Whole-body Magnetic Resonance Imaging in Chronic Recurrent Multifocal Osteomyelitis: Clinical Longterm Assessment May Underestimate Activity

Agnes M. Voit, Andreas P. Arnoldi, Hassan Douis, Felicitas Bleisteiner, Moritz K. Jansson, Maximilian F. Reiser, Sabine Weckbach, and Annette F. Jansson

ABSTRACT. ***Objective.*** (1) To examine how many patients have clinically and/or radiologically active chronic recurrent multifocal osteomyelitis (CRMO) ≥ 10 years after first onset of symptoms, and (2) to compare clinical and whole-body magnetic resonance imaging (WB-MRI) findings.

Methods. Seventeen patients (82% women) who were diagnosed with childhood-onset CRMO at least 10 years (average 12) before reexamination were reevaluated. Patients completed a standardized questionnaire, and underwent clinical and laboratory investigation and WB-MRI. Clinical features were compared with imaging findings.

Results. Five patients were found to be in clinical and radiological remission. One of these patients demonstrated 1 radiologically inactive lesion on WB-MRI. Four patients showed radiologically active lesions despite full clinical remission, 2 of them in 3 vertebral bodies. Spinal involvement in 6 patients (35%) caused vertebral compression fractures, vertebra plana, or vertebral hemifusion. Eight patients presented with ongoing clinical disease activity. When applying a CRMO activity score based on clinical and imaging findings, 2 patients were identified as having pain amplification. Overall, 22/55 known CRMO lesions were identified; 11 of them were radiologically active lesions. Additionally, 14 so far unknown clinically silent lesions were detected: 8 radiologically active lesions and 6 radiologically inactive lesions.

Conclusion. CRMO activity on longterm followup might have been underestimated. Our study demonstrates that clinical remission does not necessarily mean radiological remission. We therefore propose that all patients with CRMO, including patients in clinical remission, require longterm clinical followup and should undergo evaluation with WB-MRI on a regular basis until radiological remission or a steady state of disease is achieved. (J Rheumatol First Release May 15 2015; doi:10.3899/jrheum.141026)

Key Indexing Terms:
OSTEOMYELITIS REMISSION DISEASE ACTIVITY SCORE

From the Department of Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig Maximilians University; Institute for Clinical Radiology, Ludwig Maximilians University of Munich, Munich; Diagnostic and Interventional Radiology, University Hospital Heidelberg, Heidelberg, Germany; and the Department of Radiology, Royal Orthopaedic Hospital, Birmingham, UK.

A.M. Voit, MD, Department of Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig Maximilians University; A.P. Arnoldi*, MD, Institute for Clinical Radiology, Ludwig Maximilians University of Munich; H. Douis, MD, Department of Radiology, Royal Orthopaedic Hospital; F. Bleisteiner, MD; M.K. Jansson, Department of Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig Maximilians University; M.F. Reiser, MD, Institute for Clinical Radiology, Ludwig Maximilians University of Munich; S. Weckbach*, MD, Institute for Clinical Radiology, Ludwig Maximilians University of Munich, and Diagnostic and Interventional Radiology, University Hospital Heidelberg; A.F. Jansson*, MD, Department of Rheumatology and Immunology, Dr. von Hauner Children's Hospital, Ludwig Maximilians University. * These authors contributed equally to this study.*

Address correspondence to Dr. S. Weckbach, Diagnostic and Interventional Radiology, University Hospital Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany. E-mail: sabine.weckbach@med.uni-heidelberg.de

Accepted for publication March 3, 2015.

Chronic recurrent multifocal osteomyelitis (CRMO), also known as nonbacterial osteitis (NBO), is an autoimmune disorder that primarily affects the skeleton and may be accompanied by the inflammatory manifestations of the skin or bowel[1,2]. The etiology is still unknown, but increasing evidence suggests a genetic component in the susceptibility to the disease[1,2,3]. CRMO is characterized by the occurrence of inflammatory bone lesions with spontaneous remissions and exacerbations[4,5]. Lesions are often painful, but can present without any symptoms — so called "silent lesions"[6]. The course of disease is considered to be usually self-limiting[3,7]. Childhood CRMO may resolve before the end of puberty, but 20–25% of affected patients do not respond to nonsteroidal antiinflammatory drugs (NSAID) and show a protracted course of disease with several relapses[7,8,9]. So far, it is not known whether healed lesions may remain as "bone scars". Longterm observations based on large patient cohorts are still lacking, but a few surveys suggested that the course of disease might be more prolonged than previously

thought[8]. Thus, longterm imaging followup of patients with CRMO may further increase our understanding of the behavior of lesions.

The diagnosis of NBO remains a diagnosis of exclusion. Laboratory investigations are nonspecific. Mildly elevated C-reactive protein (CRP) and erythrocyte sedimentation rate are common while white blood cell count usually remains normal[2,3,10]. Conventional radiographs may show characteristic lesions of osteolysis and sclerosis[4,6,10], but usually do not evaluate the entirety of the skeleton and have a very low sensitivity. Whole-body (WB) bone scintigraphy has also been used to detect multifocal disease, but its specificity is low. Recently, WB magnetic resonance imaging (WB-MRI) proved to be the most sensitive imaging modality in the evaluation of CRMO[11]. WB-MRI is already an established tool in the evaluation of other systemic diseases, such as multiple myeloma or in the evaluation of skeletal metastases[12,13,14], because it allows for a fast and accurate "one-step" assessment of involved bones and soft tissue structures without the use of ionizing radiation[14], which is of particular importance in children and adolescents[14,15].

