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Research

Whole-body MRI in Pediatric Patients with Chronic Recurrent Multifocal Osteomyelitis

Kronik Tekrarlayan Multifokal Osteomiyelitli Pediatrik Hastalarda Tüm Vücut MRG

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ABSTRACT

Objective: To evaluate the clinical and radiological findings of the patients with chronic recurrent multifocal osteomyelitis (CRMO) and to present the benefits of using whole-body magnetic resonance imaging (WBMRI) in these patients and the changes we have made in the technique.

Methods: A total of 45 patients who underwent WBMRI between 2017 and 2021 were included in the study. All WBMRI scans included coronal short tau inversion recovery (STIR), coronal T1W, and sagittal spinal STIR sequences. The examination time was 40 min on average. All WBMRIs were evaluated at two different time. At first assessment, only coronal STIR images were evaluated in all patients. In the second assessment, the same patients evaluated with all the sequences. The contribution of coronal T1W and sagittal STIR sequences to the diagnosis was investigated by comparing the first evaluation with the second evaluation. Thirty five patients were diagnosed with CRMO. The remaining 10 patients had other inflammatory, infective, and neoplastic diseases. The diagnosis of 15 patients with CRMO was based on bone marrow biopsy results. Also, biopsy was performed in 10 patients diagnosed as non-CRMO.

Results: Most of the patients had multifocal bone lesions, particularly in the metaphyses adjacent to the epiphyseal region. The bones of the lower extremities were the most commonly affected. The mean delay in diagnosis was 17 months (0-96), and the follow-up period was 20 months (1-47) in a total of 35 patients, with a recurrence rate of 28%. In most patients (88%), lesions could be identified from coronal STIR images alone at the initial evaluation. However, in 5 patients whose diagnosis was missed when evaluated only from coronal STIR images, lesion identification and possible preliminary diagnosis were detected only with coronal T1W and sagittal STIR images in the second look.

Conclusion: WBMRI is an important examination of systemic diseases such as CRMO that involve multiple sites. In addition to coronal STIR sequences, coronal T1-weighted and sagittal STIR sequences are important in identifying other infective-inflammatory diseases and particularly hematological malignant processes in the differential diagnosis of CRMO.

Keywords: Pediatric radiology, chronic nonbacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, CRMO, whole-body MRI

ÖZ

Amaç: Kronik tekrarlayan multifokal osteomiyelitli (CRMO) hastaların klinik ve radyolojik bulgularını değerlendirmek ve bu hastalarda tüm vücut manyetik rezonans görüntüleme (WBMRI) kullanmanın yararlarını ve teknikte yaptığımız değişiklikleri sunmaktır.

Gereç ve Yöntem: 2017-2021 yılları arasında WBMRI uygulanan toplam 45 hasta çalışmaya dahil edildi. Tüm WBMRI taramalarında koronal kısa zamanlı inversiyon düzelme (STIR), koronal T1W ve sagital spinal STIR sekansları kullanılmıştır. İnceleme süresi ortalama 40 dakika idi. Tüm WBMRI'ler iki farklı zamanda değerlendirildi. İlk bakıda tüm hastalarda sadece koronal STIR görüntüleri değerlendirildi. İkinci bakıda aynı hastalara ait tüm sekanslar değerlendirildi. Birinci değerlendirme ile ikinci değerlendirme karşılaştırılarak koronal T1W ve sagital STIR sekanslarının tanıya katkısı araştırıldı. Otuz beş hastaya CRMO teşhisi konuldu. Geri kalan 10 hastanın diğer enflamatuvar, enfektif ve neoplastik hastalıkları vardı. CRMO'lu 15 hastanın tanısı kemik iliği biyopsi sonuçlarına dayanıyordu. CRMO tanısı alan diğer 20 hastada kesin tanı, diğer hastalıkları dışlayan klinik ve radyolojik bulguların varlığında konulmuştur.

Bulgular: Hastaların çoğunda özellikle epifiz bölgesine komşu metafizlerde multifokal kemik lezyonları mevcuttu. En sık alt ekstremite kemikleri etkilenmişti. Toplam 35 hastada ortalama tanı gecikmesi 17 ay (0-96), takip süresi 20 ay (1-47) olup, nüks oranı %28 idi. Hastaların çoğunda (%88), lezyonlar ilk bakıda sadece koronal STIR görüntülerinden bile tanımlanabilmiştir. Ancak sadece koronal STIR görüntülerinden değerlendirildiğinde tanısı atlanan 5 hastada lezyon tanımlaması ikinci bakıda değerlendirilen koronal T1W ve sagital STIR görüntüleri ile mümkün olmuştur.

