

# Correlative bone imaging in a case of Schnitzler's syndrome and brief review of the literature

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## Abstract

Schnitzler's syndrome is a rare disease characterized by a monoclonal IgM (or IgG) paraprotein, a non-pruritic urticarial skin rash, and 2 (or 3) of the following: recurrent fever, objective signs of abnormal bone remodeling, elevated CRP level or leukocytosis, and a neutrophilic infiltrate on skin biopsy. It responds well to treatment with the interleukine-1-inhibitor anakinra. We report the bone scintigraphy and MRI findings in a 45 years old man with this syndrome and compare them with data from the literature. **Conclusion:** None of the imaging findings are specific, but they lead to a differential diagnosis including infiltrative diseases (e.g. systemic mastocytosis or Erdheim-Chester disease) and dysplastic diseases (e.g. melorheostosis, Camurati-Engelmann disease or van Buchem disease). The bone scintigraphy pattern may be very suggestive of the correct diagnosis and of bone involvement in this syndrome.

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## Introduction

Schnitzler's syndrome is a rare, but increasingly recognized disorder. Since its original description in 1972 [1], some 200 patients have been reported [2-4]. The syndrome is characterized by recurrent urticarial rash and monoclonal gammopathy, associated with clinical and biological signs of inflammation.

About 15% to 20% of patients with a Schnitzler's will develop a lymphoproliferative disorder, as in other monoclonal IgM gammopathies of undetermined significance. Untreated patients may develop AA amyloidosis [5]. According to a recent consensus, definite diagnosis of Schnitzler's syndrome requires two obligate criteria: a recurrent urticarial rash and a monoclonal IgM or IgG gammopathy, and two (in the case of IgM gammopathy) or three (in the case of IgG gammopathy) of the following minor criteria: recurrent fever, objective signs of abnormal bone remodeling, elevated CRP level or leukocytosis, and a neutrophilic infiltrate on skin biopsy [2]. First-line treatment in patients with significant alteration of quality of life or persistent elevation of markers of inflammation should be anakinra [2], an interleukine-1-inhibitor. A small number of long-term remissions have been described [2]. The pathophysiology of this disorder remains unknown, although there is evidence that it may be an acquired auto-inflammatory syndrome [5].

In this case report, we present the findings on both bone scintigraphy and MRI in a patient with Schnitzler syndrome, who was treated successfully with anakinra. We compare our findings with literature data.

## Case report

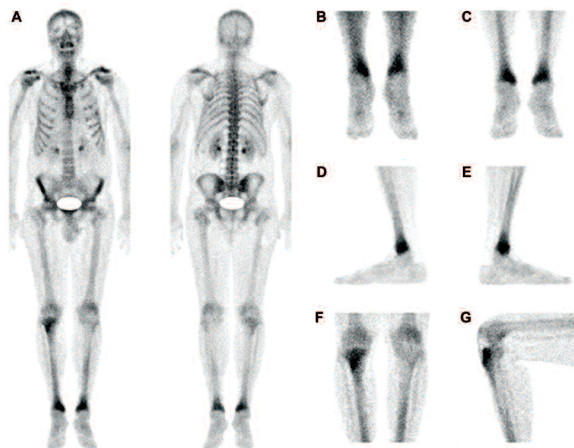
A 45 years old man complained of pain in the knees, painfully swollen ankles, and a nonpruritic skin rash since 5 months. The pain was nocturnal and the patient experienced morning stiffness. Intermittent fever was present, as were excessive sweating and fatigue. Physical examination revealed a urticarial rash on the trunk and limbs and an axillary lymphadenopathy. Both shins were tender on pressure.

Laboratory tests revealed an erythrocyte sedimentation rate (ESR) at 70mm/hr, a C-reactive protein of 1.6mg/dL (normal less than 0.5), a leukocyte count of  $12 \times 10^9/l$ , with 77% neutrophils, and a thrombocytosis of  $560 \times 10^9/L$ . Protein electrophoresis showed

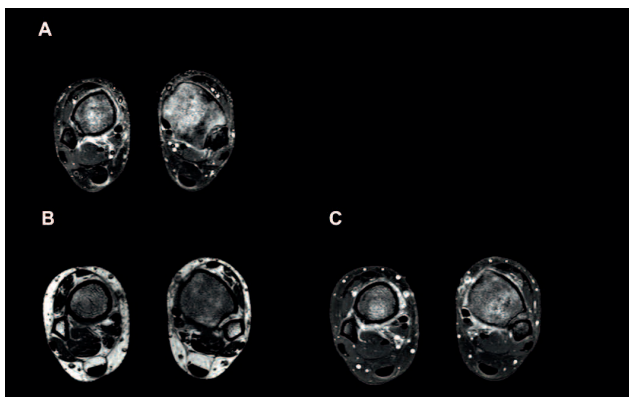
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an increased gamma fraction with a monoclonal IgM kappa paraprotein. Anti-nuclear antibody and rheuma factor were absent. Complement factors C3c and C4 were normal. Biopsy of a skin lesion demonstrated perivascular dermatitis, compatible with urticaria; immunofluorescence was negative. No arguments for immunocytoma were found on bone marrow examination. Axillary lymph node biopsy showed a reactive pattern. No hepatomegaly or splenomegaly were found on ultrasound. Radiographs of knee and ankles were normal.

