

Imaging findings in 22 cases of Schnitzler syndrome: characteristic para-articular osteosclerosis, and the “hot knees” sign differential diagnosis

Blake D. Niederhauser · David Dingli · Robert A. Kyle ·
Michael D. Ringler

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Abstract

Background and purpose Schnitzler syndrome is characterized by chronic urticaria, monoclonal gammopathy, and a risk of developing lymphoproliferative disorders. Patients frequently present with bone pain, fever, arthralgia, and lymphadenopathy. The purpose of this study is to retrospectively review and evaluate potentially attributable imaging abnormalities in a series of patients with clinically diagnosed Schnitzler syndrome.

Materials and methods Clinical and pathological chart review identified 22 patients meeting Strasbourg criteria for Schnitzler syndrome. Imaging of these patients was retrospectively reviewed by a musculoskeletal radiologist and a radiology fellow to determine and characterize significant “positive” findings that could potentially be attributed to their primary disease process.

Results Evidence of abnormal bone remodeling was present in 64 % (14/22) of patients with 40 bone abnormalities. Lesions were predominantly or entirely sclerotic and most

commonly involved the distal femora ($n=11$), proximal tibiae (nine), and innominate bones (six). Patterns of involvement were variable, but typically eccentrically intramedullary, cortical, and juxta-articular. Skeletal surveys and targeted radiographs identified only 37 % (10/27) of abnormal bones subsequently “positive” by additional modalities. PET and bone scans were all positive in patients with bone sclerosis (13/13 and 17/17 bone sites, respectively).

Conclusions Schnitzler syndrome often presents with characteristic osteosclerosis, most commonly around the knees and in the pelvis. In patients with a suggestive clinical history, the radiologist could direct an appropriate imaging strategy or might to be the first to suggest the diagnosis. Bone scan may be the most appropriate initial screening tool in suspected cases.

Keywords Schnitzler syndrome · Osteosclerosis · Monoclonal gammopathy · Urticaria

Introduction

Schnitzler syndrome is a rare, but increasingly recognized disorder characterized by chronic recurrent urticaria and monoclonal gammopathy, typically IgM $_{\kappa}$ [1, 2]. For a definitive diagnosis by the Strasbourg criteria, in addition to urticaria and monoclonal gammopathy, patients must exhibit additional minor criteria (two if IgM and three if IgG) including: recurrent fever, abnormal bone remodeling, neutrophilic dermal infiltrates on skin biopsy, or evidence of increased inflammatory markers [3]. Most are older than 40 years and often present with rash not responsive to anti-inflammatory, immunosuppressive, or antihistamine therapies [3]. Bone or joint pains, episodic fevers, malaise, and lymphadenopathy are other common presenting symptoms. Given the monoclonal gammopathy, these patients are at risk for developing lymphoproliferative disorders, including Waldenström’s

B. D. Niederhauser
Department of Radiology, Mayo E-2, 200 1st St SW, Rochester,
MN 55905, USA
e-mail: niederhauser.blake@mayo.edu

D. Dingli
Division of Hematology, Mayo Clinic, 200 1st Street SW, Rochester,
MN 55905, USA
e-mail: dingli.david@mayo.edu

R. A. Kyle
Division of Hematology, Mayo Clinic, Stable 6-28200 1st Street
SW, Rochester, MN 55905, USA
e-mail: kyle.robert@mayo.edu

M. D. Ringler (✉)
Department of Radiology, Mayo Clinic, Charlton 2-290, 200 1st St
SW, Rochester, MN 55905, USA
e-mail: ringler.michael@mayo.edu

macroglobulinemia, lymphoma, AL amyloidosis, and multiple myeloma. First described by Liliane Schnitzler in 1972, approximately 130 of nearly 200 papers have been published since 2000. This is mainly due to increased recognition of the disorder among dermatologists and hematologists as well as advances in treatment with the highly efficacious IL-1 antagonist anakinra [3–5].

Recognition of Schnitzler syndrome is important because traditional treatments for urticaria, including steroids, antihistamines, and immunomodulators are often ineffective or only temporarily helpful with subsequent recurrence. On the other hand, treatment with anakinra eliminates symptoms in most patients and has become the standard of care [3, 4]. Additionally, given the propensity of these patients to develop hematologic malignancy, regular follow-up is required. A recent study found that at one institution, only 16/62 (26 %) patients meeting criteria for Schnitzler syndrome had been diagnosed as such, suggesting that the entity remains under diagnosed and that a significant number of patients may be deprived of appropriate therapy and surveillance [6].

Case reports have described various imaging features in Schnitzler syndrome, including focal intramedullary osteosclerosis, hyperostosis, mature periosteal reaction, and increased long bone uptake on technetium-99 m methylene diphosphonate bone scintigraphy [7–10]. Radiographic abnormalities have been reported preceding development of typical clinical symptoms such as the rash [8]. Because imaging features may be characteristic and occur early in the disease, it is important for the radiologist to recognize them when present and to suggest the correct diagnosis. Further, knowledge of effective and ineffective imaging strategies may empower the radiologist to assist in the most appropriate imaging in known or suspected cases.

The purpose of this study was to retrospectively review and evaluate potentially attributable imaging abnormalities in a series of patients with clinically diagnosed Schnitzler syndrome.

Materials and methods

Informed consent

The Institutional Review Board approved this retrospective study and determined informed consent could be waived due to minimal risk.

Patients

An electronic search of the clinical notes in the institutional medical database for the terms “Schnitzler” and “Schnitzler’s” between January 2000 and July 2013 was performed, identifying 256 potential patients. Review of the clinical notes excluded patients in whom Schnitzler syndrome was not

suspected or had been excluded based on clinical findings. The list was then cross-referenced with a hematology database dating back to approximately 1975 that included patients with monoclonal gammopathy and urticarial rash. This search identified 72 patients for further review. Clinical and pathological features and outcomes of many of these patients have been reported previously [6, 11]. Patients without clinical or radiological follow-up more recently than January 2001 were excluded. Additional patients were excluded for not completely fulfilling Strasbourg diagnostic criteria. This resulted in 22 subjects consistent with “definite” and seven subjects with “probable” Schnitzler syndrome.

