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Schnitzler's Syndrome (Urticaria and Macroglobulinemia) Associated with Pseudoxanthoma Elasticum

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Schnitzler's syndrome, first described in 1974, is defined by chronic non-pruritic urticaria, osteocondentation, and a monoclonal IgM dysproteinemia, but without criteria of lymphoproliferative disease. We report a patient with chronic urticaria and macroglobulinemia. In addition, he had double monoconal dysproteinemia IgM κ (31.3 g/l) and IgA λ, osteocondensation, and some cutaneous lesions of pseudoxanthoma elasticum. Only 20 cases of Schnitzler's syndrome have been reported hitherto. This is the first case associated with pseudoxanthoma elasticum, which was localized and discovered at the same time as Schnitzler's syndrome. We discuss the possible role of monoclonal immunoglobulin in the occurrence of localized elastorrexhis. ***Key words: Monoclonal dysproteinemia; Immunoglobulin M; Interleukin 1 α.***

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Monoclonal dysproteinemia is associated with various cutaneous manifestations (1) among which the association of chronic urticaria with monoclonal IgM was described by Schnitzler et al. in 1974 (2,3). Twenty other cases have been described subseqently (1, 4-12). We report a new case of Schnitzler's syndrome which is particularly interesting because of the coexistence of pseudoxanthoma elasticum (PXE).

CASE-REPORT

A 69-year-old man presented with a 5-year history of chronic urticaria and dysproteinemia. Clinical examination revealed annular erythematous and maculopapular lesions over the trunk. The eruption was non-pruritic and almost permanent, but each lesion subsided in less than a day. Histopathological examination of an urticarial lesion showed edema of superficial dermis with moderate mononuclear and polymorphonuclear cell infiltration around superficial vessels. Direct immunofluorescence microscopy did not reveal any deposits of anti-IgM, anti-IgA, or anti-C_3.

Two macular and yellowish lesions on the left arm were noted. One followed a trauma, while the other had occurred spontaneously. Histopathological examination of a xanthomatous lesion with orcein staining showed abnormal and fragmented elastic fibres typical of pseudoxanthoma elasticum (Fig. 1). Electronmicroscopy revealed fragmented and dissociated elastic fibres, containing calcium deposits (Fig. 2.). There were no angioid streaks on fundoscopic examination and echocardiography was normal. There was no familial history of pseudoxanthoma elasticum.

There were atrophic and symmetrical lesions on the shoulders, probably following vaccination. Histopathological examination of these showed them to be consistent with a scar. General health status was good. There was no lymph node enlargement, no hepatomegaly and no splenomegaly. There was some episodic and locomotor bone pain, localized in the left ankle.

Blood cell count was normal. The ESR was 74 mm at the first hour, fibrin concentration 3.05 g/l, and C-reactive protein 8.3 mg/l (< 8 mg/l). The cholesterol level was normal and triglyceride level 2.32 nmol/l (< 1.55 nmol/l), gammaglutamyltransferase and ALAT were normal, alkaline phosphatase was slightly increased 125 UI/I (< 110 UI/I), creatinine, calcium and phosphate values were normal. Analysis of three stool specimens revealed no parasites or ova.

Serum electrophoresis showed proteinemia at 80 g/l, and gammaglobulin at 25.6 g/l, with a monoclonal aspect. Serum immunoelectrophoresis showed a double dysproteinemia IgM κ and IgA λ. IgM concentration was 31.3 g/l. IgG and IgA values were normal. A monoclonal kappa chain was present in urine at 0.2 g/l. There was no albuminuria or tubular dysfunction. Plasmatic viscosity was at 1.8 cp (normal, 1.46 ± 0.18). Complete skeletal X-ray was normal except for a condensation, with some patchy hypodensities of the neck of femur (Fig. 3.). Bone scintigraphy with technetium ^{99}m showed an intense fixation on the same area. Medullogram and osteomedullar biopsy were normal. Bone biopsy showed osteoblastic and osteoclastic hyperactivity, without any tumoral proliferation. Thoracic and abdominal tomodensitometry showed pulmonary tuberculosis sequelae. Congo red and thioflavin T staining showed no amyloid deposits on skin and rectal biopsies. Antinuclear antibodies, anticytoplasmic neutrophil antibodies and cryoglobulins were absent. The C_3 and C_4 fractions of complement and CH 50 were normal. Positive serum anti-IL_1 alpha activity was found by immunobinding. The patient was treated for one month with ibuprofen 800 mg daily, and then with colchicine (1 mg/day) and then with dapsone for the same period of time, without any improvement.

