

## Ten-year review of Danish children with chronic non-bacterial osteitis

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### Abstract

#### Objective

To compare clinical characteristics of children with chronic non-infectious osteomyelitis (CNO) with either mono- or multifocal bone lesions, and to report potential advantages of using whole-body MRI.

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#### Methods

A retrospective evaluation of 31 children (19 girls, 12 boys) diagnosed with CNO between 2001 and 2011. CNO was diagnosed as mono-, or multifocal inflammatory bone lesions (osteomyelitis, osteitis, osteosclerosis), duration of complaints more than 6 weeks and exclusion of infection and malignancy. Clinical and radiological data were registered. The definition of mono- or multifocality was based on the description of imaging results.

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#### Results

Mean age at disease onset was  $10.3 \pm 2.6$  years. Mean duration of active disease was  $44.4 \pm 25.6$  months. Twenty-two (71.0%) had two or more bone lesions and 9 (29.0%) had one lesion. Of those with multifocal lesions six were initially detected as monofocal. The most frequent location of the bone lesions was in the metaphysis of the lower extremities. MRI/CT discovered most lesions compared to x-ray and scintigraphy. MRI was performed in 93.5% of which 25.8% had a whole-body-MRI. Whole-body MRI revealed disclosure of several silent lesions. Extra-osseous involvement occurred in 64.5%. In the multifocal group 22.7% had psoriasis and 13.6% had pustulosis palmoplantaris but neither was seen in the monofocal group. All were treated with NSAIDs; 54.8% corticosteroids, 29.1% methotrexate, 9.7% pamidronate and 3.2% infliximab.

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#### Conclusion

Monofocal CNO had comparable clinical and radiological characteristics to multifocal disease. We conclude that whole-body MRI is a relevant screening instrument for the diagnosis of CNO.

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#### Key words

chronic recurrent multifocal osteomyelitis, non-bacterial osteitis, MRI, autoinflammation, children

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## Introduction

Chronic non-bacterial osteomyelitis (CNO) is a non-infectious inflammatory bone disease of unknown etiology that predominantly affects children and young adults. It is characterised by mono- or multifocal inflammatory bone lesions with swelling and pain and has an unpredictable course of exacerbations and spontaneous resolution (1). In cases with multifocal osteomyelitis the term chronic recurrent multifocal osteomyelitis (CRMO) is preferably used (2). Sometimes fever is observed and often acute phase reactants are elevated (3, 4). The mean age at onset is 9-11 years (4-6) and girls are affected more often than boys (4, 7).

CNO is frequently associated with non-skeletal inflammatory conditions such as psoriasis, pustulosis palmoplantaris, inflammatory bowel disease, acne, arthritis or pyoderma gangraenosum (2, 4, 5). Recent genetic and immunologic discoveries demonstrate involvement of the innate immune system (8). The bone lesions are typically located at the metaphyses of tubular long bones, but they can occur at other sites such as the mandible, sternum, clavicle, and vertebrae (2, 4, 9, 10). The typical radiological appearances are lytic lesions with progressive sclerosis and hyperostosis over time. During the active phase MRI shows bone marrow oedema which is a non-specific finding (11). Whole-body imaging can demonstrate clinically occult sites of lesions and can be demonstrated by whole-body MRI or bone scintigraphy after technetium injection (1). The histopathological findings are non-specific, they show a predominance of polymorphonuclear leucocytes in the early stages, and later reveal a predominance of lymphocytes and possibly granulomatous foci and reactive formation of new bone (12).

Diagnosis is based on a combination of clinical, radiological, and histopathological findings. The radiographic appearance and histopathological findings may suspect subacute or chronic osteomyelitis. Bacterial cultures are negative and laboratory findings are nonspecific (10). There is no diagnostic test for CNO and it must be excluded from other differential diagnoses like

bacterial osteomyelitis, tumours, lymphomas, and Langerhans's cell histiocytosis (13).