All available imaging and reports of studies performed both at our institution as well as those submitted from outside referring facilities for interpretation after the onset of each patient’s symptoms were retrospectively reviewed by a musculoskeletal radiologist and a radiology fellow (mdr, bdn). These two authors determined imaging findings to be “positive” if, by consensus, they were felt to be attributable to the patient’s primary disease process including lymphatic or bone abnormalities, or other imaging findings previously recognized in Schnitzler syndrome.

Imaging techniques

Because imaging was performed over a 13-year period, CT equipment and technique were variable, but generally consisted of 5-mm axial slices reconstructed with a soft tissue kernel and often included coronal reformatted images. MRI studies were performed on either 1.5-T or 3.0-T scanners (General Electric, Milwaukee, WI, USA) using dedicated knee and extremity coils, where appropriate. Most MRI exams included both pre- and post-contrast imaging with weight-based dosing of intravenous gadolinium contrast (Omniscan, GE Healthcare, Princeton, NJ, USA). Bone scans were performed with Technetium-99 m MDP and included whole-body images in all patients. Bone scan imaging in two patients included dynamic blood flow images and focused blood pool and delayed planar imaging. Both whole-body and focused delayed planar images were obtained at approximately 4 h post-injection.

PET/CT exams were performed with 3.75-mm slices for both PET and CT on GE Discovery RT or 690 PET/CT scanners (General Electric, Milwaukee, WI, USA). F-18 fluorodeoxyglucose (FDG) doses were administered on a weight-based nomogram typically in the 12–15 mCi range per injection. CT portions of the exam utilized post-processing techniques for de-noising in larger patients.

Results

All 22 patients fulfilling the Strasbourg criteria for “definite” Schnitzler syndrome had at least limited imaging performed.

Most patients presented with complaints of rash (17/22; 77 %), with arthralgias as the primary symptom in 3/22 patients (14 %), and bone pain and fatigue in one patient each, respectively (1/22; 5 %). Twelve patients had focused skeletal radiographs performed at sites of bone or joint pain (as opposed to skeletal surveys), whether it was a primary or secondary presenting symptom, while one patient only had a body CT exam, and another patient only a chest X-ray. Fourteen patients were imaged with chest and/or abdominal CT, seven patients had full skeletal surveys, five had bone scans, four had PET/CT, and seven underwent musculoskeletal MRI. Median age at symptom onset was 63 years (range, 30–76 years) with 55 % (12/22) men (M:F=1.2:1) (Table 1).

Fourteen of 22 patients (64 %) were determined to have “positive” skeletal imaging findings attributable to Schnitzler syndrome, and three patients had adenopathy (one of which had no significant skeletal findings). None of the seven patients excluded as “probable” Schnitzler syndrome had positive imaging findings.

Areas of involvement

Osseous findings

In total, 14 patients had radiologic abnormalities that affected 40 bones, if the innominate bone is counted as a single bone (Table 2). Bone lesions were purely sclerotic (18 bone sites), mixed lytic and sclerotic (five bone sites), normal radiographically, but abnormal on MRI, PET/CT, or nuclear scintigraphic exams (11 bone sites), and abnormal on MRI or nuclear scans, but not imaged with plain films or CT (six bone sites). The most commonly involved sites were the distal femur (11 bones) and proximal tibia (9 bones), typically extending into the epiphyses. The next most common location was the innominate bone (six bones in four patients). Other patients had involvement in vertebral bodies (three lesions in two patients), ribs (one lesion in each of two patients), talus (two lesions in one patient), humerus (three bones in two patients),

Table 2 Distribution of bone abnormalities

Bones involved	
Distal femur	11
Proximal tibia	9
Innominate	6
Vertebral body	3
Rib	2
Humerus	3
Talus	2
Fibula	2
Calvaria	1
Calcaneus	1
Total	40

proximal fibula (two lesions in one patient), calcaneus, and skull (one lesion each). Five sclerotic bone lesions were biopsied, four of which were done at outside institutions. Pathologic results for three outside biopsies were unavailable and the other two were reported as “mild non-specific stromal fibrosis” and “sclerotic lamellar bone with fibrosis”, respectively.

Imaging features

The density of involved bones was highly variable, ranging from radiographically normal to extremely dense. The pattern of sclerosis ranged from coarse trabecular thickening to patchy or confluent osteosclerosis (Fig. 1). Long bone involvement usually included the metadiaphysis, and often epiphysis. Isolated central diaphyseal abnormality was never observed. Medullary changes always extended to the endosteal surface of the cortex. Smaller abnormalities were positioned eccentrically in cancellous bone extending to the nearest cortex, while larger abnormalities spanned the medullary diameter. The cortex appeared either mildly hyperostotic or normal, with evidence of cortical remodeling a subtle feature.

Involvement of the ilium usually included medial (adjacent to SI joint) and anterolateral aspects, bridged by the acetabular roof, sparing the mid superior iliac wing and creating a characteristic “V” shape of osteosclerosis on frontal views of the pelvis (Fig. 2). Though periostitis was seen on MRI, we did not identify definite periostitis on radiography. Sclerotic lesions on MRI often had nodular areas of T2-hyperintensity and enhancement along the periphery (Fig. 4).

Conventional radiograph features

Complete bone surveys were obtained in seven patients. Of 12 patients with focused radiographs, eight did not have complete skeletal surveys. Conventional radiographs identified 12 abnormal bones in six patients potentially attributable to Schnitzler syndrome. Only 29 % (2/7) of skeletal surveys

Table 1 Patient demographics

Number of patients	22
Median age (range)	63 years (30–76)
Male:female	1.2 (12 M:10 F)
Presenting symptom, <i>n</i> (%)	
Rash	17 (77.3)
Bone pain/arthralgia	4 (18.2)
Fatigue	1 (5.9)
Mean duration of symptoms prior to diagnosis* (SD)	5 years, 7 months (3 years, 3 months)

*Unavailable in five patients

Fig. 1 Four different patients with Schnitzler syndrome demonstrating various patterns of osteosclerosis by conventional radiography, including lace-like iliac sclerosis (**a**, *white arrows*), a circumscribed calvarial lesion with central lucency (**b**, *open arrow*), and vague intramedullary sclerosis about the knees (**c** and **d**, *black arrows*), called normal in one patient (**c**). None of these patients had clinical histories to suggest an alternative diagnosis

