Rheumatol Int (2012) 32:1827–1829
DOI 10.1007/s00296-011-2020-x

SHORT COMMUNICATION

Adult-onset Still's disease and chronic recurrent multifocal osteomyelitis: a hitherto undescribed manifestation of autoinflammation

J. Rech · B. Manger · B. Lang · G. Schett · M. Wilhelm · J Birkmann

Received: 25 January 2011 / Accepted: 10 July 2011 / Published online: 19 July 2011

Abstract Still's disease and chronic recurrent multifocal osteomyelitis (CRMO) are febrile rheumatic diseases of unknown etiology, which predominantly affect children but can also have their initial manifestation in adults. Both can present as intermittent, relapsing episodes and are considered potential candidates within the expanding spectrum of autoinflammatory disorders, although no genetic abnormalities have been described for either of them. Here, we describe a man with an initial manifestation of abacterial multifocal osteitis at the age of 41. During a relapsing–remitting course of his illness, he increasingly developed symptoms of adult-onset Still's disease (AOSD), and the diagnosis was established according to the Yamaguchi criteria. When treated with anakinra, not only the acute symptoms disappeared promptly, but also the osteitis went into complete remission. This is to our knowledge the first description of a simultaneous occurrence of these two manifestations of autoinflammation in adulthood.

Keywords Adult-onset Still's syndrome · Chronic recurrent multifocal osteomyelitis · Anakinra

Adult-onset Still's disease (AOSD) and chronic recurrent multifocal osteomyelitis (CRMO) are inflammatory rheumatic syndromes of unknown origin. For both entities, similarities in pathogenetic mechanisms and clinical features with hereditary autoinflammatory syndromes have been postulated, but so far the occurrence of both disorders in a single patient has not been described [1, 2].

J. Rech (✉) · B. Manger · G. Schett
Department of Medicine 3, University Erlangen-Nuremberg, Krankenhausstr. 12, 91054 Erlangen, Germany
e-mail: juergen.rech@uk-erlangen.de

B. Lang
Rheumatology Practice, Nuremberg, Germany

M. Wilhelm · J Birkmann
Department of Medicine 5, Municipal Hospital, Nuremberg, Germany

Case report

In October 2003, a 41-year-old man with a positive family history for psoriasis developed low back pain and knee arthralgias in association with night sweats and fever up to 39.0°C. With local steroid injections and ibuprofen, febrile episodes and knee pain subsided, while the low back pain persisted.

During a period of increasing pain in 2005, scintigraphy revealed increased tracer uptake in both iliac bones, the right sacroiliac joint (Fig. 1a), right trochanter, both proximal tibiae (Fig. 1b), and right distal tibia (Fig. 1c). MRI confirmed an increased signal intensity of the right iliac bone adjacent to but not involving the sacroiliac joint. At that time, repeated CRP and ESR testing show mild to moderate elevations with maximal values of 13 mg/l and 54 mm/h, respectively. Ferritin was marginally increased with 374 µg/l. HLA-B 27 was negative.

Because of recurrent febrile episodes and night sweats, an iliac bone biopsy was performed to rule out lymphoma. Histology revealed a diffuse bone marrow infiltration with mainly CD3-positive T lymphocytes (Fig. 2a), with slightly more CD4- than CD8 positivity. Less than 10% of cells had the proliferation marker MIB-1 (Fig. 2b). In addition, bone marrow fibrosis and sparse infiltration with B lymphocytes (Fig. 2c) and plasma cells could be detected. Molecular analysis revealed polyclonality for rearrangements of the T-cell receptor gamma chain and immunoglobulin heavy chain.

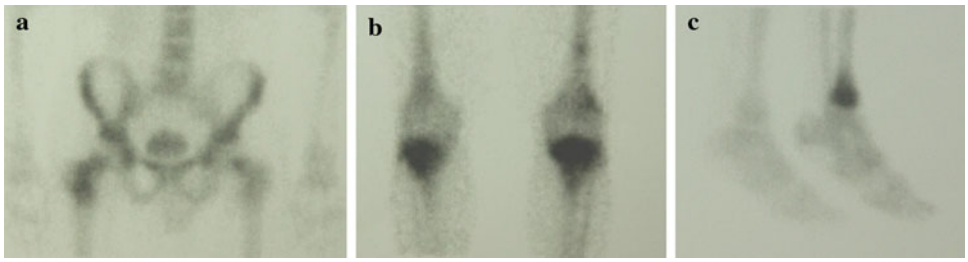

Fig. 1 3-phase bone scintigraphy showing increased tracer uptake in both iliac bones, the right sacroiliac joint (**a**), right trochanter, both proximal tibiae (**b**), and right distal tibia (**c**)