The disease was first reported by Giedion *et al.* in 1972 under the name "subacute and chronic recurrent osteomyelitis" (14). The term CRMO was first used by Probst and colleagues in 1976 (1, 15). Jansson *et al.* (2) proposed diagnostic criteria for non-bacterial osteitis dividing them in acute and chronic osteitis depending of the clinical complaints lasting less or longer than six months, respectively. Although other studies have used the Jansson criteria (19, 20) the criteria have not been validated and a consensus for the classification and the diagnostic criteria of CNO have not been reached. It is still discussed whether either unifocal or multifocal non-bacterial osteomyelitis should be regarded as one clinical disease entity (2, 12).

In a retrospective study from a single centre we collected patients with chronic recurrent osteomyelitis with the aim to compare mono- and multifocal recurrent osteomyelitis in relation to clinical characteristics, imaging and laboratory test results and extra-osseous manifestations.

## Patients and methods

We conducted a retrospective evaluation of children, under the age of sixteen, diagnosed with CRMO at the Department of Paediatrics, Aarhus University Hospital Skejby, between January 1, 2001 and June 31, 2011. We found the patients by searching the database with the key word chronic recurrent multifocal osteomyelitis (CRMO) and the ICD-code M86.3. The clinical criteria for including patients in this study were mono-, oligo- or multifocal inflammatory bone lesions (osteomyelitis, osteitis, osteosclerosis) occurring before the age of 16 years, duration of complaints more than 6 weeks and exclusion of infection and malignancy. In total, we found 35 children of which four were excluded: Two brothers with Majeeed syndrome, one girl with osteomyelitis in the third metatarsal bone lasting only 3 weeks and with a spontaneous healing, and one girl, whose diagnosis was changed to

Competing interests: none declared.

**Table I.** Demographic data of 31 children with chronic non-bacterial osteomyelitis (CNO).

	1 lesion	≥2 lesions	Girls	Boys	All
Number	9 (29%)	22 (71%)	19 (61.3%)	12 (38.7%)	31 (100%)
Age at onset (years)	10.9 ± 1.9	10.1 ± 3.0	9.8 ± 2.8	11.1 ± 2.3	10.3 ± 2.6
Age at diagnosis (years)	12.0 ± 1.8	11.7 ± 2.7	11.6 ± 2.6	12.0 ± 2.4	11.8 ± 2.5
Diagnostic delay (months)	13.2 ± 16.2	19.0 ± 15.4	21.2 ± 16.9	11.1 ± 11.5	17.3 ± 15.3
Duration of active disease (months)*	50.9 ± 21.6	42.8 ± 24.7	48.7 ± 23.3	38.7 ± 28.5	44.4 ± 25.6

Values are mean ± SD. \*: n=28.

JIA after almost two years. The cohort included 19 girls and 12 boys with a mean age of 10.3±2.6 years at disease onset (Table I).

Clinical, biochemical and demographic data as well as results from bone biopsies and imaging studies (radiographs, CT, MRI and bone Tc99-scintigraphy) were collected.

In twenty-two children bone biopsy was performed, of which four had two biopsies and one three. Repeated biopsies were made when no conclusion was drawn on the first. The patient who underwent three biopsies was at first suspected for osteosarcoma until a re-assessment and further confirmation changed the diagnosis to CNO, showing predominantly chronic inflammation. All biopsies revealed negative bacterial cultures. Chronic inflammation was most prevalently observed. The MR scans were performed with a 1.5 Tesla scanner using T1- and short tau inversion recovery (STIR)/T2-fat-saturated sequences. In eight patients whole-body MRI was performed using coronary T1 and STIR sequences.