Fig. 1. Fragmented elastic fibres in the mid-dermis (orcein stain, ×400).

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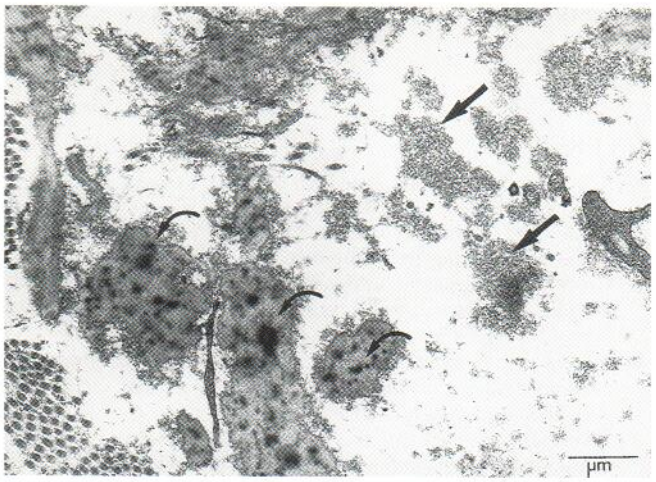

Fig. 2. Abnormal and fragmented elastic fibres with deposits of calcium (*curved arrows*); abundant microfibrillar material (*straight arrows*). Magnification: ×16000.

DISCUSSION

Our patient had pseudoxanthoma elasticum associated with Schnitzler's syndrome. Our patient showed all the signs usually encountered in this syndrome: chronic urticaria, macroglobulinemia, and osteocondensation without any evidence of lymphoproliferative disease (Table I). This syndrome, described by Schnitzler et al. (2), belongs to the large group of dysproteinemia diseases but differs from other cutaneous monoclonal gammapathic manifestations (1). Apart from the clinical manifestations, the particular characteristic of this syndrome is its benign prognosis (1) and the presence in the serum of an anti-IL_1 α antibody that could be of pathophysiological significance (4,13).

Cutaneous biopsy shows superficial dermal edema with polymorphous infiltrate and mild vasculitis in all cases. Leukocytoclasis or fibrinoid necrosis is present in half of the cases (1). Direct immunofluorescence microscopic study usually gives negative results (1,4) but, when positive, shows deposits of anti-IgM along the basement membrane zone or in the capillary walls (11). Monoclonal IgM is always present and the light chain is usually of the kappa isotype (4). In our case, two monoclonal peaks, IgM ϰ and IgA λ were present. Another patient (12) also had a double monoclonal immunoglobulin, IgM ϰ and μ, with a hypodiploid population of mononuclear cells in the bone marrow. Bone pain is present in 58% of cases, and osteocondensation in 43% (1,4). In our case, the osteocondensation was associated with some patchy hypodensities. The other radiological manifestations usually described are condensation and hyperostosis of tibia (10) condensation of the iliac crest (2,9) and vertebral condensations (5). Bone biopsy has been carried out in only 3 other cases, in one case showing evidence of lymphoid proliferation (1). The other signs frequently encountered are fever and lymphadenopathy.

One particular characteristic of this syndrome is its benign and prolonged course despite the dysproteinemia, since the first described patient has a 20-year follow-up (2,3). Evolution toward lymphoma or Waldenström disease has been reported in one case (5). Our patient has a 6-year course, without any sign of Waldenström disease or myeloma. Nevertheless, the high titre of monoclonal IgM and the double monoclonal gammapathy require careful surveillance.