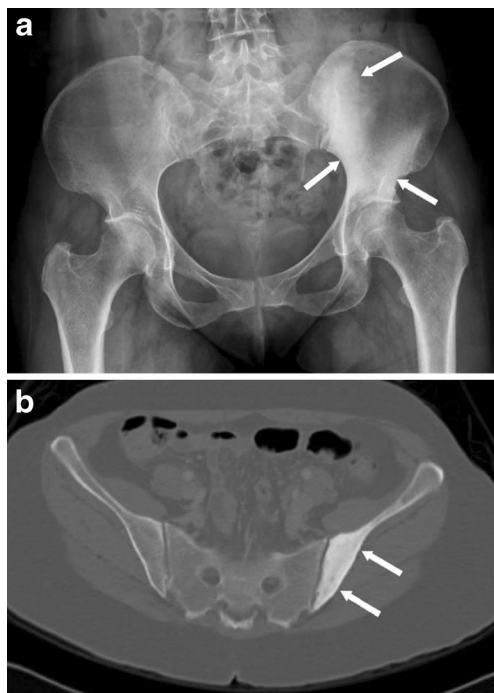
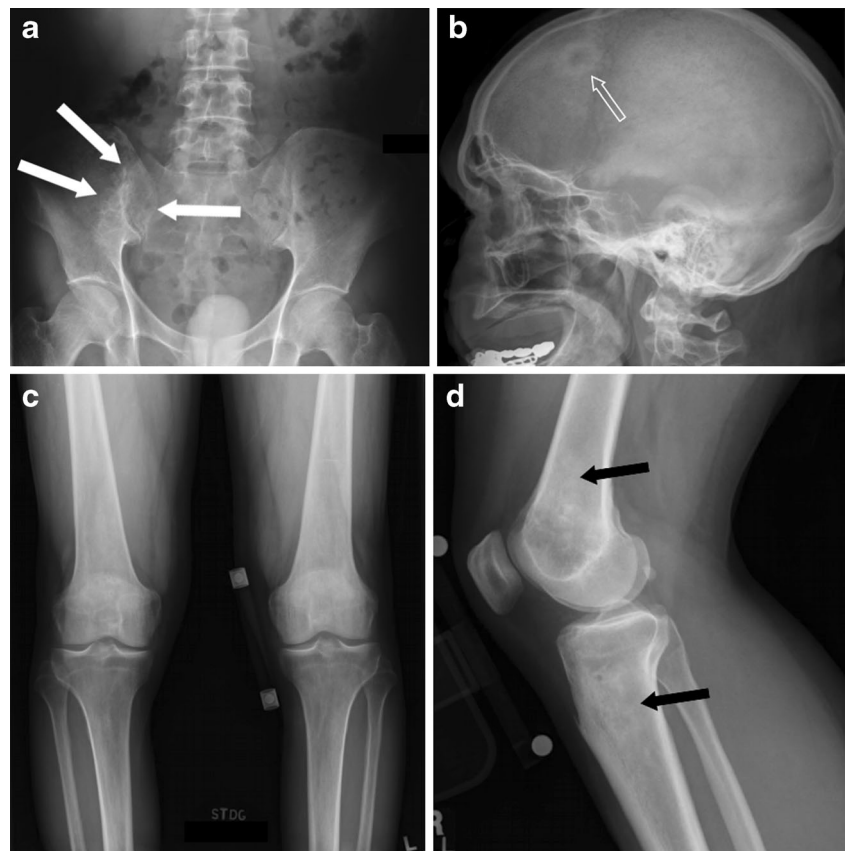


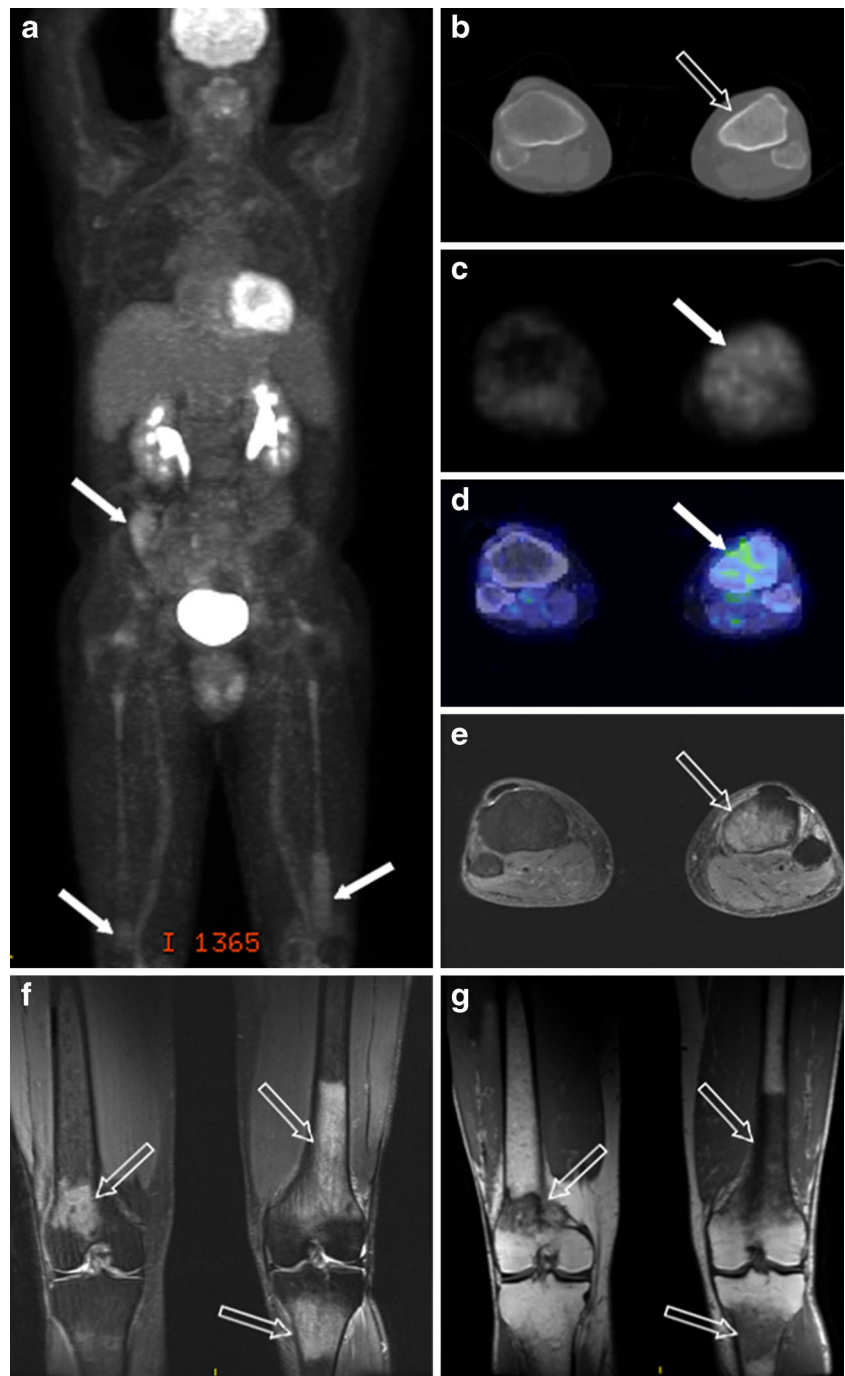
Fig. 2 AP radiograph of the pelvis (**a**) and axial CT (**b**) in a 57-year-old female with Schnitzler syndrome and left hip pain demonstrating dense intramedullary osteosclerosis (*white arrows*) of the medial left ilium, extending to the acetabular roof and anterolateral iliac wing resulting in typical “V” appearance

