Schnitzler's Syndrome – An Uncommon Radiological Manifestation

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ABSTRACT

Schnitzler´s syndrome is a rare acquired autoinflammatory disorder. Chronic urticarial rash and monoclonal gammopathy (mainly IgM, rarely IgG [1]) are essential components of the disease. Schnitzler´s syndrome can present itself with osseous lesions, often in the distal femur and proximal tibia or in the hip bones. We report a case with uncommon radiological manifestation.

CASE REPORT

INTRODUCTION

Schnitzler´s syndrome, named after a French dermatologist, is a rare acquired autoinflammatory disorder. Mostly adults are affected as the disease usually appears at the beginning of the 6th decade of life (i.e. around 51 years) [1]. A slight male predominance is observed [1]. To date, more than 300 cases are known [2]. Chronic urticarial rash and monoclonal gammopathy (mainly IgM, rarely IgG [1]) are essential components of Schnitzler´s syndrome. AA-amyloidosis and lymphoproliferative disorders (AL amyloidosis, lymphomas, IgM myeloma or Waldenström's disease) are considered complications of the disease [1,3]. Patients, suffering from Schnitzler´s syndrome, show a bone involvement in imaging in 30-40% [1] or even up to 64% [3] of cases. Niederhauser et al. retrospectively reviewed imaging characteristics of Schnitzler´s syndrome. Comparing the frequency of the distribution of bone abnormalities, the latter were located 1.) in the distal femur, 2.) in the proximal tibia, 3.) in the hip bone and 4.) in the vertebral bodies or the humerus [3]. As Schnitzler´s syndrome can present itself radiologically by a solitary sclerotic bone lesion [4], the radiologist has to take into consideration e.g. an osteoblastic metastasis as a differential diagnosis. We present a case, where sclerotic bone lesions initially led to the suspicion of osteoblastic metastasis of prostate cancer.

CASE REPORT

A 70-year-old male patient was referred to the University Medical Center Goettingen. Here, generalized erythematous, partial urticaria-like plaques and generalized hyperpigmented residuals were seen on physical examination. The patient denied pyrexia or arthralgia. The blood values showed no leukocytosis but an elevation of the C-reactive protein. New biopsies were taken. Histologically, a proliferation of neutrophil granulocytes in the upper third of the dermis was described, primarily compatible with a neutrophilic urticarial dermatosis (NUD). One biopsy could also be consistent with a Sweet´s syndrome, but in second line only. A computerized tomography (CT) scan was performed which showed a cervical and lumbar accentuated extensive sclerosis of the vertebrae (Figures 1,2) – a presentation which could be compatible with osteoblastic metastasis. As inguinal lymph nodes were enlarged and suspiciously configured as well, the radiologists recommended the exclusion of prostate cancer. In an out-patient facility no signs of prostate cancer could be found. A follow-up CT scan did not yield any significant changes. Further no splenomegaly or hepatomegaly was present. A referral to the department of hematology and oncology was arranged. During physical assessment lymphadenopathy was noticed. An IgM monoclonal gammopathy of unknown significance was diagnosed. The patient refused a biopsy of the lesion in the lumbar vertebrae, which would be interesting to definitely rule out other etiologies of sclerotic osseous lesions. By means of diagnosis by exclusion (prostate cancer) and interdisciplinary cooperation (dermatology, hematology/oncology and radiology) Schnitzler´s syndrome was diagnosed. Therefore, a therapy with an interleukin (IL)-1-antibody was suggested.

DISCUSSION

The Schnitzler´s syndrome is a rare acquired autoinflammatory disorder. Before establishing the diagnosis of Schnitzler´s syndrome, several diagnostic criteria have to be evaluated according to the Lipsker diagnostic criteria [1] or the Strasbourg diagnostic criteria [5,6] (see supplementary material, tables 1 -2). In a multicentric study performed by Gusdorf et al. both sets of criteria showed applicability for clinical practice [5]. In our case, the two major criteria (urticarial skin rash and monoclonal IgM component) and 2 minor criteria (palpable lymph nodes and abnormal findings on bone morphologic investigations) of

