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CASE REPORT

Chronic recurrent multifocal osteomyelitis with an atypical presentation in an adult man

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Abstract We present the case of a 33-year-old man with no significant medical history who developed right scapular pain, left-sided sacroiliac joint pain, and lower back pain, and was eventually diagnosed with chronic recurrent multifocal osteomyelitis (CRMO). Imaging demonstrated multiple scattered T2-hyperintense lesions on MRI at the spine and the left SI joint, some of which progressed and one regressed in size on follow-up. Histopathology demonstrated only non-specific chronic inflammation compatible with CRMO. No evidence of infectious organisms or neoplastic processes was found. The pain was relapsing and remitting in nature. Laboratory investigations were notable for no evidence of hematologic malignancy or infection, but only a mild increase in alkaline phosphatase. This case highlights that CRMO, despite being thought of as a childhood-onset disease, can present in adults as well, and also provides illustrative examples of imaging and histological findings.

Keywords Chronic recurrent multifocal osteomyelitis · Multiple bone lesions

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Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an idiopathic inflammatory skeletal disorder that manifests as recurrent painful exacerbations and remissions related to multiple foci of aseptic osteomyelitis [1]. First described in 1972 in four children as "subacute and chronic recurrent osteomyelitis", it is a rare disease with an estimated prevalence less than 1 in 1,000,000 and affects primarily children with a female predominance [2–4]. CRMO is associated with several autoimmune conditions such as psoriasis, sacroiliitis, and Crohn's disease [1]. There is likely also a genetic component, with a susceptibility locus found at 18q21.3–22 in a family-based association study [5].

Here, we describe the case of a 33-year-old man who initially presented with right scapular pain and left-sided sacroiliac joint pain; he was eventually diagnosed with CRMO after extensive evaluation. Because CRMO has no specific clinical, laboratory, imaging, or pathological findings, the diagnosis is difficult to make and as a diagnosis of exclusion the true prevalence is likely underestimated [6]. Knowledge of this unusual case of CRMO in an adult man and its illustrative imaging findings may help skeletal radiologists maintain a high index of suspicion and be the first to suggest this diagnosis.

Case report

Initial clinical presentation

A 33-year-old man with no significant medical history developed sharp right scapular pain while running for exercise. Although he was an experienced long-distance runner, the pain forced the patient to significantly curtail his exercise. A radiograph was negative for fractures or bony abnormalities,

Table 1 Table of laboratory values at initial presentation and at follow-up visits

	Ref. range	Initial presentation	3-month follow-up	6-month follow-up	8-month follow-up	10-month follow-up
WBC count (10^9/l)	3.4–10	5.9	6.4	5.1	4.9	
Hematocrit (%)	41–53	44.4	45.5	44.4	43.2	
Calcium (mg/dl)	8.8–10.3	9.3	9.9	9.3	10.0	9.2
Phosphorus (mg/dl)	2.6–4.9	4.0		3.7	3.5	3.1
Alkaline phosphatase (U/l)	31–95	165	136	119	116	106
Erythrocyte sedimentation rate (mm/h)	0–10	13		10	6	

and the pain resolved over time with chiropractic therapy and massage. However, 2 months later, he presented to the clinic with rapidly progressive left-sided sacroiliac joint pain exacerbated by activity. He denied any numbness, weakness, tingling, and bowel or bladder dysfunction. He experienced marked impairment and required a cane to walk.

On physical examination, he experienced pain in the left greater trochanter on palpation. Initial evaluation including electrolytes, coagulation panel, liver enzymes, immunoglobulin levels, serum electrophoresis, ANA and anti-dsDNA antibody levels were unremarkable, except for an elevated alkaline phosphatase and a mildly elevated ESR (Table 1). An MRI of the lumbar spine and pelvis was performed on initial presentation at our institution to rule out a sacral insufficiency fracture and nerve root impingement. It did not show either, and showed no significant abnormalities at the L-spine, but demonstrated extensive infiltrative abnormal signal involving the left iliac bone and SI-joint (Fig. 1), which was concerning for an infiltrative malignant process, such as lymphoma, or infection such as osteomyelitis, necessitating a CT-guided biopsy. A CT-guided biopsy of this left iliac lesion (Fig. 2) showed only a non-specific fibro-inflammatory infiltrate and normal hematopoietic marrow (Fig. 3a) and flow cytometric analysis showed no evidence of a hematologic malignancy. The pain, thought to be due to a sacral insufficiency fracture that was clandestine on the MRI, eventually resolved over the next 3 weeks.