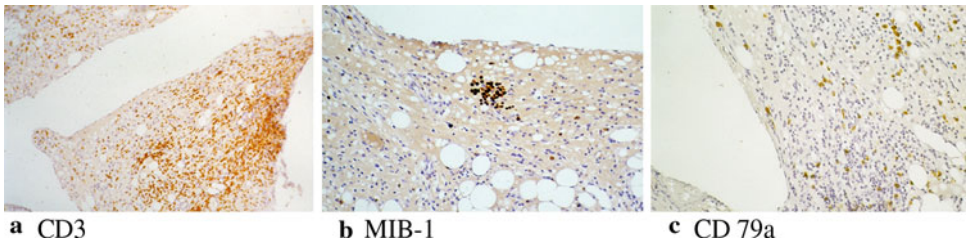

Fig. 2 **a** Histology of bone marrow biopsy showing diffuse bone marrow infiltration with mainly CD3-positive T lymphocytes, with slightly more CD4- than CD8 positivity. **b** Less than 10% of cells had the proliferation marker MIB-1. **c** Bone marrow fibrosis and sparse infiltration with B lymphocytes and plasma cells

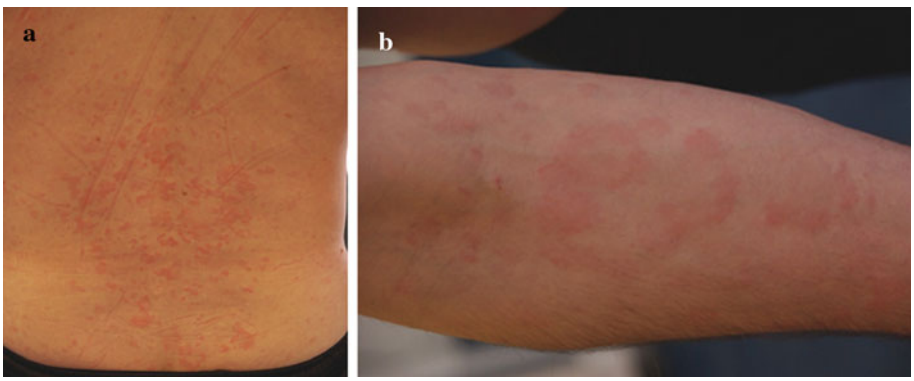

Fig. 3 Evanescent urticarial skin rash

Because of these findings, the provisional diagnosis of CRMO was made. In addition to symptomatic treatment, pamidronate was initiated, but episodes of bone pain and recurrent fever persisted. When the patient presented in November 2009, in addition, he complained about a sore throat, hoarseness, and an evanescent urticarial rash accompanying rises of the temperature usually in the evening (Fig. 3a, b). Abdominal sonography showed no hepatosplenomegaly but some moderately enlarged hepatic lymph nodes. ESR was >90 mm/h, CRP 11 mg/l, platelets 506 $\times$ 10^3/µl, ferritin 338 ng/ml, and IL-18 was highly elevated with 9292 pg/ml. All other laboratory tests including leukocytes, liver enzymes, antinuclear, and rheumatoid factors were normal. After exclusion of other infectious or neoplastic causes, the diagnosis of AOSD was made according to the criteria published by Yamaguchi et al., and therapy with the IL-1 receptor antagonist anakinra was started.

Within hours, fever and rash disappeared. Arthralgias subsided and inflammatory parameters normalized after about a week (CRP <5 mg/l, ferritin 97 ng/ml). A few weeks later IL18 (46 pg/ml) was also normalized. Therefore, the therapy was continued and the patient has been on 100 mg/day anakinra s.c. for 14 months now. A control examination after 10 months showed almost complete resolution of the inflammatory foci in bone scan (Fig. 4a, b, c) and MRI.