MRI can assess signs of acute or chronic inflammation, such as edematous or sclerotic bone marrow lesions, and additionally offers the possibility to gain information about the adjacent soft tissue structures. This allows on the one hand to detect CRMO typical patterns of lesions' locations and distribution[16], and on the other hand helps to exclude signs of the main differentials, such as bacteria-related infectious disease, arthritis, or tumor-like processes[17].

WB-MRI can therefore strongly support the diagnosis of CRMO; however, the evidence of WB-MRI in the diagnosis, assessment of disease burden, and its role in the followup of CRMO remains limited. Particularly, there is a paucity of evidence about the longterm followup of CRMO and its clinical and radiological appearances. The objectives of our study were, therefore, (1) to examine how many patients have clinically and/or radiologically active CRMO 10 years or more after the onset of symptoms, and (2) to compare clinical findings with WB-MRI findings.

MATERIALS AND METHODS

Ethics. This study was approved by the ethics committee of the medical faculty of the Ludwig Maximilians University (LMU) of Munich, Germany. All patients gave written informed consent.

Patient selection. All patients had been previously diagnosed with CRMO and had been under the care of the Department of Pediatric Rheumatology and Immunology, Dr. von Hauner Children's Hospital, LMU Munich, between 1993 and 2011. Patients were invited to participate in the study and recalled by phone or mail. Clinical diagnosis of CRMO had been defined according to the previously published diagnostic criteria and a diagnostic score[18]. The score is based on 7 predictors concerning laboratory, clinical, and radiological findings with the score ranging from 0 to 63. All included patients were scored with a median value of 44/63 points 1 year after diagnosis. Patients with CRMO were included in the current study if the onset of disease occurred at least 10 years before the current examination. All patients had undergone WB technetium-99 m-bone scintigraphy and high-resolution–dedicated MRI at disease onset to assess clinically silent and clinically active bone lesions. In total, 35 patients fulfilled the inclusion criteria, of which 20 patients agreed to participate in a WB-MRI examination. Three of the 20 patients had to be excluded from the study because of claustrophobia or metal implants. Therefore, 17 patients in total were enrolled in the study.

Clinical examination. Patients were evaluated clinically prior to WB-MRI by a pediatric rheumatologist with 19 years of experience (AJ). Clinical evaluation included medical history, a standardized questionnaire concerning onset of disease, known lesions, diagnostic procedures, disease course, associated diseases, current medication, and current complaints. General physical examination was performed with particular emphasis on the evaluation of the skeleton, joints, and skin. Laboratory investigations included full blood count and CRP in the absence of acute intercurrent infections at the time and 14 days prior to clinical evaluation. WB-MRI was performed within 4 weeks following clinical reevaluation.

MRI protocol. WB-MRI was performed on a 3-Tesla scanner (Magnetom Verio, Siemens Medical Solutions) equipped with 32 receiver channels. Patients were placed on the imaging table head first in supine position covered with a head and neck coil, spine array coils, and 3 body coils (total imaging matrix, Siemens Medical Solutions). Upper arms were positioned parallel to the chest, and lower arms and hands were positioned upon the pelvis covered by an additional body coil. A WB scanning protocol adapted to CRMO imaging was implemented using coronal and sagittal short-tau inversion recovery (STIR) and noncontrast fat-suppressed T1-w turbo spin-echo sequences. Coronal sections were obtained in 5 or 6 subsequent table positions, depending on the size of the patient. Overlapping of the sections guaranteed for continuously coherent images from facial bones to toes. The whole spine was covered with 2 overlapping sagittal sections. Sequence variables can be found in Table 1. The mean examination time including patient positioning, section adjustment, and image acquisition was 40 min.

WB-MRI evaluation. Magnetic resonance examinations were assessed in a consensus reading by 2 experienced musculoskeletal radiologists (SW: 9 yrs of MRI experience, HD: 7 yrs of MRI experience) blinded to clinical information using a standard picture archiving and communication system workstation (Syngo Imaging, Siemens Medical Solutions) for the image assessment.

Magnetic resonance images were evaluated for the presence of inflammatory bone lesions that were considered typical for CRMO based on previously described characteristics[6,11,16,17].

Accordingly, the anatomical location and distribution of the lesions such as proximity to the bone cortex or growth plates, bilateral symmetric or periarticular appearance, and predominant involvement of the clavicle, the sternum, the pelvis, the tubular bones of the lower extremity, and the spine were indicative features. Further, hyperostosis of affected bones with optional adjacent soft tissue edema was therefore regarded as in keeping with CRMO bone lesions while the absence of other signs that could suggest infection, malignancy, or arthritic diseases was mandatory. CRMO typical skeletal lesions were subsequently differentiated into radiologically active lesions and radiologically inactive lesions based on their signal characteristics. Radiologically active lesions were defined as areas of increased signal intensity (SI) on STIR images and decreased SI on T1-w images. Radiologically inactive lesions were defined as areas of decreased SI on T1-w images that showed no signal alteration on STIR images. In the vertebral column, the presence of vertebral bone deformities in the absence of a history of trauma was assumed to be caused by CRMO. Vertebral bone deformities showing increased SI on STIR images were assessed as radiologically active lesions while deformities without signal alterations were assessed as radiologically inactive lesions. The exact anatomic location of every lesion was noted. Complete radiological remission was defined as the absence of signal change in previously recorded lesions.