Subsequent imaging, pathology, and laboratory findings

The pain returned a month later in the upper cervical spine, lower thoracic spine, and left sacroiliac joint. A thoracic spine MRI and DXA scan was thus obtained. The MRI showed nonspecific diffuse low to intermediate T1 marrow signal intensity and scattered T2 hyperintense lesions involving multiple vertebral bodies, which raised concern again for an infiltrative malignant process (Fig. 4a), suggesting lymphoma in the differential. The DXA of the lumbar spine showed bone mineral density below the expected range for age with a z-score of −2.5, but bone mineral density in the femur and forearm were within normal limits. 25-hydroxy vitamin D levels were found to be low, so vitamin D supplementation was initiated.

Since the pain persisted, a PET/CT scan was performed a month later to further investigate the possibility of malignancy. It showed only mild uptake in the thoracic spine, mild uptake in the left sacroiliac joint, and widening of the left sacroiliac joint (Fig. 5). The pain continued to progress over the next 5 months and was intermittently more severe, but moderately well controlled on 100 mg of celecoxib twice daily. During this time, a repeat MRI and bone survey showed similar findings (Fig. 4b).

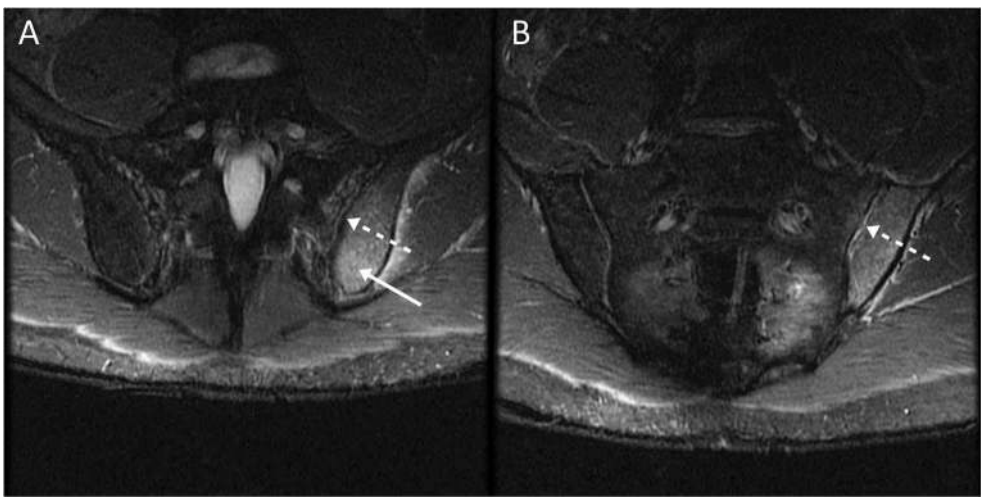

Fig. 1 Oblique coronal fat-saturated T2 (**a**) and fat-saturated T1-weighted Gd-enhanced (**b**) MR images of the SI-joints at initial presentation. Note the bone marrow edema pattern (*solid arrow*) and increased signal and contrast enhancement of the left SI-joint (*dashed arrows*)

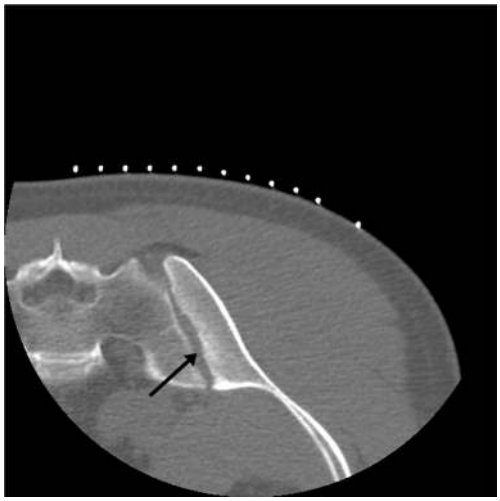

Fig. 2 CT of the left SI-joint obtained during CT-guided biopsy demonstrating erosive changes of the joint (*arrow*)