**Results**

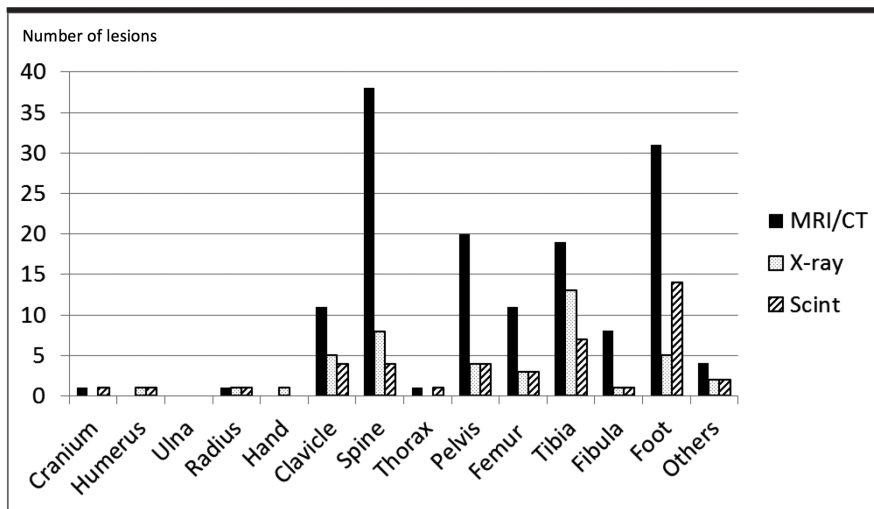
*Clinical characteristics*

Local pain of the bone was the most predominant symptom. Mean age at time of diagnosis was 11.8±2.5 years. All children were Caucasians, born and raised in Denmark. No affected family members with CNO were observed in the group. Comorbidity was observed in two: one with Lane-Hamilton syndrome (idiopathic pulmonary haemsiderosis with coeliac disease) and one with reflex sympathetic dystrophy. We found no etiology of any other inflammatory diseases. Mean duration of active disease was 44.4±25.6 months (Table I). Follow-up time was 55.8±35.3

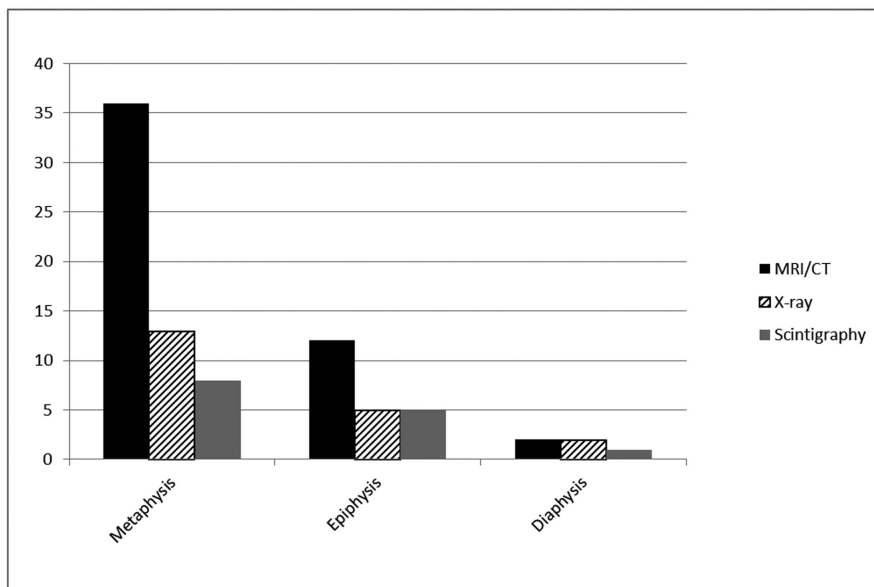
months. Twenty-three children with active CNO were still followed at our centre and one was followed by the adult rheumatologists. Four patients

were no longer followed due to remission. Three were lost to follow-up after referral to an adult centre.

The mean time from presentation of



**Fig. 1.** Anatomical distribution of osteomyelitic lesions in children with CRMO (n=31) detected by different imaging procedures. MRI: magnetic resonance imaging; CT: computerised tomography; Scint: Technetium<sup>99m</sup> bone scintigraphy.



**Fig. 2.** Anatomical location of osteomyelitic lesion in the lower extremities. MRI: magnetic resonance imaging; CT: computerised tomography; Scint: Technetium<sup>99m</sup> bone scintigraphy.

**Table II.** Changes in initial presentation from monofocal osteomyelitis to multifocal osteomyelitis.

ID	Age at onset (months)	Gender	Location 1 lesion	Location $\geq 2$ lesions	Biopsy	Time from 1 to $\geq 2$ lesions (months)	Whole-body MRI	Total lesions	
								MRI	Bone scan
4	120	F	Spine (Th8)	Spine, Pelvis	Yes	11	No	3	2
10	137	F	Radius	Tibia, Cranium	Yes	7	No	1	3
15	110	M	Tibia (distal)	Tibia (proximal and distal)	Yes	3	Yes	2	1
21	145	F	Metatars	Metatars, Midfoot, Spine, Metacarp	No	8	No	-	3
24	93	F	Tibia	Tibia, Fibula, Metatars	Yes	6	No	7	3
28	131	M	Scapula	Scapula, Femur, Tibia, Metatars	Yes	4	No	2	5

F: female, M: male.