Data management, clinical definitions, and statistics. Patients were divided into 2 patient groups: group 1, "clinically active disease": CRMO-related pain less than 6 months ago; and group 2, "clinically inactive disease": no CRMO-related musculoskeletal complaints for at least 6 months.

Table 1. Sequence variables of the CRMO-adapted WB-MRI protocol.

Description Orientation	T1-w TSE Coronal	T2-w STIR SPACE Coronal	T1-w TSE Sagittal	T2-w STIR SPACE Sagittal
TR, ms	783	4000	700	6000
TI, ms	—	210	—	210
TE, ms	12	326	11	48
Matrix, phase × read	384 × 307	320 × 259	448 × 358	384 × 326
Resolution, mm^3, phase × read × slice	1.1 × 1.1 × 5.0	1.5 × 1.5 x 5.0	1.1 × 0.9 × 3.5	1.2 × 1.0 × 3.5
FOV, mm^2	480 × 336	480 × 336	400 × 400	400 × 400
Flip angle, °	180	T2 var	180	180
Bandwidth, Hz/px	161	1116	180	250
Parallel imaging method	GRAPPA	GRAPPA	GRAPPA	GRAPPA
Acquisition time, s	106 × 5 (6)*	88 × 6	81 × 2	155 × 2

* Dependent on body size. CRMO: chronic recurrent multifocal osteomyelitis; WB-MRI: whole-body magnetic resonance imaging; TSE: turbo spin-echo; STIR: short-tau inversion recovery; SPACE: sampling perfection with application optimized contrasts using different flip angle evolution; TR: time of repetition; TI: inversion time; TE: echo time; FOV: field of view; GRAPPA: generalized autocalibrating partially parallel acquisitions.

Possible prognostic markers that included age at presentation, sex, and number of lesions at presentation were compared between the 2 groups. For clinical assessment, an activity score was used on the basis of previous reports[19,20]. This activity score was modified for childhood CRMO and consists of the following 5 measures with a maximum of 10 points: CRP, number of active radiological lesions on WB-MRI, severity of disease estimated by the physician, severity of disease estimated by the patient [visual analog scale (VAS) 0–10], and the health assessment questionnaire (HAQ; CRP < 0.5 = 0 points, 0.5–2 = 1 point, > 2 = 2 points; rheumatoid arthritis 0 = 0 points, 1 = 1 point, > 1 = 2 points; VAS physician 0 = 0 points, 1–5 = 1 point, > 5 = 2 points; VAS patient 0 = 0 points, 1–5 = 1 point, > 5 = 2 points; HAQ 0 = 0 points, 0.1–1.5 = 1 point, > 1.5 = 2 points).

Clinical data and radiological findings were compared. In patients with known CRMO, clinically active lesions were defined by local pain, swelling, and increased warmth, which were diagnosed by an experienced rheumatologist. If a patient with CRMO developed bone pain during the course of the disease, this pain was considered to be a new clinical lesion of CRMO. Clinical lesions were divided into 2 lesion groups: (1) clinical lesions with acute complaints at time of study visit, "clinically acute lesion"; and (2) clinical lesions without complaints at time of study visit, "clinically nonacute lesions".

Continuous variables were expressed as medians with interquartile ranges. Pearson chi-square was used for comparison of categorical data, while the Student t test or Mann-Whitney U test were used to compare quantitative data. P values below 0.05 were considered statistically significant. The statistical analysis was performed using IBM SPSS version 19.0 (SPSS).

RESULTS

Study cohort. Our study included 17 patients, with 82% being women (14). Median age at onset was 9 years (6–9); the study was performed 15 years (10–26) after first presentation when the patients were 23 years old (median 19–29).

Clinical disease activity. At reevaluation, 8 patients showed clinical activity and were assigned to group 1. Nine patients did not show any clinical activity and were assigned to group 2. No statistically significant differences between the 2 groups were found for age at initial manifestation (9 yrs vs 9 yrs, p = 0.606), age at time of reexamination (26 yrs vs 23 yrs, p = 0.370), and for sex (75% women vs 89% men, p = 0.576). The mean duration of disease in patient group 1 was statistically significantly longer than that in patient group 2 (16.5 yrs vs 6.0 yrs, p = 0.001; Figure 1).

Six (75%) of the 8 patients with clinical activity showed a slightly increased CRP (average 0.88 mg/dl) while the other 2 patients had normal CRP levels (average 0.25 mg/dl, normal value of CRP < 0.5 mg/dl). One of the 9 patients without clinically active disease presented with a CRP of 2.35 mg/dl that was attributable to palmoplantar pustulosis with an associated superadded streptococcal infection. All other patients in group 2 had normal CRP levels.

Treatment. All patients had previously received longterm treatment with high-dose NSAID until a symptom-free interval of at least 3 months had been achieved. Other therapies included steroids (n = 6), pamidronate (n = 4), azithromycine (n = 3), azathioprine (n = 2), sulfasalazine (n = 2), methotrexate (n = 2), and anti-tumor necrosis factor agents (n = 1).