A whole-body bone scan using Tc-99 m HDP also demonstrated a non-specific focus of radiotracer activity at the right sternoclavicular joint and the left rib, and asymmetric uptake at the level of the sacroiliac joints, more prominent on the left side (Fig. 6). Bilateral iliac crest bone marrow biopsies demonstrated normocellular marrow with tri-lineage hematopoiesis and no evidence of a lymphoproliferative disorder (Fig. 3b).

An open biopsy of the vertebral bodies of T6 and T8 was subsequently performed with intraoperative fluoroscopy, for DNA sampling and to rule out infectious disease. These biopsies, which were reviewed by experts in bone pathology, hematopathology, and dermatopathology, showed similar findings of intertrabecular fibroinflammatory infiltrate and cellular marrow (Fig. 3c). Furthermore, immunohistochemistry on histologic sections of the bone marrow biopsies was consistently negative for T-cell, B-cell, myeloid and plasma cell neoplasms as well as Hodgkin lymphoma, Langerhans histiocytosis and mastocytosis. Karyotype analysis of biopsies from both the left iliac crest and T6 and T8 vertebral bodies were also normal. Extensive evaluation for an infectious etiology was undertaken, including histochemical stains, microbiologic cultures, HIV serology, RPR, and PPD, which were all negative. Universal PCR on the biopsy tissue for fungi, bacteria, and mycobacteria were all negative as well. As none of the biopsies had a significant number of foam cells, the histopathology was not considered to be consistent with Rosai–Dorfman or Erdheim–Chester disease, the latter especially unlikely without a symmetric distribution of radiographic lesions. At this point, with an extensive negative workup for infectious and neoplastic conditions, the diagnosis of CRMO was considered most likely.

Clinical management and course

The patient's clinical course including multiple biopsies of the lesions seen on imaging was notable for multiple negative

