

Correlation between the Clinical Course of CRMO Lesions and the Imaging Characteristics on Follow-up MRIs

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Abstract:

Objective: To evaluate the correlation between the clinical course of chronic recurrent multifocal osteomyelitis (CRMO) lesions and their imaging characteristics on follow-up MRIs.

Material and Methods: Two musculoskeletal fellowship-trained radiologists retrospectively reviewed the initial and follow-up MRI images of 9 CRMO patients who were treated in our institution from 2008 to 2018. Evaluation of clinical course was based on symptomatology, lab results and physical examination and was compared to MRI findings, on follow-up MRIs.

Results: Thirty-five CRMO lesions in 9 patients were identified. Patient's ages ranged from 4 to 15 years with a mean age of 10 years (S.D.±3.22). Six of the 9 patients were female. Only 21 of 35 lesions had been longitudinally followed by MRI. Of the 39 follow-up MRI exams, there was clinical improvement 15 times, and 24 times there was no clinical improvement confirmed by the clinician. Three MRI features: 1) bone marrow edema (BME) size, 2) BME signal intensity and 3) periosteal edema, significantly correlated with the clinical course (p -value<0.001). When there was the improvement of all these three findings, the correlation with clinical improvement was high with 80% sensitivity and 100% specificity. The area under the receiver operator characteristic curve was 0.90 (95% confidence interval 0.795–1.005). Fourteen silent clinical lesions were also identified.

Conclusion: Bone marrow edema and periosteal edema correlated best with the clinical course of CRMO patients on follow-up MRIs.

Keywords: bone marrow edema, chronic recurrent multifocal osteomyelitis, clinical correlation, CRMO, MRI

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Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an uncommon auto-inflammatory disorder that usually manifests as non-specific, multifocal bone pain^{1,2}. Lesions have a predilection for femur, tibia, clavicle, pelvis, and spine³. CRMO is typically a diagnosis of exclusion, as neoplasm and infection can demonstrate similar imaging findings⁴.

Radiographic abnormalities of CRMO range from lytic to sclerotic lesions at metaphysis or metaphyseal equivalent². A previous retrospective study reported 39% of CRMO in long bone lesions had normal radiographs while magnetic resonance imaging (MRI) detected bone marrow edema (BME) in all cases⁵.

Despite increasing recognition of CRMO, there is scant data concerning the value of imaging in the follow-up evaluation of CRMO patients. Previous studies have described that CRMO lesions demonstrate any combination of BME, periosteal edema, soft tissue edema, and contrast enhancement⁶. How these findings change with successful or failed therapy has not been described in the literature.

The purpose of this study was to evaluate the correlation between the clinical course of CRMO lesions and their imaging characteristics on follow-up MRIs.

Material and Methods

Study populations

This study was approved by the institutional review board and is compliant with the Health Insurance Portability and Accountability Act; informed consent was waived.

A retrospective chart review identified 9 patients with established diagnosis of CRMO who were under the care of pediatric rheumatologists in Stony Brook University from 2008 to 2018. Seven of the patients were diagnosed by bone biopsy while the other two patients were diagnosed with typical presentation and multiple lesions on MRI.

All the identified CRMO lesions of the 9 patients were included in the study. The lesions, which were not followed by MRI or lacked detailed clinical data, were excluded.

Magnetic resonance imaging and clinical evaluation

The follow-up MRI exams of CRMO patients were initially performed on regions of clinical concern. It was scanned in all three planes, including T1-weighted and T2-weighted fat-suppressed or STIR sequences. Starting in 2013, all CRMO patients underwent whole-body MRI examinations including coronal STIR images of the whole body, sagittal STIR images of the entire spine, axial STIR images through the pelvis and both knees, and sagittal STIR images of both ankles and feet. A scanning time of less than 45 minutes was well tolerated by the patients.

Because intravenous contrast agents were not administered in the majority of the studies, we did not include such enhancement in this study.

The MRI's in regards to the CRMO patients were reviewed by two musculoskeletal fellowship-trained radiologists with 8-year-experience, who were blinded to the clinical symptoms.

Lesions were evaluated for increase, decrease, or no change in the following imaging features: 1) BME size, 2) strength of BME signal intensity, 3) periosteal edema, 4) soft tissue edema and 5) cortical expansion.