**Table III.** Laboratory data of patients with chronic non-bacterial osteomyelitis (CNO).

	1 lesion	$\geq 2$ lesions	Girls	Boys	All
Number of patients	9 (29%)	22 (71%)	19 (61.3%)	12 (38.7%)	31 (100%)
ESR at onset (mm/h)	30.9 $\pm$ 18.1	25.1 $\pm$ 20.1	19.7 $\pm$ 16.73	6.7 $\pm$ 18.9*	26.9 $\pm$ 19.3
ESR max (mm/h)	30.7 $\pm$ 19.6	30.3 $\pm$ 23.5	23.4 $\pm$ 17.5	41.5 $\pm$ 24.8*	30.4 $\pm$ 22.1
CRP at onset (mg/L)	6.8 $\pm$ 3.7	11.5 $\pm$ 20.9	5.6 $\pm$ 2.5	16.2 $\pm$ 26.1	10.1 $\pm$ 17.5
CRP max (mg/L)	30.1 $\pm$ 37.9	29.6 $\pm$ 49.9	28.5 $\pm$ 50.8	31.8 $\pm$ 39.6	29.8 $\pm$ 46.1
Haemoglobin at onset (g/dL)	12.3 $\pm$ 1.1	12.8 $\pm$ 1.1	12.2 $\pm$ 1.1	12.4 $\pm$ 1.1	12.2 $\pm$ 1.1
Haemoglobin min. (g/dL)	11.4 $\pm$ 1.4	11.8 $\pm$ 1.4	11.1 $\pm$ 1.1	11.6 $\pm$ 0.8	11.3 $\pm$ 1.4

Values are mean  $\pm$  SD. \*:  $p < 0.05$ , boys vs. girls. ESR/CRP max represent maximum values detected during follow-up. Haemoglobin min. represents minimum value detected during follow-up.

the first symptoms to the time of diagnosis was 17.3 $\pm$ 15.3 months. One patient was initially misdiagnosed having Langerhans cell histiocytosis and treated with vinblastine and prednisolone for 6 months prior to the CNO diagnosis. The time from onset of symptoms until diagnosis was 37 months. Another patient was suspected of having osteosarcoma for 3 months and received two weeks of treatment with chemotherapy before changing the diagnosis to CNO. The diagnostic delay in this case was 8.4 months.

### Imaging

Conventional x-rays were performed in twenty-seven patients (87.1%); and scintigraphy in twenty-one (67.7%) (20 whole-body and 1 plantar); MRI in twenty-nine patients (93.5%) of which eight (25.8%) had a whole-body MRI. Ten patients (32.3%) had a CT scan, of which only one did not have an additional MRI of the same region. MRI/CT discovered most lesions compared to x-ray and scintigraphy. Both MRI and CT registered sclerotic, hyperostotic and lytic lesions whereas only MRI detected bone oedema. The distribution of bone lesions is illustrated in Fig. 1.

The most frequent location was in the lower extremities with the highest incidence in the tibia followed by the axial skeleton (spine, pelvis and clavicles). In the long tubular bones the lesions were most often localised in the metaphysis (Fig. 2).

Twenty-two (71.0%) had two or more bone lesions whereas 9 (29.0%) had only one lesion. Definition of mono- or multifocality of the chronic osteomyelitis was based on the description of imaging results. Six patients had initially only one lesion detected but developed new lesions 3 to 11 months later during the disease course (Table II). Five out of these had developed additional symptoms suspecting new lesions. One patient (ID no. 15) with symptoms from the ankle showed a lesion in the distal tibia by bone scan, was 3 months later detected with lesions both in the proximal and distal part of the tibia by whole-body MRI without having developed new symptoms (Table II).

### Laboratory test results

The laboratory test results are expressed in Table III. The erythrocyte sedimentation rate (ESR) and the C-

reactive protein (CRP) were elevated in more than half of the patients (63% and 57%, respectively). Comparing the group of patients having one lesion with the group having two or more lesions we found no significant differences in either ESR or CRP values. Haemoglobin levels were all within the normal range; at disease onset the mean value was 12.2 $\pm$ 1.1 g/dL.