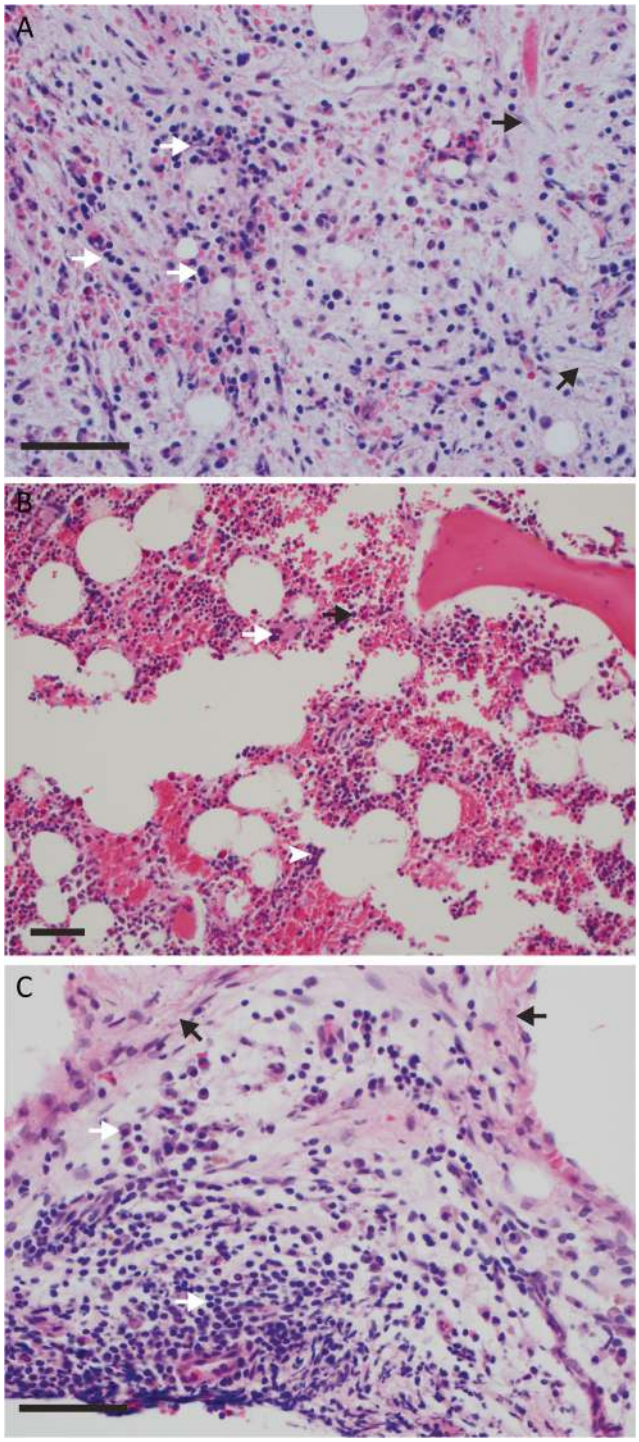

Fig. 3 Representative histopathology. Initial bone biopsy from pelvis demonstrated a nonspecific fibro-inflammatory infiltrate composed of scattered chronic inflammatory cells including lymphocytes and plasma cells (*white arrows*), in a loose fibrous stroma (*black arrows*) (**a**). Bone marrow biopsies consistently showed cellular marrow with normal trilineage hematopoiesis (myeloid, *white arrow*; erythroid, *arrowhead*; lymphoid, *black arrow*) (**b**). A repeat bone biopsy from the T6 vertebral body again showed a fibro-inflammatory infiltrate composed of chronic inflammatory cells (*white arrows*), in a loose fibrous stroma (*black arrows*) (**c**). *Scale bar*=100 μm

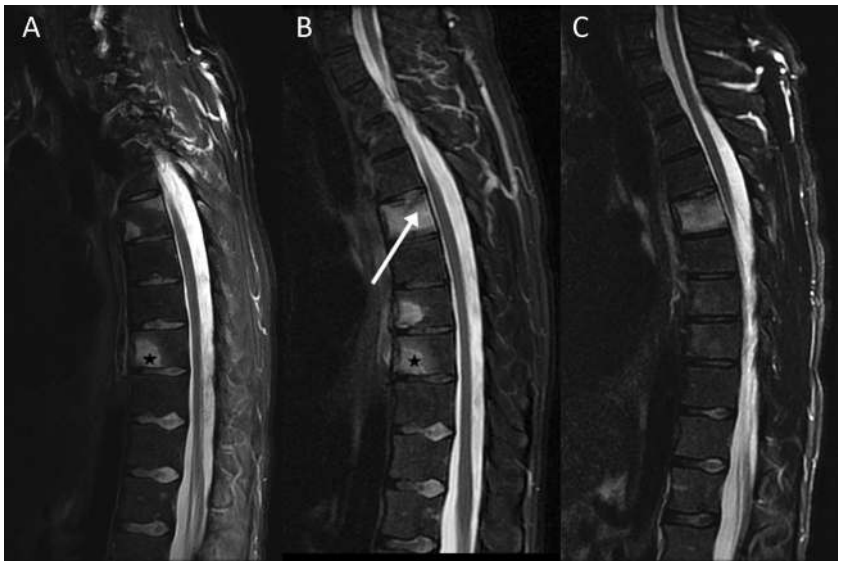

Fig. 4 Fat-saturated T2-weighted sagittal MR image of the thoracic spine performed 3 months after initial presentation (**a**). Fat-saturated T2-weighted sagittal MR image of the thoracic spine 8 months after initial presentation (**b**). There is a new end plate fracture (*white arrow*), and one of the lesions is smaller (*star*) while others demonstrate progression. Fat-saturated T2-weighted sagittal MR image 3 months after initiation of bisphosphonates (**c**) demonstrates decreased conspicuity of lesions

evaluations for malignancy or infection. However, the progressive nature of the imaging and the waxing-and-waning nature of the pain strongly suggested CRMO as the diagnosis. Although the patient did not have significant relief while on celecoxib, there were reports of CRMO being responsive to bisphosphonates [7]. The patient was empirically started on a 2-week course of 40 mg of alendronate daily, while continuing calcium and vitamin D supplementation for both CRMO and decreased bone mineral density. The patient tolerated bisphosphonates well with no significant side effects and the dose was decreased to 70 mg alendronate weekly. His pain subsided over time, with a very mild decrease in alkaline phosphatase levels. A follow-up MRI of the thoracic spine was performed after the initiation of bisphosphonate treatment about 3 months after the prior MRI and showed decreased conspicuity of all lesions (Fig. 4c), lending support to the diagnosis.