were “positive” with three bony lesions identified, while an additional 16 lesions were identified by other imaging modalities in the same patients, making the sensitivity of skeletal survey 16 % (3/19). In all, only 38 % (12/32) of abnormal bones (all modalities included) imaged with plain radiographs were considered positive, while the remaining osseous abnormalities were identified with advanced imaging (nuclear scintigraphy, PET, gallium scan, MRI, or CT).

CT features

Lymphadenopathy was readily detectable in three patients undergoing chest and abdominal CT being followed or surveyed for lymphoma. CT imaging identified all bony sclerotic lesions noted on plain radiographs including three patients with iliac sclerosis, and one patient with proximal tibial sclerosis notable on the low-dose CT component of his PET/CT (Fig. 3). Patterns of iliac sclerosis by CT were variable: one patient had coalescing patchy intramedullary iliac sclerosis, a second showed wispy or lacy intramedullary sclerosis, while another had a “pagetoid” appearance including coarse cortical and trabecular thickening noted on the low-dose CT component of his PET/CT exam (Fig. 4). One patient without bone pain had a small area of homogeneous sclerosis peripherally in the L5 vertebral body, and two additional patients had focal rib abnormalities not readily apparent on plain films.

Fig. 3 A 50-year-old male with Schnitzler syndrome presenting with rash and generalized arthralgias. Anterior maximum intensity projection image from a FDG-PET scan demonstrating increased metabolism in the medial right ilium and both distal femora (*white arrows*). Low-dose CT (**b**), attenuation corrected PET (**c**), and fusion (**d**) images from the same exam demonstrate hazy, intramedullary osteosclerosis, and cortical thickening in the proximal left tibia (*open arrow*) with corresponding hypermetabolism (*white arrows*). Axial (**e**) and coronal (**f**) fat-saturated T2-weighted, and coronal T1-weighted (**g**) MR images in the same patient demonstrate corresponding low T1 and high T2 intramedullary signal abnormality with islands of normal interspersed fatty marrow, which largely spares the epiphyses and extends to the endosteal surfaces. Mild periosteal and periarticular T2 hyperintensity is also noted, likely indicating active inflammation in this symptomatic patient



MRI features

MRI was performed on seven patients (bilateral knees, lower leg and ankle, and pelvis). Exam of the pelvis demonstrated confluent low T1 and T2 signal corresponding with dense medullary osteosclerosis noted on plain film affecting the medial and anterolateral aspects of an innominate bone in two patients. Small patchy areas of T2-hyperintensity and enhancement were seen at the margin of the osteosclerosis and in the contralateral innominate bone in both patients

(Fig. 5). MRI of the knees in one patient demonstrated nearly symmetrical extensive confluent medullary T2 hyperintensity throughout both distal femoral and proximal tibial diaphyses, metaphyses, and epiphyses with no significant periosteal or soft tissue abnormality. T1-weighted images demonstrated non-confluent signal abnormality with normal interspersed bone marrow fat. An MRI of one of the knees of the same patient 6 months prior demonstrated decreased extent of medullary signal abnormality with relative epiphyseal sparing and

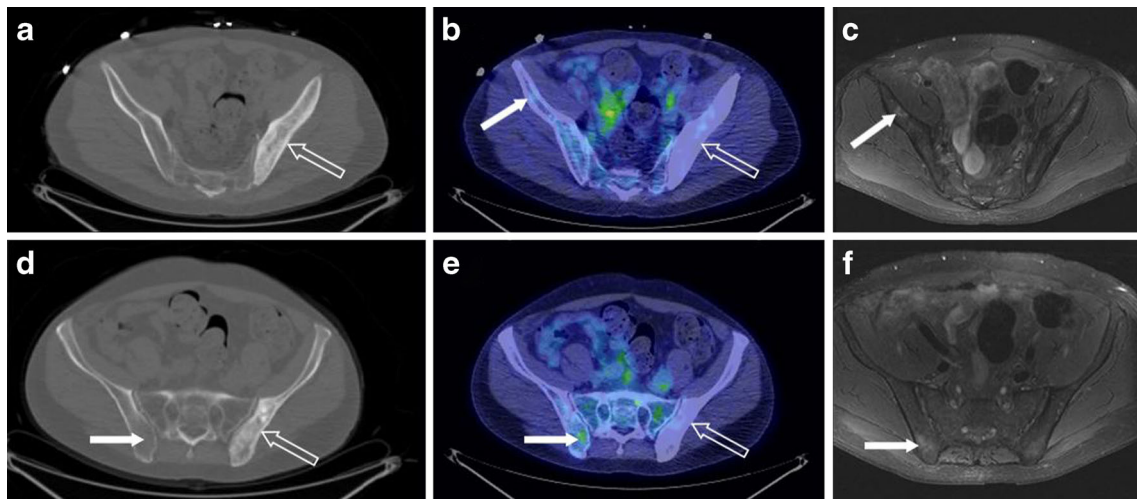


Fig. 4 Additional imaging from a 50-year-old male with Schnitzler syndrome shown in Fig. 3. Axial unenhanced CT (**a** and **d**), axial fusion images from PET/CT (**b** and **e**), and fat-saturated T2-weighted MRI (**c** and **f**) through the pelvis. Note the pagetoid appearance of the left innominate bone with smooth cortical thickening (*open arrows*), coarsened trabeculae, and intramedullary sclerosis. Areas of dense sclerosis,