We based our evaluation on a grading system of bone width abnormality on a fluid-sensitive sequence. Grade 1, grade 2 and grade 3 represented abnormal edema involving less than 25%, 25%–50% and more than 50%, respectively (Figure 1).

In terms of BME signal, we evaluated the brightness of edema on fluid-sensitive sequence (TE~60–80 ms) and whether it was equal to or less than adjacent fluid/vessel signal (internal calibration) (Figure 1).

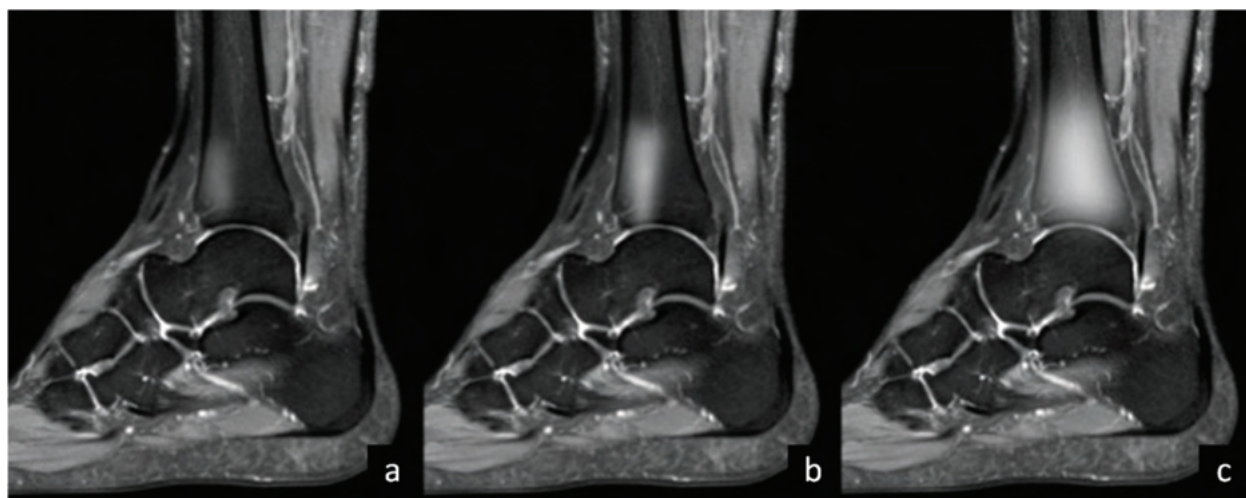


Figure 1 An illustration of the grading system of BME size and signal. The grading system was evaluated on fluid-sensitive sequence (a) Grade 1 BME size was defined as less than 25% of bone width abnormality. (b) Grade 2 BME size was defined as 25–50% of bone width abnormality. (c) Grade 3 BME size was defined as more than 50% of bone width abnormality. For BME signal evaluation, its strength was categorized as less than adjacent fluid/vessel (a) or equal to adjacent fluid/vessel (b, c).

In regards to evaluating any thickness changes of the periosteal edema, we defined periosteal edema as a linear high T2 signal intensity immediately adjacent to the outer cortical surface.

In connection to evaluating the change of the soft tissue edema, we defined it as change of extent of the edematous soft tissue on a fluid-sensitive sequence.

To evaluate the bony expansion, we assessed the change of size/shape of the affected bone such as abnormal tabulation of the metaphysis of the long bone.

The imaging findings for each lesion were compared with the clinical course (Figure 2), which was determined to be worsening, improved, or unchanged on the basis of the impression of the pediatric rheumatologists supported by the clinical parameters in the patient's chart. Clinical worsening was determined if the patients had any of the following: a new onset or progression of preexisting

joint/bone pain, worsened inflammatory marker of ESR and CRP, clinical examination of tenderness or swelling leading to increased amount of medical treatment. Clinical improvement was determined if there was absence of pain and/or improvement in inflammatory markers. If there was no significant change of clinical symptoms, a stable clinical course was determined.