### Extra-osseous manifestations

Extra-osseous involvement was noted in twenty patients (64.5%) of whom five (16.1%) had psoriasis and three (9.7%) had pustulosis palmoplantaris (PPP) (Fig. 3). The extra-osseous manifestations were equally seen in both girls and boys. Of the patients with multifocal disease, 77.3% had extra-osseous manifestations, with arthritis (45.5%) and psoriasis (22.7%) as the most common and 13.6% was found with PPP. In patients with monofocal disease extra-osseous manifestations was observed with cervical adenitis (44.4%) and arthritis (11.1%) as the most common but neither had psoriasis nor PPP. The extra-osseous manifestations were typically registered at the time of diagnosis.

### Treatment

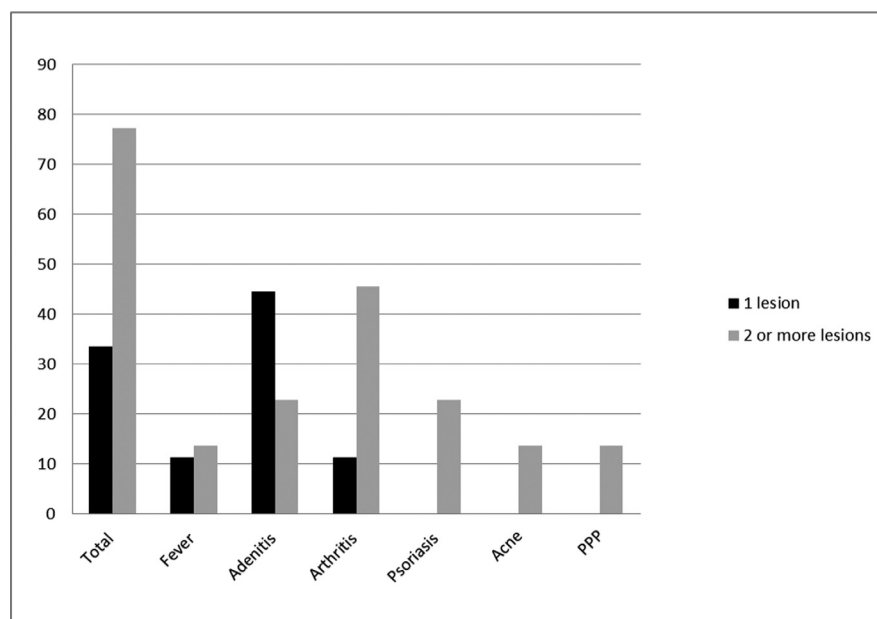
All patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs). Seventeen received corticosteroids (54.8%), nine methotrexate (29.1%), three pamidronate (9.7%) and one infliximab (3.2%). Because therapy was reviewed retrospectively, effectiveness of the used drugs could not be evaluated appropriately. The mean sum of lesions was higher in the group of patients treated with prednisolone, MTX, infliximab or pamidronate (6.2–13 lesions) compared to the patients not receiving immunosuppressants (5.1 lesions).

### Discussion

Since CRMO was first described more than four decades ago the term has been widely used in the literature for diseases with chronic non-infectious inflammatory bone lesions. However, the umbrella term chronic non-bacterial osteomyelitis/osteitis (CNO), also including monofocal lesions (2), has now been generally accepted, but the clinical criteria are still debated. There is increasing awareness that both unifocal and multifocal courses of recurrent non-bacterial osteomyelitis should be regarded as a clinical entity and that the recurrent episodes of seemingly unprovoked inflammation in the absence of autoantibodies and autoreactive T-cells places CNO as an autoinflammatory disease (8, 17).

We were able to confirm the findings of female preponderance previously described. In our material the female/male ratio was only 1.6:1 compared to 2.3–10:1 described by others (5, 18) but in a recent British study the sex distribution was equal (19). We could not find any significant difference in the disease course between boys and girls. We found a mean age at onset of 10 years, a typical location of the bone lesions predominantly in the tubular bones of the lower limbs and an association to other inflammatory conditions (2, 4–6).