Median time between first diagnosis and reevaluation was 15 years (range 10–26 yrs). At reevaluation, all clinically inactive patients (n = 8) reported not to be under followup with a rheumatologist and were not on any medication for CRMO. All clinically active patients (n = 9) consulted a rheumatologist (n = 6) or a general practitioner (n = 3) and were receiving medication for CRMO.

Number and localization of clinical lesions. Owing to previous clinical and imaging records, overall 55 lesions had been described in the study group [median 3 lesions (1–4) per patient] since the first presentation in the following locations: vertebra (14), tibia (12), pelvis (7), femur (8), clavicle/sternum (6), radius/ulna (3), foot-bones (3), humerus (1), and patella (1).

At the time of reevaluation, pain was reported in 18 of the 55 previously known lesions: vertebra (4), tibia (2), pelvis (3), femur (2), clavicle/sternum (4), foot-bones (2), and humerus (1).

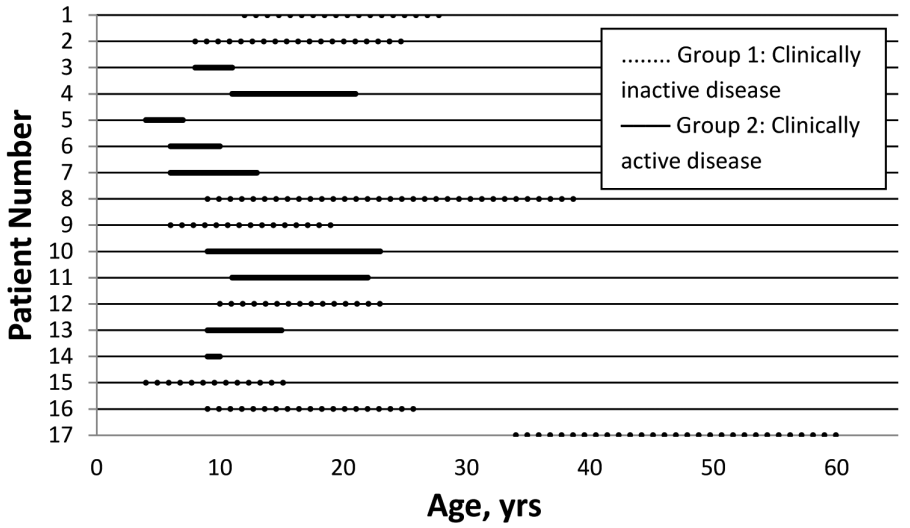

Figure 1. Onset, duration, and end of clinically active disease, where applicable.

WB-MRI findings. In 13/17 patients, WB-MRI depicted altogether 36 inflammatory bone lesions. In 4 patients, no lesions were seen. Twenty lesions in 10/13 patients were classified as radiologically active lesions and 16 lesions in 11/13 patients were classified as radiologically inactive lesions. Coexistent radiologically active and radiologically inactive lesions were detected in 8/13 patients while unifocal lesions were detected in 3/13 patients (Figure 2).

The mean number of multifocal lesions was 3.3 with a maximum of 6. Periosteal reaction was found adjacent to 2 radiologically active lesions and in 1 radiologically inactive lesion.

Vertebral lesions were depicted in 6/17 patients: 8 radiologically active lesions in 4 patients; and 9 radiologically inactive lesions in 6 patients, including hemifusion formation (1), compression fractures (3), and vertebrae planae (3).

Comparison of clinical condition and WB-MRI findings.

I. Lesion-based analysis.

Clinically active lesions appeared as radiologically active in 10/18 and as radiologically inactive in 2/18 lesions. Six of 18 clinically active lesions did not show signal alterations on WB-MRI. Additionally, 14 clinically silent lesions were detected: 8 radiologically active lesions and 6 radiologically inactive lesions that could not be correlated with known lesions. Radiologically inactive lesions were associated with pain in 2/16 locations (12.5%). Of the known lesions, 37/55 were clinically inactive.

II. Patient-based analysis.

Radiologically active lesions were found in 10 patients, 6 belonging to group 1 (patients with clinical activity, n = 8). In group 2 (patients without clinical activity, n = 9), 4 patients did not show any lesions. Clinically silent but radiologically active lesions were found in 4 patients — coexisting with radiologically inactive lesions. Eight radiologically active lesions and 6 radiologically inactive lesions were detected that could not be allocated to any known clinical lesions (Table 2).

Until reevaluation, unifocal CRMO had been diagnosed in 5 patients. WB-MRI revealed 2 additional lesions in 2/5 patients, 1 radiologically active lesion (ilium), and 1 radiologically inactive lesion (tibia).

Thoracic pain was reported in 2/6 patients from disease-related abnormalities of a vertebral body, both of them showing radiologically active lesions. In 2 patients with clinically inactive disease, WB-MRI revealed 3 unknown radiologically active vertebral lesions (T9, T10, and T11) with endplate irregularities of the T9-vertebral body and small endplate depression affecting the T11-vertebral body.