Statistical analysis

To assess the association between the clinical course and MRI findings, the clinical course was grouped into clinical improvement and no clinical improvement, and MRI findings into the improved and not improved MRI findings, resulting in the contingency table. The association between clinical course and MRI findings was assessed by Fisher Exact's test. Logistic regression followed by receiver-operating characteristic (ROC) curves was performed to

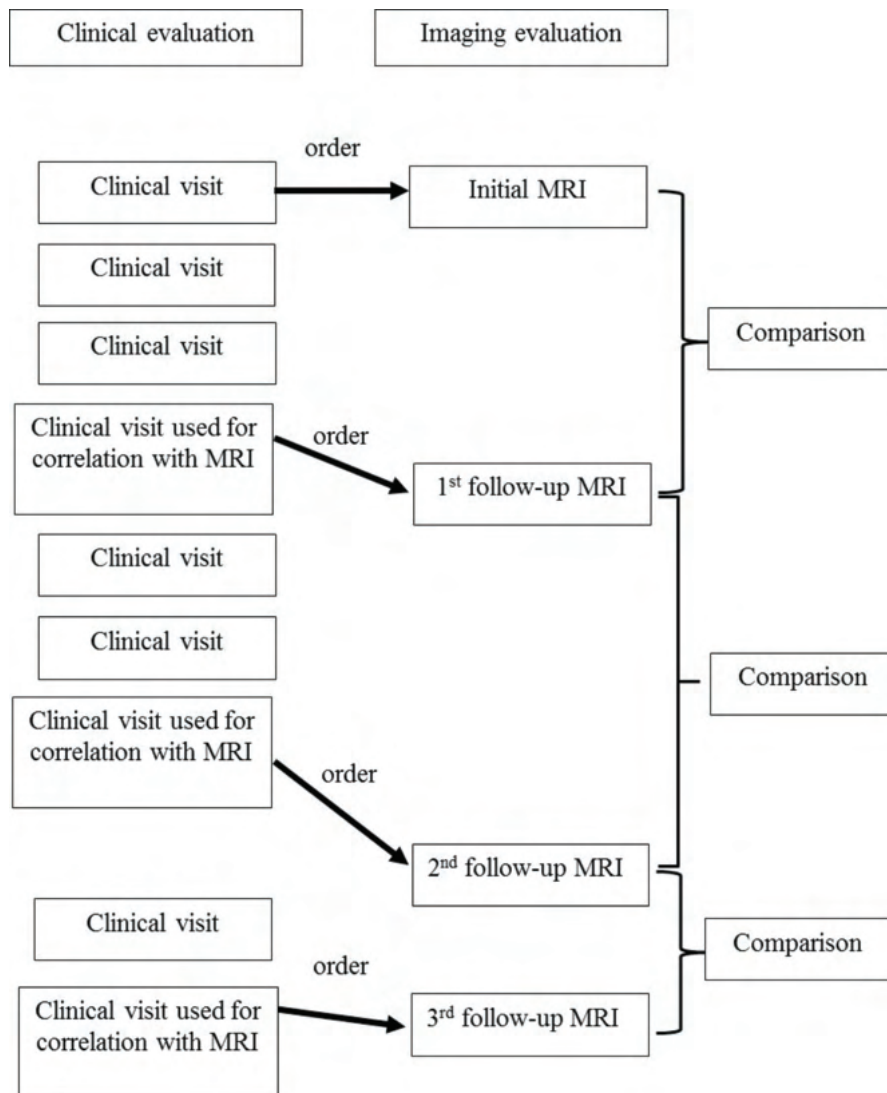


Figure 2 Flow chart of the method for imaging and clinical comparison

determine the best MRI findings associated with the clinical course. Cohen’s Kappa was run to determine if there was an agreement between the two radiologists. The agreement was considered excellent if kappa was more than 0.80, good if ranged from 0.61 to 0.80, moderate if it ranged from 0.41 to 0.60, and poor if it was 0.40 or less⁷. Statistical analysis was performed with R program version 3.5.2.

Results

Nine patients with a diagnosis of CRMO were included in the study with a mean age of 10 years (S.D.±3.22, range 4–15) (Table 1). There were 6 females and 3 males. All patients presented with joint pain without concomitant fever.