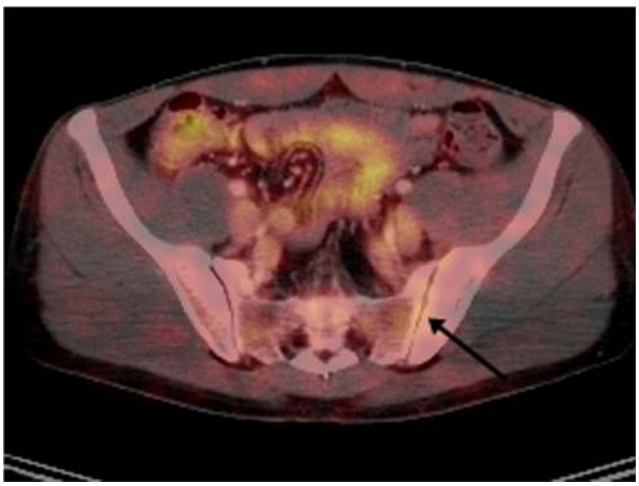

Fig. 5 Axial PET/CT image at the level of the sacroiliac joints. There is widening of the sacroiliac joint and mild uptake (*solid arrow*) seen on the left correlating with the patient's symptoms

Discussion

CRMO typically presents with non-specific musculoskeletal complaints such as pain, tenderness, swelling, or limited range of motion. This pain tends to predominate in the metaphyses and epiphyses of long bones, the most common being the distal tibia, proximal tibia, pelvis, proximal femur, clavicle, and calcaneus [1]. Involvement of the clavicle is characteristic because it is a site that is seldom affected by hematogenous osteomyelitis. The spinal involvement seen in this patient is rare, and in a review of 35 cases of 157 lesions, only 3 % were present in vertebral bodies [8]. However, initial presentation with isolated vertebra plana or other primary spinal involvement has been previously described in children, although not in adults [9]. Systemic symptoms, although possible, are not common. Upon whole-body imaging, other asymptomatic sites of disease can often be identified. CRMO is also associated with the presence of cutaneous lesions, with a prevalence about 25 % in children [10]. The differential diagnosis includes subacute and chronic infectious osteomyelitis, histiocytosis, hypophosphatasia, and infiltrative malignancies such as leukemia, lymphoma, and Ewing's sarcoma in children [11].

CRMO is regarded by some to be part of a spectrum of disease with SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome, whereas others consider it to be a separate clinical entity [12, 13]. Some consider CRMO to be the pediatric presentation of SAPHO syndrome, which generally affects adults, although as in this case, CRMO-like presentations can occur in adults. Presentations of CRMO in adults, as with children, occur more commonly in women [14, 15]. These patients are often febrile, and while their complaints are usually