Activity score. The activity score ranged from 0 to 8. Three patients with unifocal disease after reevaluation scored an average value of 3.0 while patients with multifocal disease demonstrated an average score of 2.4. Five of 17 patients showed a score of 0 (5 patients with clinically inactive disease: 4 without any lesions on MRI and 1 patient with 1 radiologically inactive lesion). Four clinically inactive patients were scored with values between 1 and 4. The elevated score values were because of clinically silent but radiologically active lesions and elevated CRP levels in these patients. Two of the 4 patients without complaints presented with radiologically active lesions in vertebral bodies and were scored with a value of 2 (Table 3).

DISCUSSION

To the best of our knowledge, this is the first report presenting WB-MRI findings not only in symptomatic, but also in symptom-free patients diagnosed with pediatric CRMO more than 10 years ago. It is known that clinically silent lesions

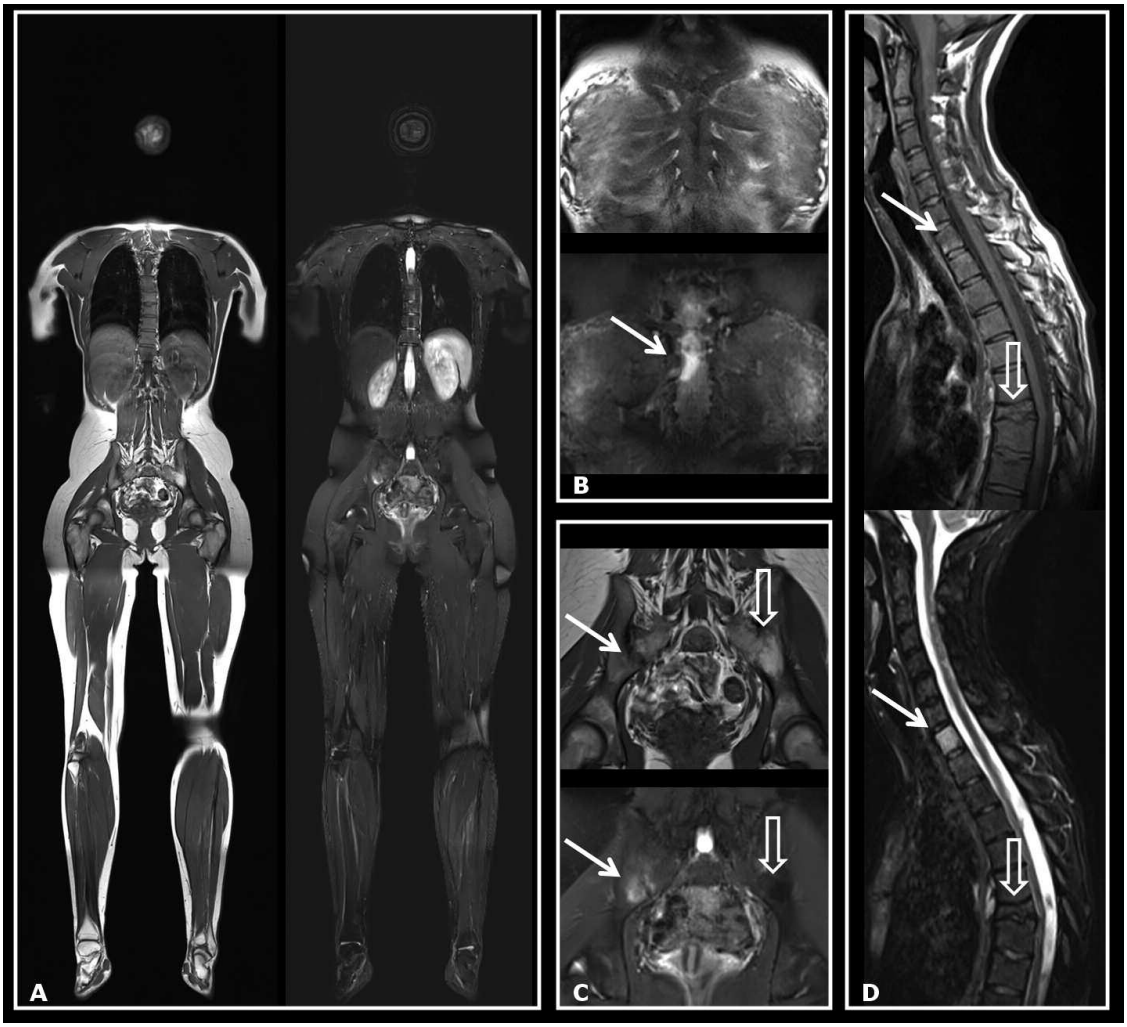

Figure 2. WB-MRI of a 19-year-old woman with a history of CRMO for longer than 10 years presenting with clinically symptomatic lesions in the sternum, the right sacroiliac joint, the right proximal humerus and femur, and the middle third of the thoracic spine. (A) Composed coronal whole-body images in T1 and STIR weighting. (B) Enlarged coronal images of the sternum in T1 and STIR weighting revealing a focal BME in the center of the body of the sternum consistent with a radiologically active lesion (thin white arrow). (C) Enlarged coronal images of sacroiliac joint revealing a focal BME at the inferior aspect of the right sacroiliac joint consistent with a radiologically active lesion (thin white arrows). A subtly pronounced fatty signal change adjacent to the left sacroiliac joint (broad hollow arrows) was not taken into account by the readers, but could represent a remnant of an old lesion. (D) Enlarged sagittal images of the cervical and upper thoracic spine show a global BME in the vertebral body Th1 consistent with a radiologically active lesion (thin white arrows) and a vertebra plana Th7 (broad hollow arrows). WB-MRI: whole-body magnetic resonance imaging; CRMO: chronic recurrent multifocal osteomyelitis; STIR: short-tau inversion recovery; BME: bone marrow edema.

may be detected by WB-MRI (or bone scintigraphy)[11], but there is a lack of evidence in the longterm followup of asymptomatic patients with CRMO. Our results show that CRMO has a more prolonged course than previously presumed[7,8], and that the number of lesions in patients even in clinical remission over more than 8 years is higher than clinically suspected.