Of the 35 total lesions identified, 20 lesions were in the lower extremities, 1 lesion in the upper extremities,

Table 1 CRMO patient demographics and location of lesions

| Patient no. | Age at initial MRI | Gender | Initial CRP | Initial ESR | Number of lesions | Location of lesions (number of follow-up) |
|-------------|--------------------|--------|-------------|-------------|-------------------|--|
| 1 | 15 | M | Normal | Normal | 2 | Left acetabulum (3), Left 2 nd metatarsal (1) |
| 2 | 11 | F | Normal | NA | 2 | Left clavicle (1), left 3 rd rib (1) |
| 3 | 4 | F | Normal | Normal | 3 | T6 (3), left tibia (4), left calcaneus (4) |
| 4 | 12 | M | NA | NA | 2 | Left distal femur (0), left proximal tibia (0) |
| 5 | 8 | F | Normal | Normal | 5 | T9 (1), T10 (1), T11 (1), L2 (1), left distal fibula (1) |
| 6 | 12 | M | Abnormal | NA | 3 | Right distal tibia (4), right talus (4), left scapula (3) |
| 7 | 8 | F | Normal | NA | 6 | Right femur (1), left acetabulum (1), left superior pubic rami (1), left superior iliac crest (0), right SI joint (1), left SI joint (1) |
| 8 | 9 | F | NA | NA | 2 | T5 (1), proximal left tibia (0) |
| 9 | 12 | F | Abnormal | NA | 10 | Left distal femur (0), left proximal tibia (0), right distal tibia (0), left distal tibia (0), right navicular (0), left navicular (0), right talus (0), left talus (0), right calcaneus (0), left calcaneus (0) |

CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, NA=not applicable, M=male, F=female

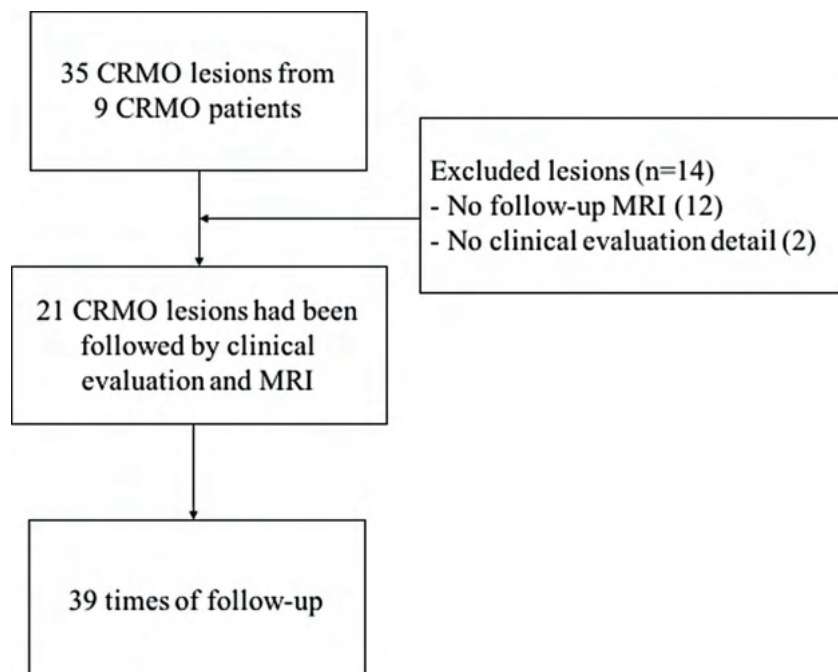
**Figure 3** Flow chart of our retrospective study

Table 2 Correlation between MRI characteristics and clinical course of lesions

| MRI characteristics | Clinically improved (n=15) | No clinically improved (n=24) | p-value |
|--------------------------|----------------------------|-------------------------------|---------|
| Bone marrow edema size | | | <0.001 |
| -Decrease | 8 (53.33) | 0 | |
| -No change/Increase | 7 (46.67) | 24 (100) | |
| Bone marrow edema signal | | | <0.001 |
| -Decrease | 8 (53.33) | 0 | |
| -No change/Increase | 7 (46.67) | 24 (100) | |
| Periosteal edema | | | <0.001 |
| -Decrease | 7 (46.67) | 0 | |
| -No change/Increase | 8 (53.33) | 24 (100) | |
| Soft tissue edema | | | 0.08 |
| -Decrease | 6 (40) | 1 (4.17) | |
| -No change/Increase | 9 (60) | 23 (95.83) | |
| Cortical expansion | | | 0.05 |
| -Decrease | 3 (20) | 0 | |
| -No change/Increase | 12 (80) | 24 (100) | |

Data are number (%) of follow-up MRIs.

and 14 lesions in the axial skeleton. Of the 35 lesions, 21 lesions had been followed with MRI with adequate clinical assessment detail.