Schnitzler´s syndrome were detected (according to the Lipsker diagnostic criteria). Therapeutic options comprise steroids [7] or IL-1 inhibitors like anakinra, canakinumab or rilonacept [8]. Hence, an IL-1-antibody was suggested to our patient. As in our case hyperostosis (i.e. periosteal thickening or osteosclerosis) is a typical radiological finding in patients with Schnitzler´s syndrome [3, 9]. Lytic lesions are unusual [10]. In terms of the distal femora and the proximal tibiae the diametaphysis is affected [9]. Osteosclerosis in the os ilium often manifests itself in a "V" shape in the anterior-posterior view, since the osteosclerosis of the os ilium is located in the anterolateral bone and adjacent to the sacroiliac joint [3].

On magnetic resonance imaging (MRI) the bone marrow of the femoral diametaphysis and the diametaphysis of the tibiae present hypointensity on T1-weighted images and hyperintensity on T2-weighted images [3, 9]. On post intravenous gadolinium images contrast enhancement is observed [3]. A high signal intensity can be found on inversion recovery sequences [9, 10]. According to Niederhauser et al. (2014) alterations in the signal intensity of the bone marrow can be found during the course of the disease. Furthermore, soft tissue edema can emerge [3].

On scintigraphy an increased perfusion in the distal femur and the proximal tibia can be detected [3,9]. Additionally, in the blood pool phase an increased activity can be observed in the region of these bones [3, 9, 10]. During the delayed (or metabolic) phase on technetium scintigraphy an increased uptake of the tracer in the diametaphysis of the distal femora and the proximal tibiae becomes visible [3, 9, 10]. According to Alix et. al a 99^{m} Technetium scintigraphy may correlate with the disease activity, as opposed to ^{18}F fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) [11].

Comparing the frequency of the distribution of bone abnormalities, the latter are located 1.) in the distal femur, 2.) in the proximal tibia, 3.) in the hip bone and 4.) in the vertebral bodies or the humerus [3]. In the present case, the osseous lesions of the Schnitzler´s syndrome presented as osteosclerosis in the vertebral bodies. Hence at first, this manifestation led to the presumptive diagnosis of osteoblastic metastases e.g. in the context of prostate cancer. To conclude, this uncommon radiological appearance accentuates that radiologists should be aware of the rare differential diagnosis of the Schnitzler´s syndrome when confronted with osteosclerosis.

TEACHING POINT

Hyperostosis (i.e. periosteal thickening or osteosclerosis) is a typical radiological finding in patients with Schnitzler´s syndrome. Therefore, osteosclerosis in terms of Schnitzler´s syndrome can be misinterpreted as osteoblastic metastases.

QUESTIONS

Question 1: Which of the following describes the etiology and the epidemiology of Schnitzler´s syndrome best?

a) Schnitzler´s syndrome is a rare acquired autoinflammatory disorder. Mostly adults are affected. (applies)

b) Schnitzler´s syndrome is a rare acquired autoinflammatory disorder. Mostly children are affected.

c) Schnitzler´s syndrome is an infectious disease. Mostly adults are affected.

d) Schnitzler´s syndrome is an infectious disease. Mostly children are affected.

e) Schnitzler´s syndrome is an infectious disease. Mostly women are affected.

Explanation: Schnitzler´s syndrome is a rare acquired autoinflammatory disorder. Mostly adults are affected as the disease usually appears at the beginning of the 6th decade of life (i.e. around 51 years) [1].

Question 2: Which of the following aspects does not describe Schnitzler´s syndrome best?

a) Urticarial rash.

b) Monoclonal IgM component.

c) Fever.

d) Arthralgia or arthritis.

e) Aspergillus fumigatus in bronchial lavage. (applies)

Explanation: Schnitzler´s syndrome can be diagnosed according to the Lipsker or Strasbourg criteria. The finding of Aspergillus fumigatus in bronchial lavage does not belong to these criteria.