It is known that WB-MRI can reveal clinically silent lesions in patients with CRMO[11,21] and that WB-MRI is more sensitive than WB bone scintigraphy[11]. In our patient cohort, disease onset was before 1999 and WB bone scintigraphy was used for detecting clinically silent lesions. None of the patients underwent WB-MRI before our reevaluation. Therefore, some of the 14 newly detected clinically silent lesions might have been present previously. It is, nevertheless, a new finding that half of the patients in clinical longterm remission without any followup demonstrated radiologically active lesions on WB-MRI. In 1 asymptomatic patient, 1 radiologically inactive lesion was found. Such inactive CRMO lesions can thus be regarded as "bone scars" in patients without pain.

Only 2 patients of group 1 presented with painful inactive

Table 2. Number and localization of previously known CRMO lesions, painful, radiologically active, and radiologically inactive CRMO lesions at the time of clinical and WB-MRI–based reevaluation and of all detected lesions during the course of disease.

Patient, n = 17	No. and Loc. of Previously Known Lesions, n = 55	No. and Loc. of Painful Lesions at Time of Reevaluation, n = 18	No. and Loc. of Radiologically Active Lesions at Time of Reevaluation, n = 20	No. and Loc. of Radiologically Inactive Lesions at Time of Reevaluation, n = 16	No. and Loc. of Detected Lesions During Course of Disease, n = 67
1	1 Tibia proximal r	1 Tibia proximal r	0	1 Tibia proximal r	1 Unifocal
2	1 Clavicle r	1 Clavicle r	1 Clavicle r	0	1 Unifocal
3	2 Sacroiliac joint r Ulna proximal l	0	0	0	2 Multifocal
4	6 Sacroiliac joint r, l Femur distal r Tibia distal r, l Radius distal r	0	1 Mandible r	1 Sacroiliac joint l	7 Multifocal
5	1 Femur proximal l	0	0	0	1 Unifocal
6	3 Femur proximal l Tibia distal r, l	0	0	0	3 Multifocal
7	2 Femur proximal r, l	0	0	0	2
8	6 Thoracic vertebrae 7–9 Sacroiliac joint r, l Clavicle l	2 Sacroiliac joint r, l	0	3 Thoracic vertebrae 7–9	6 Multifocal
9	7 Thoracic vertebrae 7–9 Femur proximal r Humerus proximal r Sacroiliac joint r Sternum	7 Thoracic vertebrae 7–9 Femur proximal r Humerus proximal r Sacroiliac joint r Sternum	5 Thoracic vertebrae 1, 8, 9 Sacroiliac joint r Sternum	1 Thoracic vertebra 7	8 Multifocal
10	3 Thoracic vertebra 5 Femur proximal r Calcaneus r	0	2 Clavicle l Sacroiliac joint l	3 Thoracic vertebra 5 Femur proximal r, l	5 Multifocal
11	5 Tibia proximal r, l Radius distal r Thoracic vertebrae 8, 9	0	4 Sacroiliac joint l Tibia proximal l Thoracic vertebrae 8, 9	2 Thoracic vertebrae 11, 12	8 Multifocal
12	1 Clavicle r	1 Clavicle r	1 Clavicle r	1 Tibia distal r	2 Multifocal
13	2 Thoracic vertebrae 4, 6	0	2 Thoracic vertebrae 10, 11	1 Thoracic vertebra 6	4 Multifocal
14	2 Tibia proximal l Tibia distal r	0	0	1 Talus r	3 Multifocal
15	9 Thoracic vertebrae 6,7 Tibia proximal r, l Sacroiliac joint l Os naviculare r, l Sternum Lumbar vertebra 2	3 Thoracic vertebra 7 Os naviculare r, l	1 Thoracic vertebra 7	1 Thoracic vertebra 6	9 Multifocal
16	3 Tibia distal l Femur proximal l Patella r	2 Femur proximal l Tibia distal l	2 Femur proximal l Tibia distal l	0	3 Multifocal
17	1 Sternum	1 Sternum	1 Sternum	1 Sacroiliac joint r	2 Multifocal

CRMO: chronic recurrent multifocal osteomyelitis; WB-MRI: whole-body magnetic resonance imaging; Loc.: location; r: right; l: left.