Among the 21 lesions, all of them had been followed up with MRI examinations, comprising a total of 39 times (Figure 3). The detailed numbers of follow-up MRI examinations of each lesion are displayed in Table 1. On average, two follow-up MRIs occurred 397 days apart (S.D.±359) and patients were evaluated clinically every 3–4 months. The time interval between the clinical evaluation and the ordered MRI at follow-up was 42 days (S.D.±39).

Of the 39 MRI exams, 15 times there was a clinical improvement. While 13 times, the patient was clinically stable and 11 times, the patient showed clinical progression. We combined these two groups into one group of no clinical improvement. Only three MRI characteristics (BME size, BME signal intensity and periosteal edema) were significantly correlated with the clinical course (p-value<0.001). The

correlation between MRI characteristics and clinical course can be found in Table 2.

Among the clinical improvement group (15 follow-up MRIs), 8 follow-up MRIs demonstrated decreased BME size and signal intensity (sensitivity 53%, p-value<0.001) and 7 follow-up MRIs demonstrated decreased periosteal edema (sensitivity 47%, p-value<0.001) (Figure 4).

Among the group of no clinical improvement (24 follow-up MRIs), all of them demonstrated no improvement of BME size and signal (specificity 100%, p-value<0.001) and again all of them demonstrated no improvement of periosteal edema (specificity 100%, p-value<0.001) (Figure 5).

By using these three MRI characteristics, correlation with clinical course showed 80% sensitivity, and 100% specificity. The area under the ROC curve was 0.9 (95% confidence interval 0.795–1.005) (Figure 6).

Concerning interobserver agreement in BME size, BME signal intensity was moderate (0.52) and fair (0.37),



Figure 4 An 8-year-old girl (patient 5) with diagnosis of CRMO presented with left ankle pain and swelling. a and b, Sagittal T1-weighted image (a) T2-weighted fat-suppressed image (b) of the left ankle at initial presentation. There was a BME (long arrow); grade 3 of BME size and equal to vessel/fluid of BME signal, of the metaphysis of the distal fibula that appeared to extend across the growth plate to the epiphysis. Prominent soft tissue edema (short arrow) and periosteal edema (arrowhead) was also noted. (c) Coronal STIR image of the both ankles as the part of the MRI whole body (about 1 year later) showed resolution of the left distal fibula lesion. Patient had clinical improvement at the time of follow-up MRI.