Unlike the concept from earlier literature regarding CNO as a benign and self-limited disease (19) it now seems clear that CNO may have a long-term course with a significant morbidity (5,



**Fig. 3.** Extra-osseous findings in children with mono- and multifocal non-bacterial osteomyelitis, n=31. Total: percentage of total number of extra-osseous findings. PPP: pustulosis palmo-plantaris.

18). In our study the mean duration of active disease was 44.4 months  $\pm$  25.6 months. Only four patients had limited disease duration, with active CNO disease ranging from 2.5 to 5.1 years. Disease remission was defined when patients were asymptomatic for a minimum of 6 months at clinical control and follow-up was estimated not being necessary afterwards. At the time of evaluation the majority had persistent activity. Twenty-three children with active CNO were still followed at our centre and one was followed by the adult rheumatologists. Three were lost to follow-up after referral to an adult centre. In our cohort one female patient, now aged nineteen, still has active CNO. Cases of CNO either extending into adulthood or with a late adult onset have been reported up to the age of 55 years (12, 21).

Our findings contribute to the discussion of the diagnostic criteria of CNO as we find that patients with a monofocal disease have comparable clinical, radiological and histological characteristics to those patients with multifocal lesions (1, 18). It is not our impression that the children with a monofocal disease simply represent a milder course of the disease as previously reported (5). In fact, we found an even longer disease duration and higher sedimentation rate in children with a monofocal

disease. Further, we found no significant difference in the diagnostic delay between the two groups (Table I).

Conventional MRI has a higher sensitivity in detecting early, subclinical lesions than conventional radiography (9). Typical MRI-findings during the active phase of CNO is marrow oedema, which generates low signal on T1 weighted images and high signal on STIR/T2-fat-saturated images. The use of whole-body MRI can be used to assess the extent, the multifocality and the activity of the disease (1, 9). Areas of new activity demonstrate marrow oedema, with the surrounding sclerotic bone appearing hypointense on both T1- and T2-weighted images. MRI can demonstrate details like associated periosteitis, soft tissue inflammation, joint effusion and transphyseal disease, which are findings that are typically underestimated on plain radiographs (1, 21).

Of the eight patients who underwent whole-body MRI in our study, three had corresponding results with conventional radiography; three had only MRI performed; and two had substantial differences in the amount of lesions when compared to conventional radiography. In these patients MRI disclosed silent lesions, not visible on conventional radiography. Thus, the risk of overlooking possible silent foci when targeting



only one part of the body, as with conventional radiography, could be overcome when using whole-body MRI without causing irradiation hazards. Our data support that whole-body MRI is an essential tool when classifying the CNO into monofocal and multifocal involvement and that this division should not be based solely on clinical findings. The term chronic non-bacterial osteomyelitis (CNO) has been proposed instead of CRMO (2, 18). Jansson *et al.* developed clinical criteria to diagnose non-bacterial osteitis by reviewing the literature and summarising their clinical and laboratory findings (2). Patients with multiple bone lesions, or one bone lesion plus palmoplantar pustulosis (PPP), and recurrent flares with remissions were defined as having CRMO. Since none of our patients with monofocal disease had dermatological manifestations our results support that the term CRMO, if used, should be restricted to multifocal disease only. Other extraosseous findings like cervical adenitis, which was most often seen in patients with monofocal lesions, has not been described previously in the literature. This could, however, be explained by differences in clinical recordings of the retrospective data. Important limitations of this and other retrospective analyses are the lack of stringent uniformity in the radiological and clinical measures. Considering CNO being a relatively rare disease our study material, however, comprises a relatively large number of patients collected from one single centre and with almost all patients having performed a MRI at the same radiological department. We find whole-body MRI as a relevant screening instrument for the

diagnosis of CNO, as it is a non-invasive investigation without causing any radiation hazard. It clearly illustrates characteristic findings of the disease, is highly sensitive and has an acceptable acquisition time (30-90 minutes). The limitations of MRI are the use of general anesthesia for smaller children and the relatively high cost. We did not find substantial differences in the clinical presentation of monofocal and multifocal disease and our results underscores the necessity of the collected term chronic non-bacterial osteomyelitis instead of CRMO.

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