Table 3. Patient activity scores, consisting of relative activity points that were assigned to the value of the variables HAQ (0 = 0 pts, 0.1–1.5 = 1 pt, > 1.5 = 2 pts), patient-estimated VAS (0 = 0 pts, 1–5 = 1 pt, > 5 = 2 pts), physician-estimated VAS (0 = 0 pts, 1–5 = 1 pt, > 5 = 2 pts), CRP (< 0.5 = 0 pts, 0.5–2 = 1 pt, > 2 = 2 pts), and number of radiologically active CRMO lesions (0 = 0 pts, 1 = 1 pt, ≥ 2 = 2 pts).

Patient, n = 17	HAQ, 0–3 / Activity Points	VAS Patient, 0–10 / Activity Points	VAS Physician, 0–10 / Activity Points	CRP, mg/dl / Activity Points	No. Active Lesions on WB-MRI / Activity Points	Activity Score, 0–10
1	0 / 0	4 / 1	4 / 1	0.76 / 1	0 / 0	3
2	0 / 0	9 / 2	7 / 2	0.71 / 1	1 / 1	6
3	0 / 0	0 / 0	0 / 0	0.19 / 0	0 / 0	0
4	0 / 0	0 / 0	0 / 0	< 0.01 / 0	1 / 1	1
5	0 / 0	0 / 0	0 / 0	< 0.01 / 0	0 / 0	0
6	0 / 0	0 / 0	0 / 0	< 0.01 / 0	0 / 0	0
7	0 / 0	0 / 0	0 / 0	< 0.01 / 0	0 / 0	0
8	0.25 / 1	4 / 1	3 / 1	0.15 / 0	0 / 0	3
9	0.375 / 1	10 / 2	10 / 2	1.94 / 1	5 / 2	8
10	0 / 0	0 / 0	0 / 0	2.35 / 2	2 / 2	4
11	0 / 0	0 / 0	0 / 0	< 0.01 / 0	4 / 2	2
12	0 / 0	0 / 0	0 / 0	0.35 / 0	1 / 1	1
13	0 / 0	0 / 0	0 / 0	< 0.01 / 0	2 / 2	2
14	0 / 0	0 / 0	0 / 0	< 0.01 / 0	0 / 0	0
15	0 / 0	7 / 2	3 / 1	0.58 / 1	1 / 1	5
16	0 / 0	7 / 2	7 / 2	1.2 / 1	2 / 2	7
17	0 / 0	4 / 1	7 / 2	0.76 / 1	1 / 1	5

HAQ: Health Assessment Questionnaire; VAS: visual analog scale; CRP: C-reactive protein; CRMO: chronic recurrent multifocal osteomyelitis; WB-MRI: whole-body magnetic resonance imaging.

lesions. Applying the modified activity score[19,20], we could identify both patients as having pain amplification syndrome. As in other rheumatic diseases, this is an important differential diagnosis with significant therapeutic consequences. However, it can be challenging to differentiate clinically between pain amplification and disease activity because inflammatory markers are not always elevated[1,2,3,10] in chronic NBO. WB-MRI is therefore a powerful tool that may aid in the differentiation of the 2 conditions. Thus, the introduction of WB-MRI in the detection and staging of CRMO may offer patients a more individualized treatment plan and the possibility of avoiding the use of ineffective and potentially harmful drugs in patients with pain amplification.

Active lesions were diagnosed in nearly 60% of all longterm patients. There was again good agreement between the radiological diagnosis and the clinical findings. It is, however, of concern that 45% of patients in clinical remission had radiologically active lesions (time since last complaints: median 8 yrs, minimum 5 yrs). This finding highlights the potentially crucial role of WB-MRI in the assessment of disease activity in CRMO[11,16,21]. Additionally, 2 of these patients had 3 unknown vertebral lesions. These patients underwent the proposed standard clinical followup according to a recent German consensus statement[22]. So far, these patients have not developed fractures or vertebra plana deformity: each received NSAID and 3 monthly local MRI followups. In case of increasing bone destruction, the treatment plan would be to administer pamidronate[23].

It remains unclear whether all vertebral lesions require treatment with bisphosphonates[9,23]. We know, however, that patients with vertebral involvement may have compression fractures, vertebra plana, and longterm sequelae[7]. Therefore, patients with CRMO should be assessed by a rheumatologist and evaluated with WB-MRI on a regular basis until complete radiological remission or stable disease is achieved.

In fact, there remains uncertainty about the healing processes in CRMO. For instance, we do not know why some patients develop hyperostotic lesions while others do not. By using an activity score and WB-MRI on a regular basis (e.g., yearly) in a larger patient cohort, we may be able to define subgroups of patients with CRMO with respect to the behavior of inflammatory skeletal lesions.

A limitation of our study is the small sample size of our patient cohort. Additionally, the selection of patients may have been biased by the severity of the disease because more severely affected patients could have been more inclined to participate in the study. Thus, the preponderance of female participants might point to a more severe disease course in women even if the comparison of sex groups in our study did not point to this conclusion.

Further, the HAQ, which we used in our study to evaluate disease activity, was originally designed for use with patients with chronic arthritis. Because there is no established activity tool for CRMO, the activity score used in our study requires further development and validation.

Finally, we cannot be certain that all magnetic resonance lesions are attributable to CRMO without biopsy because MRI might be nonspecific and the magnetic resonance findings in some cases could potentially be the result of non-CRMO–related findings. However, biopsy of all lesions

identified on MRI would not be feasible and in fact would be unethical. Further, biopsy of suspected CRMO lesions may only demonstrate nonspecific findings and may thus not result in a definite diagnosis.