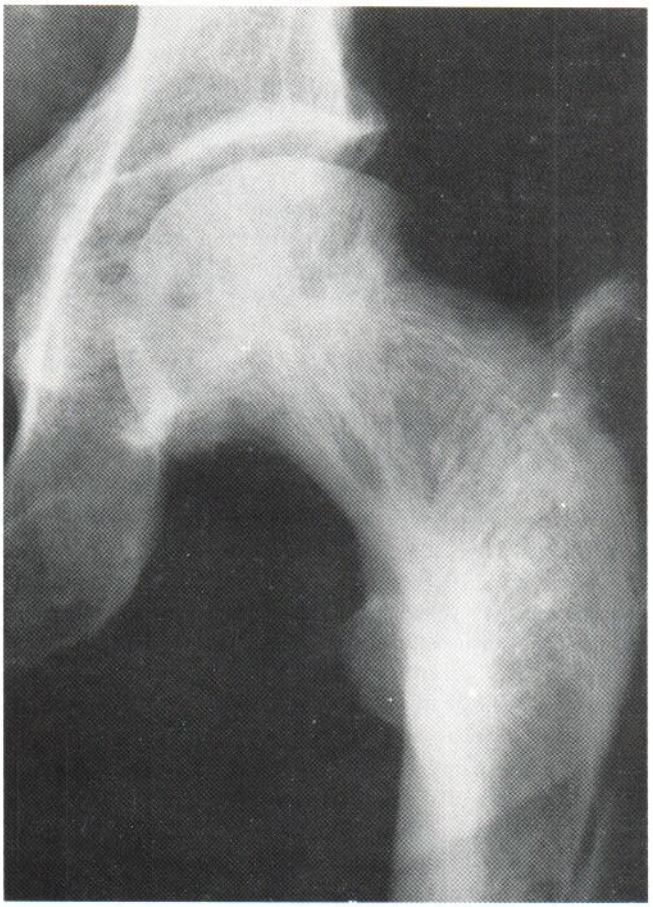

Fig. 3. X-ray of the neck of femur with osteocondensation and patchy hypodensities.

The pathophysiology of this syndrome has recently been linked to an anti-IL_1 α activity in the serum of the patients.

Table I. *Main clinical, biological and pathological features of the 21 cases of Schnitzler's syndrome*

	Number of cases tested	Number of positive cases tested
Duration of urticaria > 5 years	21	13
Superficial urticaria	21	21
Angioedema	21	4
Osteocondensation	18	7
Fever and/or weight loss	21	16
Increased ESR	21	20
Elevated fibrinogen > 6 g/l	10	6
Monoclonal IgM	21	21
IgM k	17	15
IgM > 10 g/l	17	6
Urine Bence Jones protein	9	7
Lymphoid proliferation in:		
1. Medullogram	17	0
2. Bone marrow biopsy	11	1
3. Bone biopsy	4	1

This activity was present in our case and in seven others (13), which could explain the fever and urticaria. Indeed, IL_1 α is known to have inflammatory properties in human skin, causing persistent erythema with mixed dermal leukocyte infiltrate by intradermal injection (14). Additionally, IL_1 α has been demonstrated to have a potent bone resorption-stimulating factor activity (15). Another explanation for the development of urticaria could be the deposition of immunoglobulins and complement in the walls of small capillaries (11), though, as in our case, direct immunofluorescence microscopy usually proves negative (1,4).

Treatment is difficult: anti-H_1 is ineffective, but anti-H_2, ibuprofen, colchicine, dapsone and oral corticosteroids have been reported to be effective in some cases (1,4,10,11). In our case, ibuprofen, dapsone and colchicine proved ineffective.

The association of Schnitzler's syndrome and pseudoxanthoma elasticum has not been reported previously. Our patient had only two acquired lesions, one occurred on a scar, which is usual in PXE, and the other occurred spontaneously and consisted of a yellowish annular and papular lesion 1 cm in diameter. Its histopathological appearance and the electron microscopy study were typical of PXE, showing fragmented and calcified elastic fibres.

The pathogenesis of PXE is now explained either by a primary abnormality of the molecular sequence of elastin fibres. The role of monoclonal IgM in the development of pseudoxanthoma elasticum is not clear. Monoclonal immunoglobulins are known to possess varying degrees of antibody activity (16), and elastic tissue disorders, such as generalized acquired cutix laxa, have been reported in association with multiple myeloma (17). Moreover, the acral localized form of cutis laxa has also been reported recently in 2 cases of myeloma (18). The deposit of monoclonal immunoglobulin, which has an antielastin effect on the elastic fibres, has been proposed as an explanation for the coexistence of these two rare conditions (17). Another explanation for the development of elastolysis could be the release of proteolytic enzymes by the inflammatory infiltrate (18). Indeed, inflammatory urticarial lesions usually precede or accompany the development of cutaneous laxity in acquired cutis laxa. In these cases, histopathological examination reveals dermal edema with infiltration by mononuclear and polymorphonuclear leukocytes.

If a link exists between PXE and macroglobulinemia it may be via one of these two mechanisms. In our case, though we did not find IgM deposits on elastic fibres, we speculate that our patient had monoclonal IgM and urticaria, which led to a secondary development of localized PXE, because of the chronic inflammatory infiltrate.

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