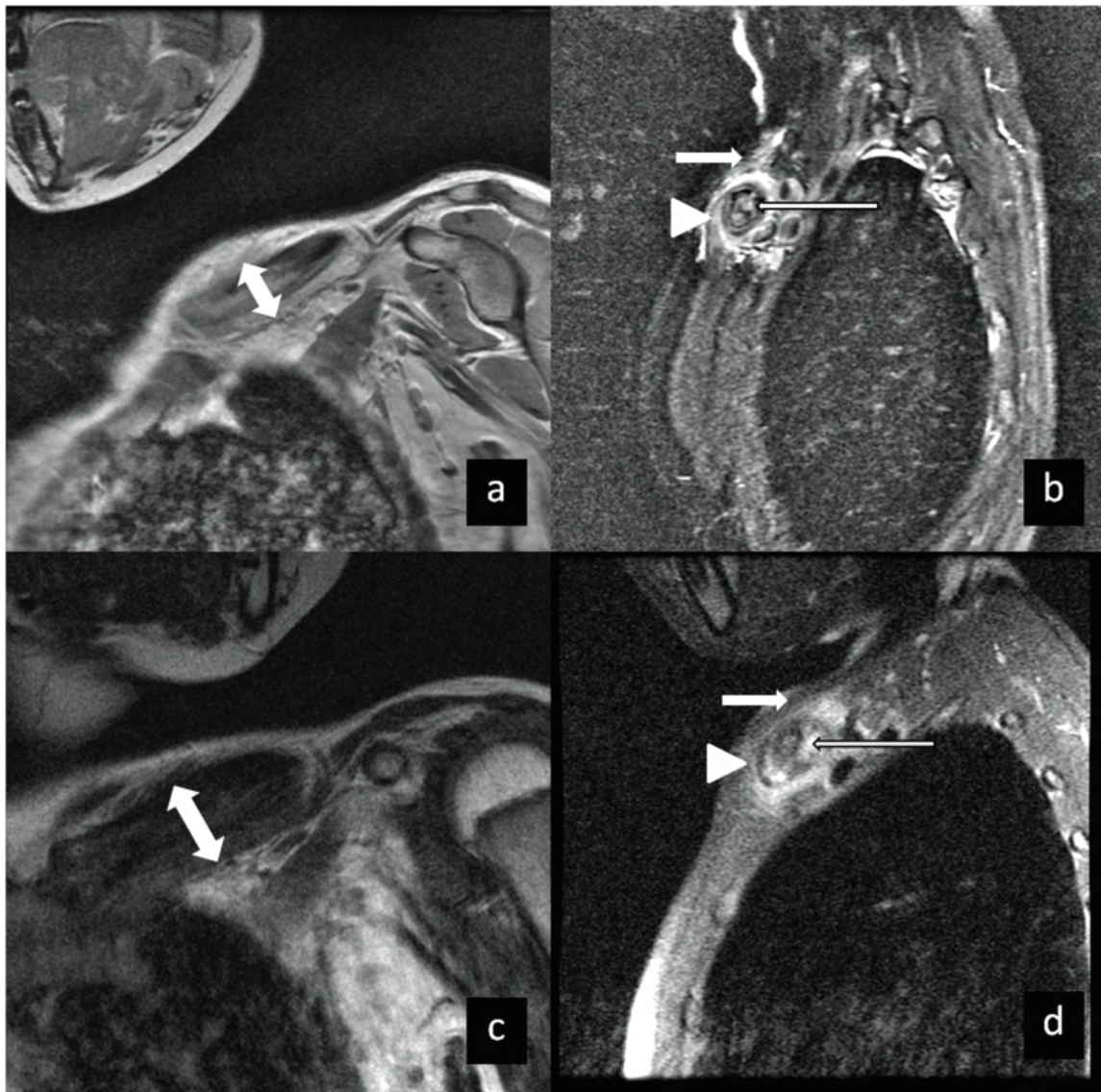


Figure 5 An 11-year-old girl (patient 2) with diagnosis of CRMO with local swelling and pain of the left shoulder. a and b, Coronal T1-weighted image (a) sagittal T2-weighted fat-suppressed image (b) of the left clavicle. There was a sclerotic expanded lesion (double arrow head) affecting the medial left clavicle with also BME (long arrow); grade 2 of BME size (according to its length, not shown here) and less than vessel/fluid of BME signal, circumferential periosteal (arrow head) and soft tissue edema (short arrow). c and d, Coronal T1-weighted image (c) and sagittal T2-weighted fat-suppressed image (d) of the left clavicle at follow-up MRI (about 7 months later since a and b). The follow-up MRI was ordered due to exacerbation of the left shoulder pain. Worsening of the MRI findings were depicted including BME (long arrow); grade 3 of BME size (according to its length, not shown here) and equal to vessel/fluid of BME signal, periosteal edema (arrowhead), soft tissue edema (short arrow) and cortical expansion (double arrowhead).