The bone scan obtained 3h after injection of 740MBq of  $^{99m}\text{Tc}$ -oxidronate (Figure 1-whole body scan, panel A; spot views of the ankles, B-E, and the right knee, F-G) revealed diffuse slightly increased tracer uptake in both tibial diaphyses, with more marked uptake proximally anteriorly in the right tibia, and especially in both ankle regions. Three phase bone scan of the ankles showed a similar pattern in the blood pool phase (B) as was present on the bone phase (C). On ultrasound, subcutaneous edema was seen in both ankles.



**Figure 1.** Whole body bone scan (panel A), blood pool (B) and bone phase views of the ankles (C-D) and bone phase views of the knees (F-G) show diffuse slightly increased tracer uptake in both tibial diaphyses, with more marked hot spots anteriorly in the right tibial metaphysis, and especially in both distal tibial epiphyses.



**Figure 2.** MRI TIR images of the ankles (panel A) shows diffusely increased signal in the medullar bone of the distal third of both tibiae and, less markedly, fibulae. The signal is increased in the cortical bone as well. On T1 images (panel B), patchy hypointensity is seen in the marrow. After injection of gadolinium (panel C), enhancement can be seen in the marrow as well as in the periost and the surrounding soft tissue.

MRI was performed (Figure 2). TIR images of the ankles (panel A) showed diffusely increased signal in the medullar bone of the distal third of both tibiae and less markedly in the distal third of both fibulae. The signal was increased in the cortical bone as well. On T1 images (panel B), the marrow was hypointense in a patchy fashion, and was enhanced after injection of gadolinium (panel C), as were the periost and the surrounding soft tissue. The MRI findings were thought suggestive of diffuse bone infiltration by a hematological proliferation.

At the time of the patient's diagnosis, diagnostic criteria for Schnitzler syndrome consisted of the presence of a chronic nonpruritic urticarial skin rash, a monoclonal immunoglobulin (IgM) component and at least 2 of the following: fever, arthralgia or arthritis, bone pain, palpable lymph nodes, liver or spleen enlargement, increased ESR, leukocytosis and abnormal bone morphologic investigation findings [5]. Most of these criteria were present. Accordingly, the bone pain and urticaria subsided within one day after the first subcutaneous injection of 100mg of the interleukin-1 receptor antagonist anakinra. Treatment has since been successfully continued for over 5 years, although the dose has varied between 50mg b.i.d. and 100mg b.i.d.

## Discussion

Bone pain is present in about 70% of patients with Schnitzler's syndrome [6]. Arthralgias and sometimes arthritis can occur [5]. Radiographically, bone lesions characteristically are sclerotic, and may begin by periosteal bone thickening [7-10]. Hyperostosis may slowly progress [1]; it has been reported in 5 of 25 patients [6]. Lytic lesions are possible [11-13]. The iliac bone and the tibia and femur are most commonly involved, but the spine, ribs, humerus, forearm, clavicle, fibula, talus, calcaneus and skull may be involved as well [7, 9]. Isolated diaphyseal abnormalities are never observed and medullary changes always reach into the endosteal surface of the cortex [9].

Other researchers reported abnormal bone scans in 3 of 8 patients [6] and others in 5 of 5 patients [9]. Bone scintigraphy reveals the areas of sclerosis [7, 9, 10, 14]; all areas of sclerosis identified by radiological means lead to positive scans, but the bone scan may show lesions that are not recognized on plain radiographs [9, 15]. Combined involvement of femur and tibia is common [7-9, 14, 16-18] and has been termed the 'hot knees sign' [9]. It has once been suggested that Schnitzler's syndrome spares the bone epiphyses [7], but the patient described here and numerous others prove otherwise. One report [19] described a bone scan suggestive of polyarthritis involving the metacarpal, proximal interphalangeal, knee and shoulder joints, another [20] showed symmetric pathological uptake in the elbows, wrists, knees and ankles, which subsided after cyclophosphamide treatment. Three-phase bone scans may be positive in all 3 phases [9], as it was in the patient presented here.

MRI shows thickening of the cortical bone and marrow infiltration without space occupying features, giving low sig-

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nal on T1 images and high signal on T2 or STIR images [7, 9, 10, 14, 21, 22]. Mature fully sclerotic lesions may show low signal on both T2 and T1 weighted images, but the margins of those lesions may still show high T2 signal and enhancement; in early disease the periostitis and surrounding soft tissue edema and enhancement may be present [9], like in the patients presented here. One patient showed an arthritis of the right tarsus on MRI [23].

None of the imaging findings are specific, but they lead to a differential diagnosis including infiltrative diseases (e.g. systemic mastocytosis or Erdheim-Chester disease) and dysplastic diseases (e.g. melorheostosis, Camurati-Engelmann disease or van Buchem disease). Taking the clinical history and laboratory investigations into account, however, the bone scintigraphy pattern may be very suggestive of the correct diagnosis. Moreover, it has been suggested that bone scanning is the most appropriate initial screening tool for bone involvement in suspected cases of this syndrome [9]. Awareness of this condition is important because of the excellent therapeutic results with anakinra [2, 5, 12, 18, 22-24].

*The authors declare that they have no conflicts of interest.*

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