low signal intensity on T2-weighted MRI (**c** and **f**) do not show abnormal hypermetabolism by PET, however, areas of increased T2 signal along the margins of the lesions correspond with focal hypermetabolism (*solid arrows*), likely indicating active disease. Although this patient presented primarily with left hip pain, there was no abnormal T2 signal in the periosteum or surrounding soft tissues

exuberant periostitis with surrounding soft tissue edema and enhancement (Fig. 6). In a second patient, bilateral knee MRI demonstrated similar medullary T1 and T2 signal abnormalities, both with marked asymmetry in extent between the two sides. A third knee MRI demonstrated minimal eccentric medullary signal abnormality in the distal femoral metadiaphysis only. Similar mild patchy medullary signal abnormality was noted in the distal tibial metadiaphysis of the fourth patient.

PET features

In all four patients undergoing PET scans, the primary purpose of the study was to better evaluate a known or suspected lymphoproliferative disorder. PET findings included diffuse low-level increased FDG uptake throughout the bone marrow, low-level uptake within enlarged lymph nodes, and increased FDG uptake within an enlarged spleen. Additionally, 13 sites of bone sclerosis and abnormal FDG uptake were identified,

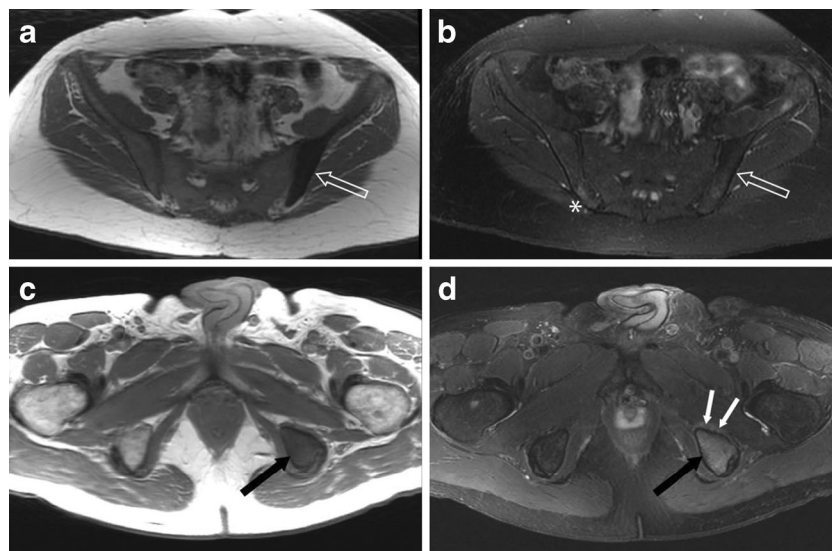


Fig. 5 Axial T1-weighted (**a** and **c**) and fat-saturated T2-weighted (**b** and **d**) images of the pelvis in a 57-year-old female with Schnitzler syndrome and left hip pain. Extremely low signal intensity in the medial left iliac crest on both T1 and T2 images (*open arrows*) correspond with dense sclerosis on CT (Fig. 2), however, intermediate to low T1 abnormality in

the left ischial tuberosity corresponds with hyperintense T2 signal (*black arrow*). Note abnormal surrounding T2 signal in the adjacent soft tissues (*solid white arrows*). Focal T2 hyperintensity in the medial right iliac bone corresponds with a recent bone marrow biopsy (*)

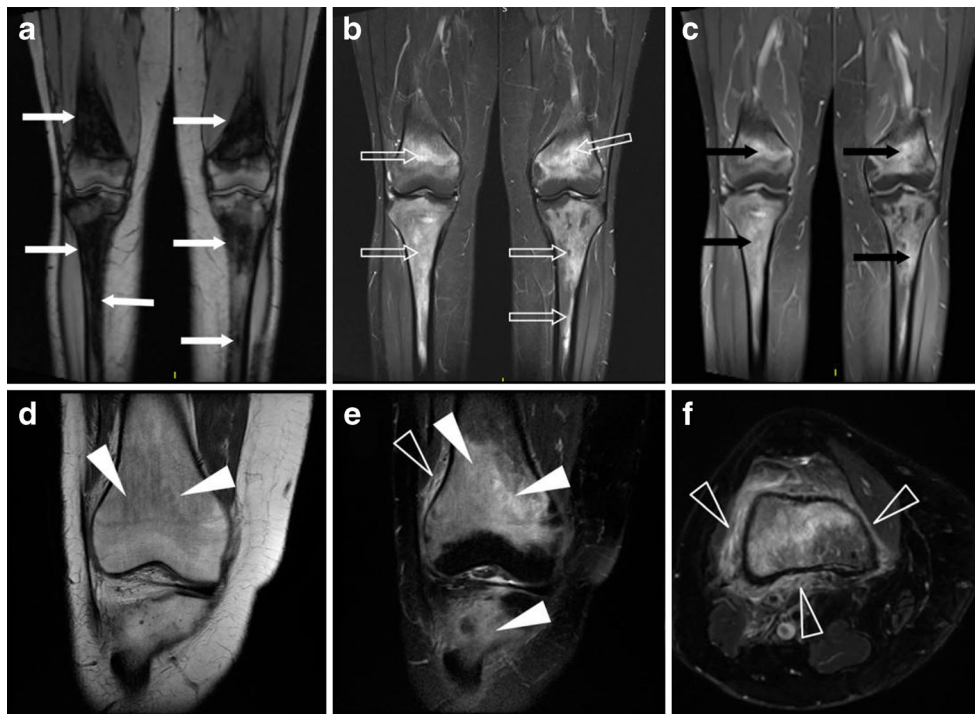


Fig. 6 Typical MRI findings in a 43-year-old female with Schnitzler syndrome, imaged during episodes of bone pain in June 2011 (*top row*) and December 2010 (*bottom row*). Coronal T1 (**a**), T2 with fat saturation (**b**), and fat-saturated T1 post-gadolinium (**c**) MRI through both knees demonstrate intramedullary infiltration manifest as low T1 signal (*white arrows*), high T2 signal (*open arrows*), and avid enhancement after intravenous gadolinium (*black arrows*) in the distal femora and proximal tibiae, corresponding with vague, ill-defined bone sclerosis on