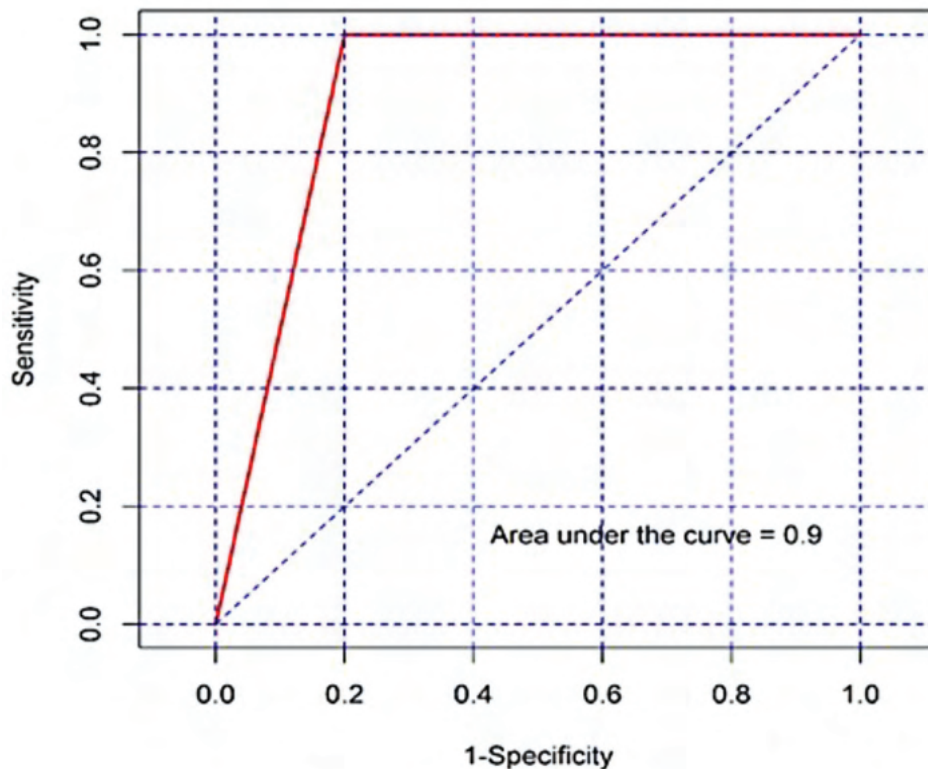


Figure 6 Receiver operator characteristic (ROC) curve was performed to determine the best MRI findings associated with clinical course. With using MRI findings of decreased BME size, BME signal and periosteal edema, it correlated with clinical improvement with 80% sensitivity, 100% specificity. The area under the ROC curve was 0.9 (95% CI 0.795–1.005).

respectively while an almost perfect agreement was seen in periosteal edema (0.944), soft tissue edema (1) and cortical expansion (1). The interobserver agreement was calculated from a total 21 follow-up lesions.

Seven patients underwent whole body MRI which allowed for a more global assessment of skeletal lesions (Figure 7). Fourteen clinically silent lesions were found in three patients.

CRMO complications were also seen. Of the 6 vertebral lesions, there were two vertebral plana. Of the 13 tubular bone lesions, 12 lesions showed growth plate involvement.

Discussion

Imaging plays an important role in objectively assessing CRMO patients. Even though radiography remains the first imaging modality, it has a very limited