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ÖZ

Sonuç: WBMRI çekim süresinin uzunluğu ve çocukların uyumu açısından zor bir inceleme yöntemidir. Doğru teşhis ve tedavi için gerekli tüm sekansların yapılması esastır. CRMO'nun ayırıcı tanısında koronal STIR sekanslarına ek olarak koronal T1W ve sagital STIR sekansları diğer enfektif-enflamatuvar hastalıkları ve özellikle hematolojik malign süreçleri belirlemede önemlidir.

Anahtar Kelimeler: Pediatrik radyoloji, kronik bakteriyel olmayan osteomiyelit, kronik tekrarlayan multifokal osteomiyelit, CRMO, tüm vücut MRG

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is a subacute and chronic idiopathic autoinflammatory bone disorder also known as sterile non-bacterial osteomyelitis.

CRMO is characterized by exacerbation and recovery periods with clinical findings and affecting children and adolescents. Despite advances in imaging and microbiological diagnostic techniques and a significant increase in the number of cases over the past decade, the true incidence of CRMO is not yet fully known.

Non-infectious osteomyelitis can be observed in several inherited monogenic autoinflammatory conditions, such as the juvenile form of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO), Majeed syndrome, pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome, and deficiency of IL-1R antagonist syndrome (1).

Long-term clinical follow-up with whole-body magnetic resonance imaging (WBMRI) may be needed until the patient is in radiological remission or a steady-state is achieved.

Non-steroidal anti-inflammatory drugs, immunosuppressive drugs, and biological agents are used for treating CRMO. Long-term clinical follow-up with WBMRI may be required until the patient is in radiological remission or a steady state is achieved.

Although CRMO is classified in the benign group, it significantly impairs the quality of life of patients due to recurrent symptoms and permanent sequelae. The diagnosis of exclusion was based on clinical presentation, imaging findings, and culture-negative bone biopsies (2,3). Direct radiographic findings are characteristic but not pathognomonic. It may appear completely normal, particularly in the early stages of the disease.

Bone surveys, scintigraphy, and positron emission tomography are generally used for whole-body imaging. However, all of these modalities involve ionizing radiation. WBMRI is used less frequently in children than in adults because of the need for sedation in younger age groups. Among the non-oncological applications of WBMRI, the most important ones are rheumatological diseases, including multifocal recurrent osteomyelitis, arthritis, dermatomyositis, connective tissue diseases, and fever of unknown origin (4). In CRMO, the characteristic patterns of bone involvement and roadmap for possible biopsy can be determined using WBMRI (Figure 1). Furthermore, the response to treatment can be evaluated, and complications can be identified.

There is no standard technique for WBMRI, and the aim is to achieve maximum coverage of the body with the minimum number of images in the shortest possible time. Patients are usually scanned in the supine position with their arms on the sides and legs extended (4). Scanning is performed in the coronal plane to cover most of the body. However, it has a lower sensitivity for the head and thorax than axial plane scans. As in many centers, the main sequence of the examination is the coronal short tau inversion recovery (STIR). Although there is no consensus, one or more of the coronal T1-weighted (T1W), sagittal T2, STIR, T1W, and diffusion-weighted imaging (DWI) sequences can be used in addition to coronal STIR images. T1W images are necessary to better evaluate bone marrow involvement, especially in hematological malignant processes. Therefore, sagittal plane sequences can be added to better assess the vertebral column (5,6).

In this study, we evaluated the use of WBMRI in the clinical and radiological evaluation of patients with CRMO patients and the benefits of changes in the technique we used for diagnosis.

METHODS

Data of 45 patients who presented to the pediatric rheumatology clinic and underwent WBMRI between January 2017 and December 2021 were retrospectively screened. Of these, 35 patients diagnosed with CRMO were included in this study. Ten patients were excluded because they were diagnosed with other, infectious, rheumatological, and hematological diseases. This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (decision no: 283, date: 30.09.2021).