conventional radiographs (not shown). Note minimal soft tissue edema or enhancement (**a–c**). Coronal proton density-weighted (**d**), coronal fat-saturated T2-weighted (**e**), and axial fat-saturated T1 post-gadolinium (**f**) images in the same patient 6 months prior demonstrate less extensive intramedullary abnormality (*white arrowheads*), but increased soft tissue and periosteal edema and contrast enhancement (*open arrowheads*), likely indicating progression of active disease to more senescent sclerosis on later exams

while conversely, there were no sites found to be normal by PET which were abnormal by other modalities. The low-dose CT component of the exam was useful in demonstrating bone sclerosis, while increased FDG uptake was present in areas of vague sclerosis (Figs. 3, 4). FDG uptake was diminished in one iliac lesion with dense sclerosis, but elevated in the periphery of the lesion, corresponding to edema and enhancement on a subsequent MRI.

Bone scan features

Bone scans were positive (focally increased radiotracer uptake) in all cases of bony sclerosis identified by other radiographic means and in two additional cases demonstrated uptake in the distal femora and proximal tibiae when plain radiographs were negative (20/20 bone sites total; Fig. 7). Three of our cases demonstrated abnormally increased, slightly asymmetric, focal radiotracer uptake in the distal femora and proximal tibiae with nearly identical appearances. A three-phase scan (dynamic blood flow, blood pool, and delayed images) was obtained in one patient, which showed increased radiotracer about the knees in all phases.

Discussion

Our series of patients exhibits many imaging findings of Schnitzler syndrome reported in previous case reports, including osteosclerosis, particularly in the distal femora, proximal tibiae, and iliac bones, as well as increased uptake in the same regions on bone scan [1, 7–10, 12]. In concordance with previous reviews, all of our patients were over the age of 40 at initial medical evaluation, and presented primarily with symptoms of skin rash, although some younger patients had symptoms beginning in their 30s. This series also characterizes different MRI findings ranging from dense bony sclerosis with marginal marrow edema to extensive bone marrow edema or infiltration with patchy intramedullary enhancement and periostitis.

Focal uptake within the distal femora and proximal tibiae, as could be termed the “hot knees” sign, has been reported multiple times previously in Schnitzler syndrome patients and was seen in five of our patients. This appearance has been considered “almost”, “nearly”, or “quasi-” pathognomonic for Erdheim-Chester disease in previous reports [13–16]. While both Erdheim-Chester and Schnitzler syndrome are rare diseases, we feel they should both be considered when encountering this sign (Fig. 8). Clinical or pathological history would

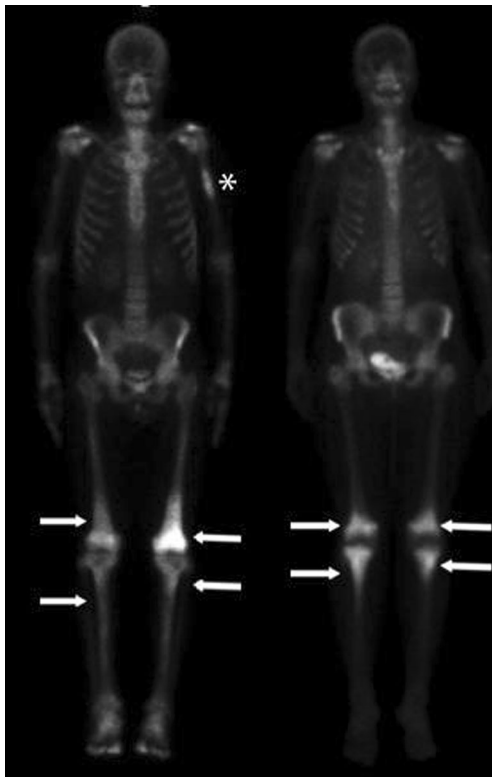


Fig. 7 Anterior projection technetium-99 m-MDP whole-body bone scans in a 61-year-old male (*left*) and 43-year-old female (*right*) with Schnitzler syndrome demonstrating intense abnormal radiotracer uptake in the distal femora and proximal tibiae (*arrows*). The patient on the right also has abnormal uptake in the distal tibiae and tali. Uptake in the proximal humerus on the patient on the left (*) corresponded with a typical-appearing enchondroma by conventional radiographs (not shown). MRI and bone scan of abnormal areas were universally concordant, while conventional radiographs were negative

likely differentiate the two in most cases [17]. This series is important because recognition of Schnitzler syndrome can lead to proper and efficacious therapy with an IL-1 antagonist (anakinra) and early appropriate hematologic monitoring for lymphoproliferative disease [3, 4, 18, 19].

Our results suggest positive imaging findings are present in the majority of patients with Schnitzler syndrome, a frequency in range with what has previously been reported [3]. While a prior case series described periostitis as a prominent feature, we did not observe periosteal reaction by plain radiography, only mature hyperostosis [1]. One could hypothesize that the majority of our cases were chronic and may have had more acute periosteal reactions at an earlier time. Serial MRIs of an affected knee in one of our patients support this theory with exuberant periostitis and surrounding soft tissue edema seen originally, followed by near-complete resolution of periosteal reaction, but with increased medullary abnormality 6 months later (Fig. 6). Finally, it has been reported that the epiphyses in long bones are usually spared, however, in our series, the intramedullary abnormality frequently extends into the