Discussion

CRMO a non-bacterial inflammatory disease of the bone predominantly affects children, but can also have its first presentation in adulthood. As in our patient, fever, bone, and joint pain usually are the initial symptoms. In adults, non-infectious multifocal osteitis is usually seen in the context of SAPHO syndrome together with palmoplantar pustulosis and frequently involves bones of the anterior chest wall. Our patient had a family history of psoriasis vulgaris, but he did not have any psoriatic skin lesions of palms, soles, or any other body area. No single therapy of CRMO

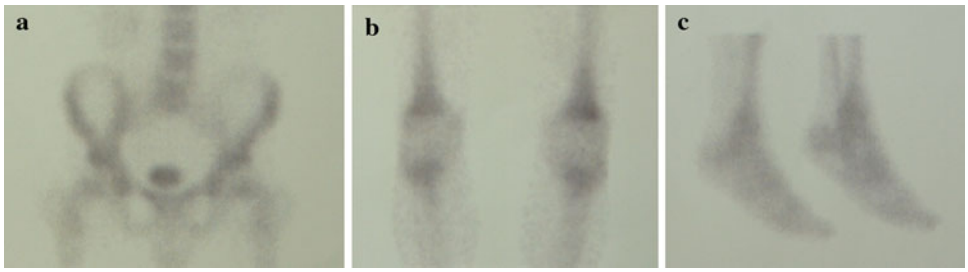

Fig. 4 3-phase bone scintigraphy after 10 months showing complete resolution of infammatory foci

has proven to be effective, but non-steroidal anti-inflammatory drugs and bisphosphonates are frequently used, occasionally also corticosteroids, sulfasalazine, or methotrexate. There exist several publications about successful therapies of CRMO or SAPHO syndrome with inhibitors of tumor necrosis factor (infliximab and etanercept), however only one case of a 6-year-old girl with CRMO, who had been treated with anakinra. Her symptoms resolved at week six, but there was no sustained response to treatment at 1-year follow-up [3].

In periodic fever syndromes with known genetic mutations, a sterile osteomyelitis usually is not the leading symptom. Only in two hereditary disorders with an early onset within the first 2 years of life, this is part of the clinical picture. One is Majeed syndrome, characterized by CRMO in association with microcytic dyserythropoietic anemia, an autosomal-recessive disorder caused by mutations in the *LPIN2* gene [2]. The other is the newly described deficiency of the IL-1 receptor antagonist gene (DIRA), presenting with severe skin and bone inflammation within the first months of life [4]. Recently, also one case of Muckle–Wells syndrome with osteitis, responsive to anakinra, in an 8-year-old girl has also been described [5]. Our patient, however, did not have any family history suggestive of a hereditary autoinflammatory disorder. Genetic testing did not reveal any mutations in genes responsible for cryopyrin-associated periodic syndromes, familial Mediterranean fever, hyper-IgD syndrome, or tumor necrosis factor receptor 1–associated periodic syndrome. One other periodic fever syndrome in adults can also be associated with lymphocytic bone infiltrations, i.e., Schnitzler's syndrome [6]. However, we did not find a monoclonal gammopathy in our patient at any time.

For AOSD, on the other hand, there is an enormous variety of inflammatory organ manifestations described in the literature [1]. However, to the best of our knowledge, there is no report of an abacterial osteitis or osteomyelitis in association with this disease. Not only does our case illustrate that AOSD and CRMO can be simultaneous presentations of autoinflammation, because the good response to anakinra suggests a major role of the inflammasome in the pathogenesis. This is also the first description of an excellent long-term response of the inflammatory bone lesions to an IL-1 blocking therapy.

Conflict of interest None.

References

1. Fautrel B (2008) Adult-onset still disease. Best Pract Res Clin Rheum 22:773–792
2. Ferguson PJ, El-Shanti HI (2007) Autoinflammatory bone disorders. Curr Opin Rheumatol 19:492–498
3. Eleftheriou D, Gerschman T, Sebire N, Woo P, Pilkington CA, Brogan PA (2010) Biologic therapy in refractory chronic non-bacterial osteomyelitis of childhood. Rheumatology 49:1505–1512
4. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A et al (2009) An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med 360:2426–2437
5. Klein AK, Horneff G (2010) Rückbildung der Schwerhörigkeit bei einer Patientin mit Muckle-Wells-Syndrom unter Therapie mit Anakinra. Klin Padiatr 222:266–268
6. De Koning HD, Bodar EJ, van der Meer JWM, Simon A (2007) Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. Semin Arthritis Rheum 37:137–148