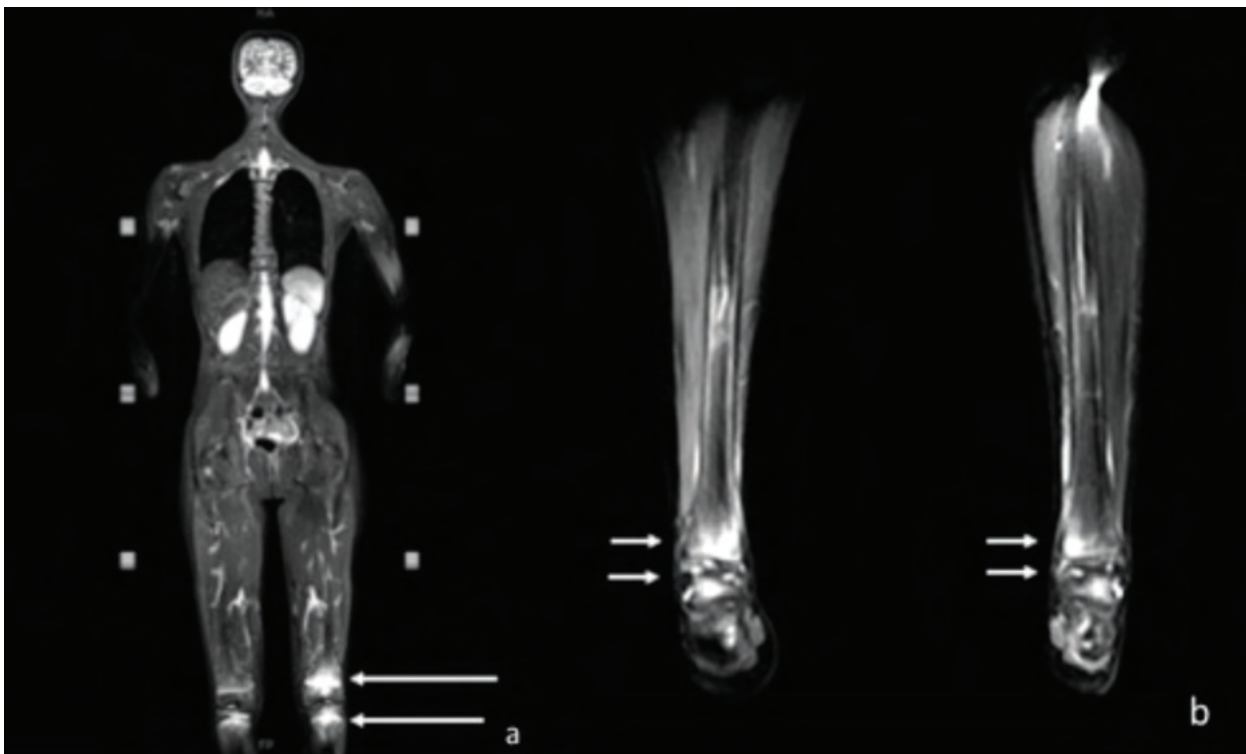


Figure 7 A 12-year-old girl (patient 9) with diagnosis of CRMO presented with pain and local swelling at left knee. a and b, Coronal STIR images of whole-body MRI scan through body, both knees (a) and both ankles (b) were. Multiple asymptomatic lesions at both ankles (short arrow) were detected in addition to the left knee lesions (long arrow).

role at the follow-up. MRI with high sensitivity of marrow edema and no radiation is the top choice for the follow-up imaging in CRMO.

Our study is the first, to our knowledge, to assess the correlation between the clinical course of CRMO lesions and their changes in MRI features. We found that changes in BME size, BME signal and periosteal edema are best correlated with clinical response in CRMO patients. These are likely supported by the facts that bone marrow and periosteum is known as richly innervated and potential candidates for pain sources⁸. Decreasing BME and periosteal edema after therapeutic intervention was observed in several case

reports with CRMO and SAPHO syndrome which is usually regarded as the adult type of CRMO⁹⁻¹¹. Since pain is the cardinal clinical feature of CRMO, our result of a significant correlation between clinical symptoms of pain and BME in CRMO patients may help increase the understanding of the pathophysiology of the disease and aid in the selection of therapeutic targets. The close relationship between pain and BME was also suggested in several diseases like OA, trauma, and osteonecrosis^{8,12,13}. It was postulated that intraosseous hypertension due to an increase of water, blood, or other fluids inside the bones could be considered as the source of pain¹⁴. Even though histopathologic findings

in CRMO are variable and nonspecific, the predominance of polymorphonuclear leukocytes and osteoclast bone resorption with or without multinucleated giant cells could be found in the acute phase².

MRI is also useful in the identification of clinically silent lesions. Especially, the usefulness of whole-body MRI has been recognized in CRMO. Recent literature has described the utility of whole-body MRI for surveillance of CRMO lesions, as CRMO lesions are not always clinically detectable. Still, if there are multifocal lesions including clinically silent BME, it strongly suggests the diagnosis of CRMO^{15,16}.

This study had several limitations. Firstly, the sample size was small, but it is known that CRMO is a relatively rare disease and longitudinal analysis using MRI has not been well documented. Secondly, the interobserver agreement in the BME size was fair to moderate. This could be due to the ill-defined border of BME, thus different visual perception. Thirdly, while whole body-MRI may identify more lesions, the signal-to-noise ratio of each lesion can be limited. In the future, we plan to confirm our results in a larger patient population with a multi-center prospective study.

Our study demonstrated that CRMO lesions could be effectively followed via MRI. The improvement of three imaging features of BME size, BME signal and periosteal edema correlated well with clinical changes in CRMO patients.

Conflict of interest

The authors have no competing interests to declare.

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