°C. A diffuse urticarial rash was noted on his torso and limbs, with areas of confluent rash on both ankles. There was a mild tenderness on passive and active movement of both ankles with no signs of arthritis. The laboratory results showed anemia with hemoglobin 9.2 g/dl, leukocytosis 18,800 mm^3, and thrombocytosis 540,000 mm^3. Sodium, potassium, creatinine, urea and glucose were normal, as was the immunologic laboratory workup including antinuclear, antimitochondrial and anti-smooth muscle antibodies and complement levels. No abnormality was noted on chest, skull and bilateral femur and tibia X-rays, and on chest abdomen and pelvic computerized tomography. Erythrocyte sedimentation rate was 125 mm/hour and protein electrophoresis revealed an immunoglobulin M kappa paraprotein in the serum. Bone marrow biopsy showed a mild increase in plasma cells, which were positively stained immunohistochemically for IgM-kappa, consistent with the diagnosis of plasma cell dyscrasia [Figure]. The diagnosis of Schnitzler syndrome was reached.



Bone marrow biopsy showing mild increase in plasma cells. The cells are monoclonally stained immunohistochemically for IgM-kappa, consistent with the diagnosis of plasma cell dyscrasia.

Treatment with prednisone 60 mg and aspirin 100 mg once daily was initiated. There was complete resolution of all symptoms within 3 days. Corticosteroid treatment was slowly tapered off to 10 mg/day. The patient is currently asymptomatic after one year of follow-up.

Comment

Schnitzler syndrome is characterized by chronic urticaria, recurrent fever, bone pain and osteocondensation in association with monoclonal IgM gammopathy. Since its first description by Schnitzler in 1974, only a few dozen cases have been reported, mostly in Europe [1]. Patients with Schnitzler syndrome share several distinct features. Urticaria involving the trunk and extremities, usually sparing the face, is universal. Recurrent bouts of fever, bone pain and arthralgia occur in approximately 80% of the patients. Uncommon features include lymphadenopathy and hepatosplenomegaly.

Laboratory results include an IgM gammopathy, elevated ESR, leukocytosis and thrombocytosis. Anemia is present in one-third of the cases. Complement levels are normal and antinuclear antibody, rheumatoid factor and cryoglobulin are usually absent.

Other conditions involving chronic urticaria or angioedema associated with an M component that should be considered in the differential diagnosis are acquired C1 esterase inhibitor deficiency in association with B cell lymphoproliferative disorders

Ig = immunoglobin

ESR = erythrocyte sedimentation rate

(such as chronic lymphocytic leukemia and multiple myeloma), systemic capillary leak syndrome, systemic lupus erythematosus, and hepatitis B virus infection with antigenemia and narcotizing vasculitis. Adult Still's disease, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin lesions) and Waldenstrom's disease should also be considered.

The pathophysiology of Schnitzler disease is unknown. Interleukin-1 binding activity was observed in some patients but not in others, as were elevations in IL-6, granulocyte macrophage colony-stimulating factor, and G-CSF. IL-1 is known to have inflammatory properties in human skin and could explain the urticaria in the syndrome [2]. A recently published article by Lipsker et al. [3] reports the presence of IgM anti-skin autoantibodies in two patients. Immune staining showed sparse IgM deposits in the epidermis around the keratinocytes and near the desmosomes in one patient, and dense deposits below the lamina densa in the other. Anti-skin IgM antibodies of the same isotype as their monoclonal gammopathies may be present in the serum of some patients with the Schnitzler syndrome. The authors suggested that these findings point to direct involvement of the monoclonal gammopathy in the skin rash [3].

The course of the disease is usually benign although the urticaria is resistant to treatment. Long-term follow-up of patients [4] revealed that two patients developed lymphoplasmacytic lymphoma, two died of opportunistic infections and one had hypoploid mononuclear cell population on bone marrow biopsy, suggesting the potential future development of lymphoma. The relapsing nature of the syndrome resembles other episodic diseases such as familial Mediterranean fever, and suggests a possible role of a cytokine surge in the pathogenesis. Such a surge, however, has not been documented so far.

The appropriate treatment of Schnitzler syndrome is not clear. Various treatment modalities were proposed, including H1 and H2 blockers, chloroquine, sulphones, colchicine, NDAIDs, cyclophosphamide, chlorambucil, azathioprine and high dose intravenous immunoglobulins. However, none has been proven effective. An analgesic effect of ibuprofen and pamidronate on bone pain was recently described [5]. Low and high dose corticosteroids for the treatment of skin rash have yielded disappointing results. Their use is indicated when systemic symptoms are disabling and there is no response to NSAIDs. As our patient's main complaint was disabling fever and arthralgia, we consequently initiated corticosteroid treatment. To the best of our knowledge, a sustained prolonged response to corticosteroids, such as the one reported here, has not been previously described.

Schnitzler syndrome is probably underreported. Once the syndrome is suspected, based on the reported features of chronic urticaria, recurrent fever and arthralgia, we suggest performing immune electrophoresis to confirm the diagnosis. Treatment should be initiated with NSAIDs and may be combined with other agents (sulphones and colchicine). If systemic symptoms persist, corticosteroids may be considered as an alternative. Vigilant follow-up is needed since these patients may have an increased risk for malignancies [2].

References

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IL = interleukin
G-CSF = granulocyte colony-stimulating factor
NSAIDs = non-steroidal anti-inflammatory drugs