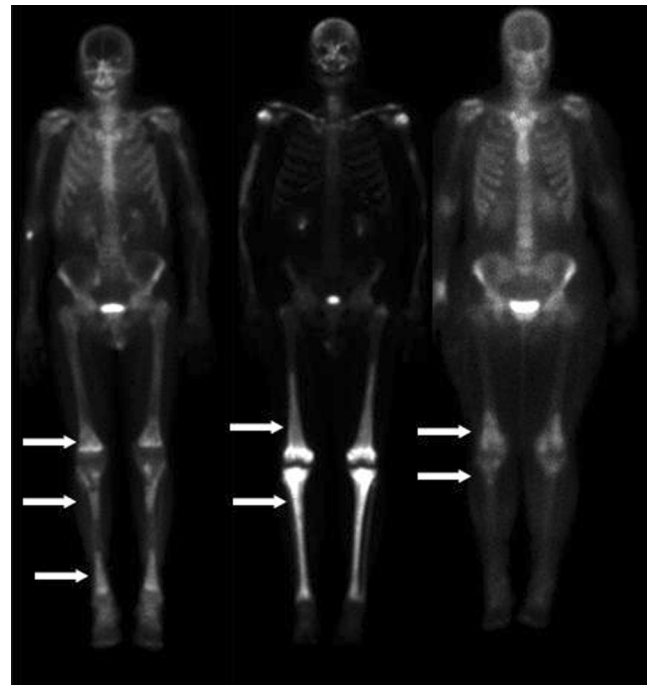
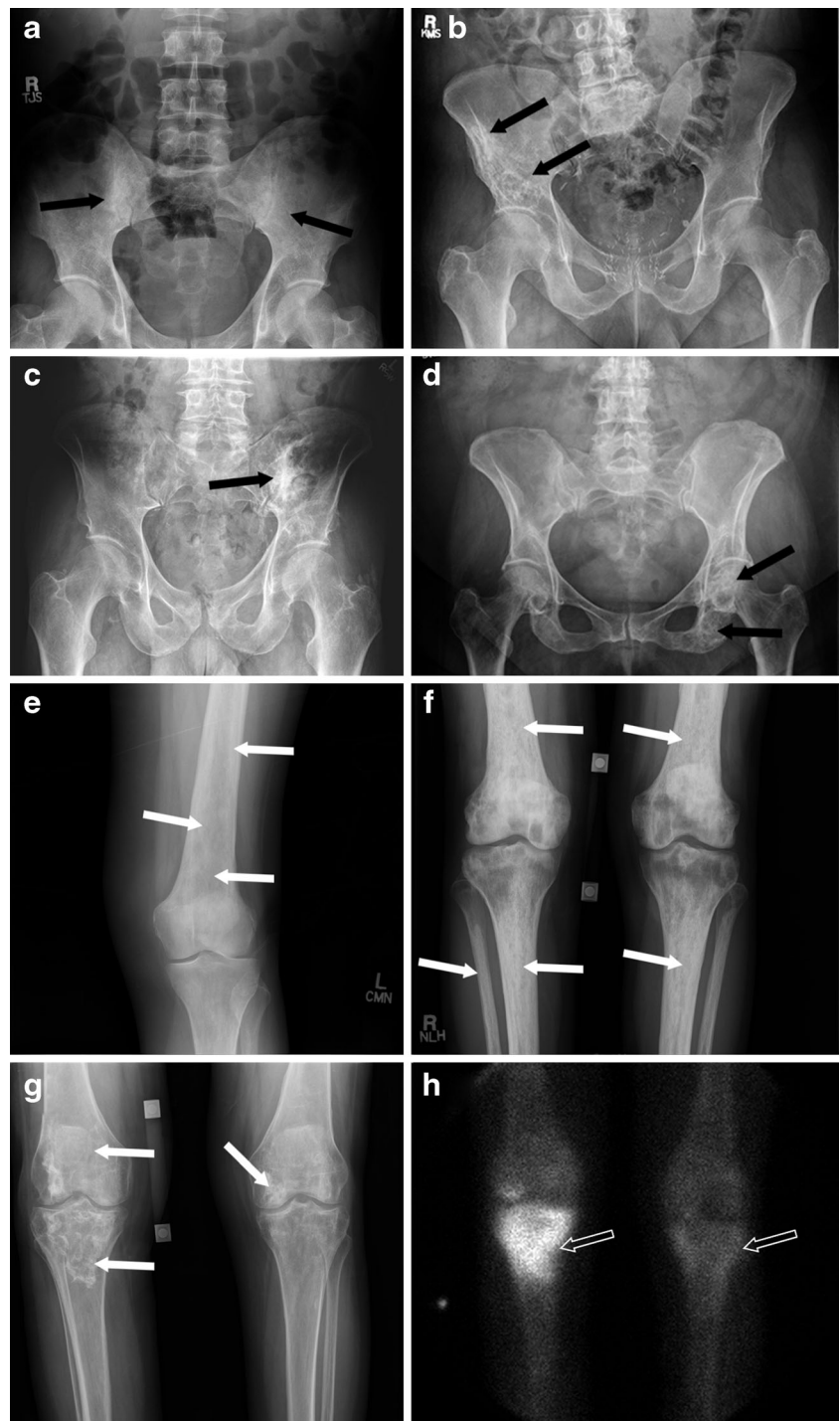


Fig. 8 Anterior projection technetium-99 m-MDP whole-body bone scans in three different patients with biopsy-proven Erdheim-Chester disease (ECD) demonstrating “classic” intense radiotracer uptake in the distal femora and proximal tibiae (*arrows*), reported to be nearly pathognomonic for ECD, but noted in the current study to be typical for Schnitzler syndrome as well

epiphyses, and we, therefore, do not think that this is an accurate or useful feature [8].