More than 10 years after disease onset, WB-MRI was performed and revealed radiologically active lesions in childhood-onset CRMO in more than 50% of patients — even in patients in longterm clinical remission. Active vertebral involvement that may require therapy was found in 2 patients. The clinical significance of these silent lesions warrants further research.

REFERENCES

1. Jansson A, Renner ED, Ramser J, Mayer A, Haban M, Meindl A, et al. Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. Rheumatology 2007;46:154-60.
2. El-Shanti HI, Ferguson PJ. Chronic recurrent multifocal osteomyelitis: a concise review and genetic update. Clin Orthop Relat Res 2007;462:11-9.
3. Golla A, Jansson A, Ramser J, Hellebrand H, Zahn R, Meitinger T, et al. Chronic recurrent multifocal osteomyelitis (CRMO): evidence for a susceptibility gene located on chromosome 18q21.3-18q22. Eur J Hum Genet 2002;10:217-21.
4. Jansson A, Jansson V, von Liebe A. [Pediatric osteomyelitis]. [Article in German] Orthopade 2009;38:283-94.
5. Jansson A, Golla A, Schneider K, Jansson V, Belohradsky BH. [CRMO: overview and first results of a genetic-rheumatological study]. [Article in German] Monatsschr Kinderheilkd 2002;150:477-89.
6. Khanna G, Sato TS, Ferguson P. Imaging of chronic recurrent multifocal osteomyelitis. Radiographics 2009;29:1159-77.
7. Huber AM, Lam PY, Duffy CM, Yeung RS, Ditchfield M, Laxer D, et al. Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. J Pediatr 2002;141:198-203.
8. Catalano-Pons C, Comte A, Wipff J, Quartier P, Faye A, Gendrel D, et al. Clinical outcome in children with chronic recurrent multifocal osteomyelitis. Rheumatology 2008;47:1397-9.
9. Hospach T, Langendoerfer M, von Kalle T, Maier J, Dannecker GE. Spinal involvement in chronic recurrent multifocal osteomyelitis (CRMO) in childhood and effect of pamidronate. Eur J Pediatr 2010;169:1105-11.
10. Wipff J, Adamsbaum C, Kahan A, Job-Deslandre C. Chronic recurrent multifocal osteomyelitis. Joint Bone Spine 2011; 78:555-60.
11. Fritz J, Tzaribatchev N, Claussen CD, Carrino JA, Horger MS. Chronic recurrent multifocal osteomyelitis: comparison of whole-body MR imaging with radiography and correlation with clinical and laboratory data. Radiology 2009;252:842-51.
12. Schaefer JF, Schlemmer HP. Total-body MR-imaging in oncology. Eur Radiol 2006;16:2000–15.
13. Lenk S, Fischer S, Kotter I, Claussen CD, Schlemmer HP. [Possibilities of whole-body MRI for investigating musculoskeletal diseases]. [Article in German] Radiologe 2004;44:844-53.
14. Darge K, Jaramillo D, Siegel MJ. Whole-body MRI in children: current status and future applications. Eur J Radiol 2008;68:289-98.
15. Weckbach S. Whole-body MR imaging for patients with rheumatism. Eur J Radiol 2009;70:431-41.
16. von Kalle T, Heim N, Hospach T, Langendörfer M, Winkler P, Stuber T. Typical patterns of bone involvement in whole-body MRI of patients with chronic recurrent multifocal osteomyelitis (CRMO). Rofo 2013;185:655-61.
17. Jurik AG. Chronic recurrent multifocal osteomyelitis. Semin Musculoskelet Radiol 2004;8:243-53.
18. Jansson AF, Müller TH, Gliera L, Ankerst DP, Wintergerst U, Belohradsky BH, et al. Clinical score for nonbacterial osteitis in children and adults. Arthritis Rheum 2009;60:1152-9.
19. Beck C, Morbach H, Beer M, Stenzel M, Tappe D, Gattenlöhner S, et al. Chronic nonbacterial osteomyelitis in childhood: prospective follow-up during the first year of anti-inflammatory treatment. Arthritis Res Ther 2010;12:R74.
20. Assmann G, Kueck O, Kirchhoff T, Rosenthal H, Voswinkel J, Pfreundschuh M, et al. Efficacy of antibiotic therapy for SAPHO syndrome is lost after its discontinuation: an interventional study. Arthritis Res Ther 2009;11:R140.
21. Falip C, Alison M, Boutry M, Job-Deslandre C, Cotten A, Azoulay R, et al. Chronic recurrent multifocal osteomyelitis (CRMO): a longitudinal case series review. Pediatr Radiol 2013;43:355-75.
22. Jansson AF, Borte M, Hospach A, Kallinich T, Oommen PT, Trauzeddel R, et al. [Diagnostics and therapy of non-bacterial osteitis. Consensus statement of the 16th Worlitz expert meeting 2013 for the Deutsche Gesellschaft für Kinder- und Jugendrheumatologie]. [Article in German] Monatsschr Kinderheilkd 2014;162:539-45.
23. Miettunen PM, Wei X, Kaura D, Reslan WA, Aguirre AN, Kellner JD. Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitis (CRMO). Pediatr Rheumatol Online J 2009;7:2.