Question 3: Which bone is not affected by Schnitzler´s syndrome most likely?

a) Distal femur.

b) Proximal tibia.

c) Hip bone.

d) Vertebral bodies.

e) Distal Phalanges of the feet. (applies)

Explanation: Comparing the frequency of the distribution of bone abnormalities in patients with Schnitzler´s syndrome, the bone abnormalities were located 1.) in the distal femur, 2.) in the proximal tibia, 3.) in the hip bone and 4.) in the vertebral bodies or the humerus [3]. An affection of the distal phalanges of the feet is not likely.

Question 4: Which radiological aspect characterizes Schnitzler´s syndrome best?

a) Lytic lesions.

b) Periosteal thickening or osteosclerosis. (applies)

c) Hyperintensity on T1-weighted images.

d) Hypointensity on T2-weighted images.

e) Missing of contrast enhancement on post intravenous gadolinium.

Explanation: Hyperostosis (i.e. periosteal thickening or osteosclerosis) is a typical radiological finding in patients with Schnitzler´s syndrome [3,9]. Lytic lesions are unusual [10]. On magnetic resonance imaging the bone marrow of the femoral diametaphysis and the diametaphysis of the tibiae present hypointensity on T1-weighted images images and hyperintensity

on T2-weighted images [3,9]. On post intravenous gadolinium images contrast enhancement is observed [3].

Question 5: Which medication is most unlikely indicated in patients suffering from Schnitzler´s syndrome?

a) Steroids.
b) Gentamicin. (applies)
c) Anakinra.
d) Canakinumab.
e) Rilonacept.

Explanation: Schnitzler´s syndrome is a rare acquired autoinflammatory disorder. Therapeutic options comprise steroids [7] or IL-1 inhibitors like anakinra, canakinumab or rilonacept [8]. Antibiotics are not used in terms of treatment.

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Consent: The patient´s consent was obtained.

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FIGURES

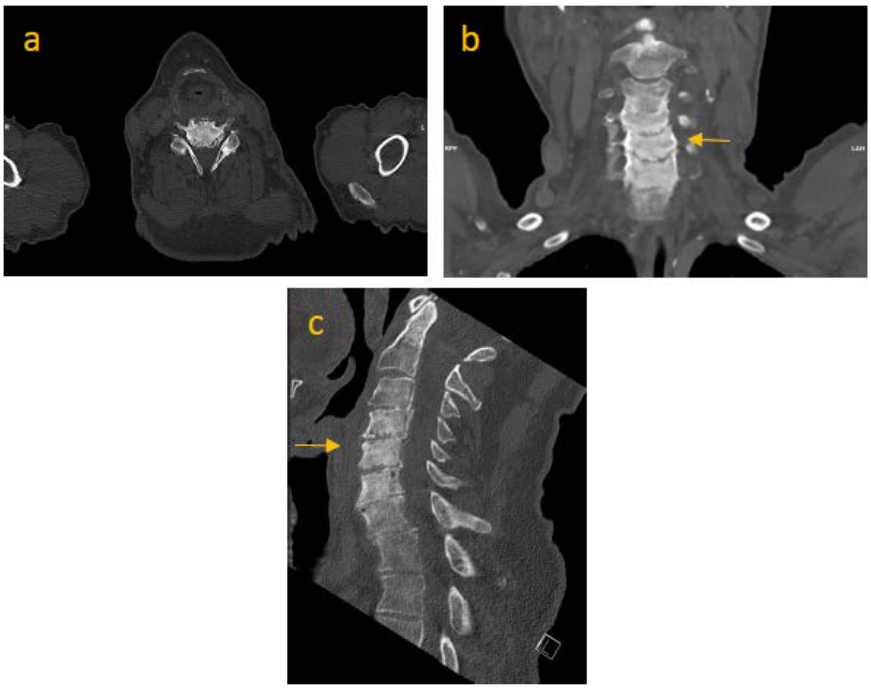

Figure 1: Computrized Tomography (CT) of vertebral column (a-c). Axial view at C5-level (a). Coronal view; C5 of the cervical spine is highlighted by an arrow. Saggital view; C5 of the cervical spine is highlighted by an arrow. Accentuated extensive sclerosis of cervical vertebrae is detected.