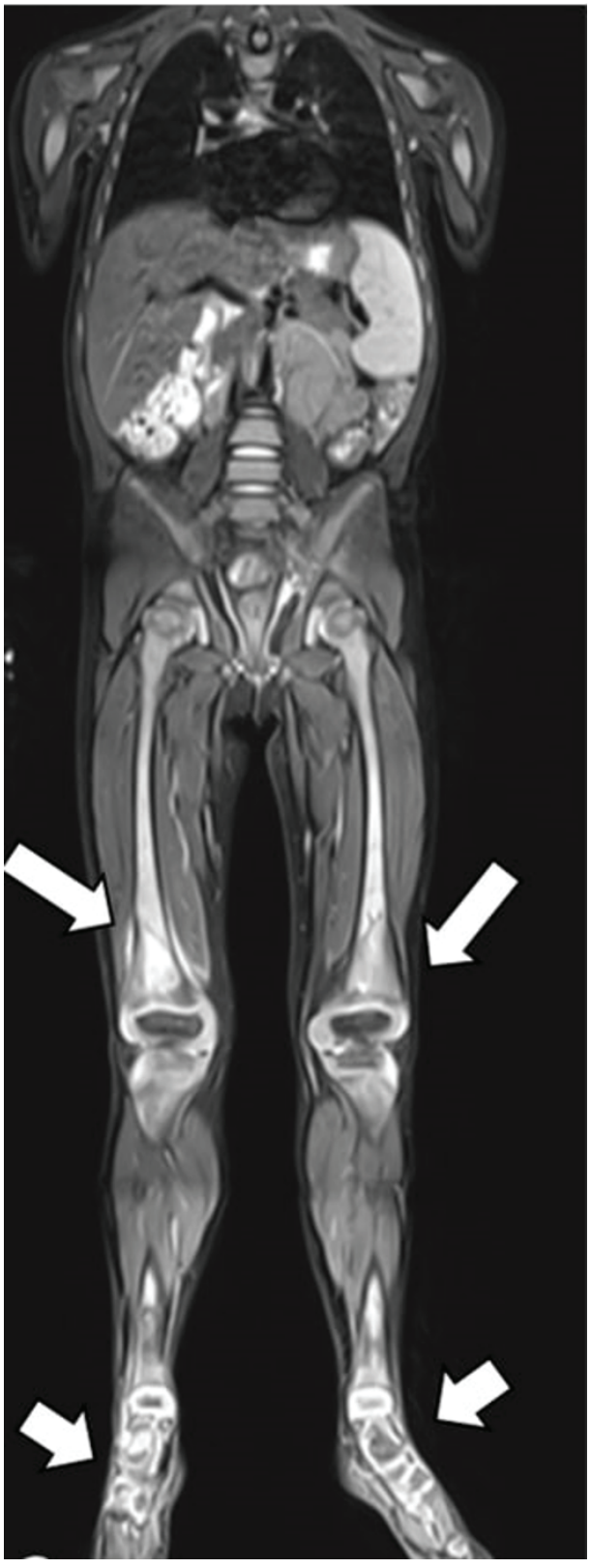

Figure 1. In the whole body coronal STIR image shows diffuse T2W hyperintense pathological signal changes are observed in the distal diaphyseal parts and metaphyses of the bilateral femur and tibia. Also diffuse involvement is observed in the tarsal bones

STIR: Short tau inversion recovery

Patients' clinical, laboratory, and pathological findings were obtained from their electronic files. The radiological data of the patients were re-evaluated using the picture archiving communication system and classified. Plain radiography, computed tomography (CT), and MRI of the patients were completely re-evaluated by a pediatric radiologist with 15 years of experience in radiology.

All WBMRIs were evaluated at two different time. At first assessment, only coronal STIR images were evaluated in all patients (Figure 1). It was then evaluated in the same patients with all their sequences, including coronal T1W and sagittal STIR images. The contribution of coronal T1W and sagittal STIR sequences to the diagnosis was investigated by comparing the first evaluation with the second evaluation.

The radiologic diagnosis of CRMO was based on the presence of at least one lesion consistent with osteomyelitis with radiological and/or histopathological features, excluding infectious, inflammatory, and oncological diseases.

The final diagnosis of 15 patients with CRMO was based on bone marrow biopsy results. In the other 20 patients diagnosed with CRMO, the final diagnosis was made in the presence of clinical and radiological findings, excluding other diseases.

Technical Details of the Radiological Evaluation

Depending on the patient's height, the number of stations scanned in the coronal plane was between five and seven. Additionally, two stations were used to visualize the spine in sagittal STIR images. The images were combined without repositioning to shorten the scanning time.

We analyzed the STIR and T1W sequences in the coronal plane. Additionally, sagittal STIR images of the vertebral column were obtained at the two stations.