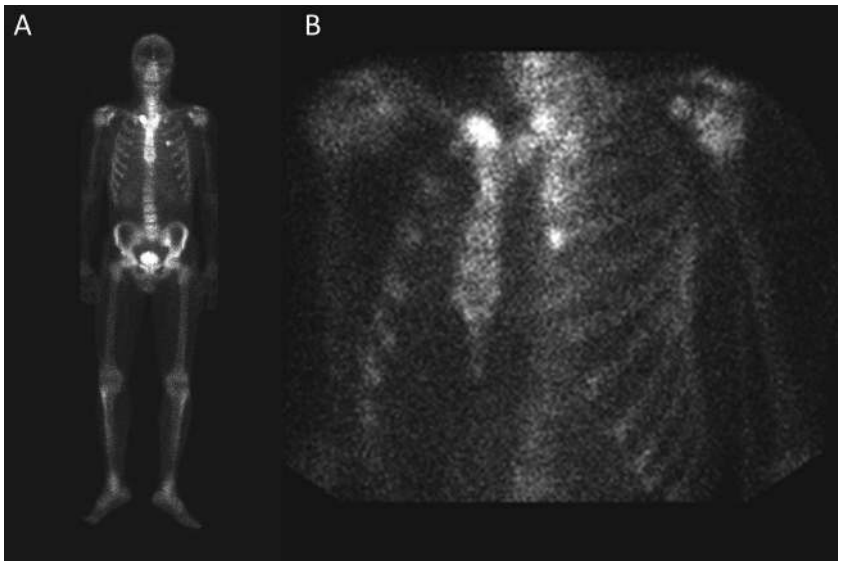

Fig. 6 Whole-body Tc-99 m HDP bone scan demonstrates greater uptake on the left than right in the sacroiliac joints (**a**) and foci of radiotracer activity at the right sternoclavicular joint and left third rib (**b**)

focused on a specific site, imaging reveals other sites of disease involvement that are typically asymptomatic [14–16]. In one other case of CRMO in an adult man, he subsequently developed adult-onset Still's disease and was successfully treated with anakinra [16]. CRMO and SAPHO share numerous characteristics such as osteitis, and unifocal or multifocal presentation, and pustulosis in a generally healthy individual [17]. However, CRMO usually affects the extremities, whereas SAPHO presents in the axial skeleton, classically the anterior chest wall. Given that the patient had no typical skin findings and no typical involvement of the sterno-clavicular joints, the diagnosis of CRMO was favored.

Because of the suggestive but non-specific imaging findings, histological analysis from biopsies of the affected lesions is often required to exclude infectious osteomyelitis and infiltrative neoplastic processes such as lymphoma, leukemia, or Langerhans cell histiocytosis. However, the use of a clinical chronic non-bacterial osteitis score may avoid biopsies in 25 % of cases [18, 19]. Histologically, CRMO begins as an acute inflammatory process with a predominance of polymorphonuclear lymphocytes, and at later stages, feature predominantly lymphocytes in the inflammatory infiltrates [20]. These findings are non-specific and may be seen in a variety of inflammatory and neoplastic conditions affecting bone and marrow. Therefore, the role of histopathology is to exclude infection or neoplasms that can be more definitively classified. During acute attacks, about two-thirds of patients develop moderate increases in the systemic inflammatory markers, although this was not clearly demonstrated in this patient [6]. The non-infectious nature of CRMO is supported by the fact that antibiotics do not alter the course of the disease [3]. If CRMO is suspected, whole-body imaging evaluation can also be performed to identify clinically occult sites of disease and lend additional support for the diagnosis [21, 22].

Nonsteroidal anti-inflammatory drugs are first-line therapy and usually effective with a response rate up to 80 % [10]. Other possible pharmacologic treatments include bisphosphonates, sulfasalazine, methotrexate, colchicine, interferons, and gamma globulins [23]. Oral glucocorticoids are likely to be effective as well, but should be used sparingly given the adverse long-term side effects, especially in children and adolescents [24].

This patient experienced significant decrease in pain and decreased conspicuity of his MR-visible lesions after the initiation of bisphosphonates, although it is possible that this could also be attributed to the natural history of the disease or a decrease in physical activity levels in light of his prior history. The disease course is unpredictable, and although long-term outcomes for children appear generally good, it is not a benign condition, and 25 % of patients will have long-term sequelae such as noticeable skeletal deformities [3, 19, 25].

This case demonstrates that CRMO can present in adult men, who are generally not thought to be at high risk for the disease. CRMO has actually been described in adults as old as 55 years old, although mostly in women [26]. Although considered to be a rare disorder, CRMO is likely underdiagnosed as it has no specific clinical, laboratory, imaging, or pathological findings. As such, the diagnosis requires a high index of suspicion and a team effort from the clinician, orthopedic surgeon, radiologist, and pathologist. It is important for skeletal radiologists to become familiar with the varied imaging findings of CRMO, as imaging plays a vital role in the workup of this condition and they will be often the first to suggest the diagnosis [26].

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Conflict of interest The authors declare that they have no conflicts of interest to declare.

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