The imaging differential diagnosis for bony sclerosis is broad and non-specific. Because osteosclerosis represents a major criterion in POEMS syndrome, another syndrome involving bony findings and monoclonal gammopathy [19, 20], these patients often undergo skeletal surveys and we have seen a similar trend for suspected Schnitzler syndrome patients in our practice. The sclerotic lesions of POEMS, Schnitzler syndrome, Erdheim-Chester disease, or metastatic disease, in our opinion, can be indistinguishable (Fig. 9). Chronic recurrent multifocal osteomyelitis (CRMO) has also been suggested as an important entity in the differential diagnosis for Schnitzler syndrome given potentially similar clinical and imaging presentations, although CRMO typically occurs in younger patients (mean age of 10) [21, 22]. Many other disease processes such as mastocytosis, sclerotic myeloma, treated lymphoma, enchondroma, bone infarction, or post-radiation change could all have a similar appearance [23]. Furthermore, many of these processes (mastocytosis, bone infarctions, enchondroma, and Erdheim-Chester) occur in the same locations as the osteosclerosis of Schnitzler syndrome, and therefore interpretation in the absence of clinical history and laboratory results is not recommended. The presence of characteristic “arcs and rings” pattern on radiographs (enchondroma), linear/serpentine bone sclerosis (bone

Fig. 9 Osteosclerosis in the innominate bone and about the knees is a non-specific finding, not unique to Schnitzler syndrome. AP radiographs of the pelvis in four patients demonstrate ill-defined innominate bone sclerosis (*black arrows*) due to mastocytosis (**a**), treated lymphoma (**b**), POEMS syndrome (**c**), and metastatic breast cancer (**d**). Similarly, osteosclerosis in the distal femora and proximal tibiae (*white arrows*) can also be seen as in these three patients with mastocytosis (**e**), Erdheim-Chester disease (**f**), and bone infarctions (**g** and **h**). These entities can similarly all present with abnormal uptake on bone scan (*open arrows*) as in this patient with bone infarcts (**g** and **h**)



infarcts), or additional perivascular, intracranial, perinephric, or cardiac findings (Erdheim-Chester) would certainly help exclude Schnitzler syndrome from a differential diagnosis.

Schnitzler syndrome as currently understood is an idiopathic inflammatory condition, with systemic symptoms likely the result of cytokines and other acute phase reactants. Interleukin (IL) 1 β and IL-6 have been suspected given the highly effective treatment with the anti-IL-1 and anti-IL-6 therapy and the

known association of these interleukins with bone remodeling [24–26]. The exact cause of bony sclerosis is unclear, but a recent study showed high levels of osteoblastic factors bALP, osteocalcin, and osteoprotegerin without an increase in bone resorption factors CTX and sRANKL in 13 patients with Schnitzler syndrome [12]. This study also showed high levels of VEGF, which has been implicated in the osteosclerosis of POEMS [27]. In order to better understand the mechanisms

that lead to the patterns of bone abnormalities seen in Schnitzler syndrome and to afford more effective treatments, more research is clearly needed.

While patients with suspected or newly diagnosed Schnitzler syndrome often undergo skeletal surveys for detection of sclerotic bone lesions, our findings suggest a low yield with this approach, and that bone scan may be a more appropriate modality for initial screening given its high sensitivity in detecting bony abnormalities in these patients. We saw no cases that were positive by radiography, PET, or MRI that were “cold” on bone scan whereas there were cases with positive bone scans in the absence of corresponding plain film or CT findings. This suggests that Tc-99 m MDP nuclear scintigraphy may be the most sensitive and cost-effective test for Schnitzler lesions. This is supported by a report primarily on serum bone turnover factors that noted scintigraphic abnormalities in all 11 patients imaged (100 %) with only 4/13 (30.7 %) patients showing bone sclerosis on plain film [12]. The decision to pursue bone biopsy should be made on a case-by-case basis, but negative or non-specific results such as stromal fibrosis are to be expected in Schnitzler syndrome [18].

While 18 F FDG PET/CT remains the standard of care for initial evaluation and treatment follow-up in patients with lymphoma, the cost and sensitivity of PET/CT for initial evaluation in suspected Schnitzler syndrome may make it unwarranted. Others could argue, however, that PET/CT may eventually be valuable as a “one-stop shop” for the initial evaluation of these patients since it is able to assess FDG avidity, lymphadenopathy, and bony sclerosis with one exam, but screening these patients would require extending imaging range through the lower extremities, thus significantly prolonging scan times and reducing practice efficiency.

18 F NaF PET/CT may be an attractive option due to its higher spatial resolution and accuracy compared to Tc99m-MDP bone scintigraphy, as well as the added benefit of cross-sectional imaging fusion, but its potential as a screening tool in Schnitzler syndrome remains undefined as no cases have yet been reported to our knowledge [28]. Increased spatial resolution is likely to be less helpful for Schnitzler syndrome than for metastatic disease. High cost and limited reimbursement are additional obstacles [28]. Finally, whole-body MRI as a screening tool is another consideration. While we did not employ this technique in our cohort, our focused MRI results suggest it would likely be a sensitive and accurate option given the size and distribution of osseous Schnitzler syndrome abnormalities. However, in the light of the bone scan results, issues of economy once again may mitigate utility of whole-body MRI.

This study has several limitations, including its retrospective nature. Because Schnitzler syndrome is rare and likely under-recognized, our patient cohort is small. Additionally, Schnitzler syndrome may represent a spectrum of diseases and significant radiological findings may only be present in a

select subset of Schnitzler syndrome patients or disease phases. Repeat imaging was not available for most of our patients and correlation of physical complaints to specific imaging findings was sometimes not possible based on the available clinical notes alone. Because imaging approaches were individualized, our imaging modality cohort is heterogeneous, which precludes valid scientific assessment of true sensitivity and specificity of each modality.

One could hypothesize that perhaps bone scans may be the first study to show “positive” findings and osteosclerosis might only represent a late or senescent process. Continued investigation is warranted to fully understand both the etiology of the radiologic findings as well as the natural history of the disease and possible evolution of the associated imaging findings. Additionally, because Schnitzler syndrome is incompletely understood, there remains a distinction even within the Strasbourg criteria between “probable” and “definite” Schnitzler syndrome. Further elucidation of the pathogenesis of Schnitzler syndrome may refine clinical or pathological diagnostic criteria and some patients in our cohort may eventually be categorized differently.

We conclude that Schnitzler syndrome is a rare condition with potentially typical imaging findings in the majority of patients, which may assist with the diagnosis. These findings include osteosclerosis and bone scan, PET, and MR signal abnormalities about the knees and iliac bones. Though non-specific, when these findings are present with the clinical history of a chronic urticarial rash, the radiologist may be the first to suggest the diagnosis and direct appropriate treatment and follow up. In patients with known or suspected Schnitzler syndrome, bone scan may be the most appropriate tool to screen for osseous abnormalities as plain radiographs are insensitive.

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