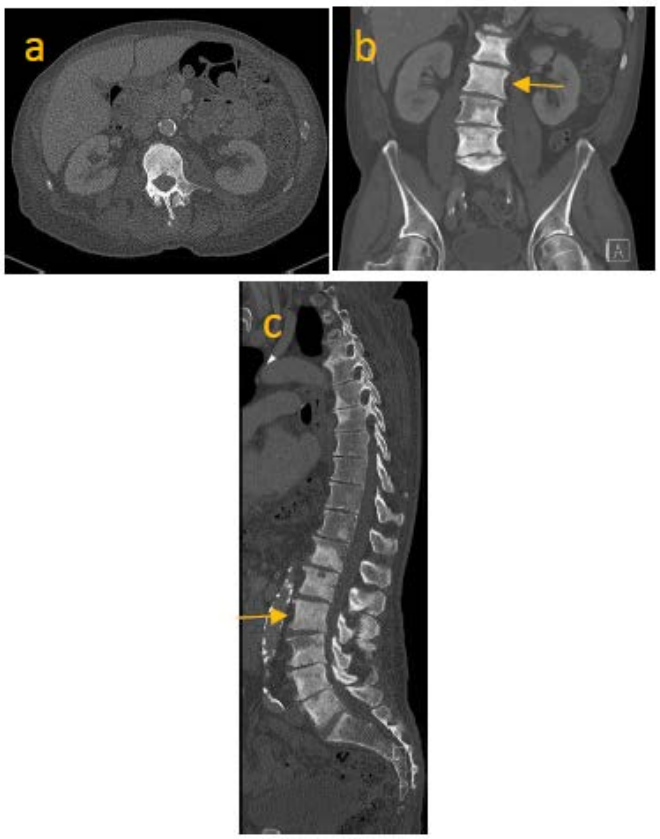

Figure 2: Computerized Tomography (CT) of vertebral column (a-c). Axial view at L2-level (a). Coronal view; L2 of the lumbar spine is highlighted by an arrow. Saggital view; L2 of the lumbar spine is highlighted by an arrow. Accentuated extensive sclerosis of lumbar vertebrae is detected.

Table 1: Diagnostic criteria of Schnitzler´s syndrome according to Lipsker ("the Lipsker diagnostic criteria") [1, 5]. If all other symptoms of Schnitzler´s syndrome are present apart from a major criterion, a Schnitzler-like syndrome is diagnosed [1].

Urticarial rash and monoclonal IgM component plus ≥ 2 of the following criteria:
- fever
- arthralgia or arthritis
- bone pain
- palpable lymph nodes
- liver or spleen enlargement
- elevated erythrocyte sedimentation rate
- leukocytosis
- abnormal findings on bone morphologic investigations

Table 2: Diagnostic criteria of Schnitzler´s syndrome according to an expert conference hold in Strasbourg ("the Strasbourg diagnostic criteria") [5,6].

obligate criteria - chronic urticarial rash and - monoclonal IgM or IgG
minor criteria - recurrent fever [1] - objective findings of abnormal bone remodeling with or without bone pain[2] - a neutrophilic dermal infiltrate on skin biopsy[3] - leukocytosis and/or elevated C-reactive protein[4]
definite diagnosis if - both obligate criteria plus at least 2 minor criteria if IgM - both obligate criteria plus at least 3 minor criteria if IgG
probable diagnosis if - both obligate criteria plus at least 1 minor criterion if IgM - both obligate criteria plus at least 2 minor criteria if IgG

[1]body temperature >38°C plus otherwise unexplained
[2]diagnosed by bone scintigraphy, magnetic resonance imaging or elevation of bone alkaline phosphatase
[3]usually consistent to neutrophilic urticarial dermatosis; absence of fibrinoid necrosis and significant dermal edema
[4]neutrophils >10 000/mm^3 and/or C-reactive protein >30 mg/l

KEYWORDS

Schnitzler´s syndrome; Osteoblastic metastasis; Prostate cancer; Sclerosis

ABBREVIATIONS

NUD = Neutrophilic Urticarial Dermatosis
CT = Computerized Tomography
MRI = Magnetic Resonance Imaging
PET/CT = Positron Emission Tomography/Computed Tomography

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