The same coil and precisely matched slice selection gradients were used at each station to generate automatic image alignment and whole-body images after the acquisition.

Only two patients were examined under anesthesia. Average shooting time was 35-40 min.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 21. Percentages, medians, and minimum and maximum values were used, where appropriate, to present descriptive statistics.

RESULTS

The main demographic and clinical characteristics of the 35 pediatric patients are included in Table 1. Most patients had multifocal bone lesions at the time of diagnosis. Unifocal involvement was observed in four patients. The distribution of bone lesions is shown in Table 2 (Figure 2). Most patients had periphyseal bone lesions, particularly in the metaphyseal region. In 40% of the patients, only bone marrow edema was detected on MRI, and no abnormal radiological findings were observed on direct radiography or CT, if performed. The mean follow-up period was 20 months (standard deviation, 14 months). Recurrence was observed in 10 patients.

In nine patients (25.7%), there was soft tissue inflammation and periosteal reaction accompanying bone lesions. One patient had osteoporosis and two had vertebral insufficiency fractures (Figure 2). Fourteen patients (40%) had sacroiliitis, four (11.4%) had palmoplantar pustulosis, one (2.9%) had psoriasis, and one (2.9%) had inflammatory bowel disease.

Table 1. Demographic, clinical, and laboratory findings of patients with non-bacterial chronic osteomyelitis

	Total (n=35)
Demographics	
Male (%)	23 (65.7%)
Female (%)	12 (34.3%)
Age at disease onset, years, median (range)	11.8 (5-17)
Delay in diagnosis, months, median (range)	17.4 (0-96)
Follow-up, months, median (range)	19.8 (1-47)
Symptoms	
Bone pain	35 (100%)
Swelling	10 (28.5%)
Limping	9 (25.7%)
Fever	1 (2.8%)
Laboratory findings	
Leukocytes $\times 10^3/mm^3$, range	7.6 (4.2-14)
Erythrocyte sedimentation rate, mm/h, range	27.9 (2-100)
C-reactive protein, mg/dL, range	7.7 (0-58)
Positive antinuclear antibodies, n (%)	8 (22.8)
HLA-B27 positive, n (%)	7 (20)
Syndromic patients	4 (11.4)
SAPHO, n (%)	3 (8.6)
Majeed, n (%)	1 (2.9)

SAPHO: Synovitis, acne, pustulosis, hyperostosis, and osteitis, HLA: Human leukocyte antigen

The unilateral hip dislocation developed in one patient. None of the patients had any clinical or radiological evidence of enthesitis. Three patients were diagnosed with SAPHO, and one with Majeed syndrome.

Joint involvement was present in 20 patients, with some involvement in more than one joint. The sacroiliac joint was the most commonly involved joint, followed by the knee, the sternoclavicular joint, and the ankle (Table 3).

Analysis of biopsy samples revealed osteomyelitis with negative culture results. A mixed inflammatory pattern associated with sclerosis was also observed.

In the WBMRI evaluation of 45 patients, radiological data were insufficient for diagnosis in 5 patients who were evaluated first with coronal STIR. Pathological findings that could not be detected only when evaluated with coronal STIR images could be evaluated after coronal T1W and sagittal STIR images were examined. Of these 5 patients, 2 were diagnosed with acute lymphoblastic leukemia (ALL), one with acute myeloid leukemia (Figure 3), one with brucellous spondylodiscitis, and one with IgG4-related spondylodiscitis (Figure 4).

DISCUSSION

If clinical symptoms are compatible with CRMO, WBMRI should be performed to evaluate multifocal bone lesions, including nonpainful silent lesions. WBMRI is useful not only for diagnosis but also for follow-up and in the detection of possible growth disorders and deformities (7,8). Our study also showed that in addition to routinely applied coronal STIR sequences, the addition of coronal T1W and sagittal STIR images is very valuable in differential diagnosis.

WBMRI is a screening tool that is primarily used for detecting bone marrow edema. Coronal STIR imaging is therefore essential. Some studies have suggested adding T1W and DWI images to the evaluation. In addition, the sagittal plane examination is recommended to evaluate the spinal vertebral column (5,9,10). Damasio et al. (9) stated that T1 imaging is necessary to distinguish between normal bone marrow signals and lesions. The red bone marrow and a CRMO lesion are both hyperintense on STIR images, but the former has an intermediate signal, while the latter is hypointense on T1W images. Additionally, on T1W images, fat, blood products, and proteinaceous material can be differentiated (9,11). There are limited studies on the use of DWI for CRMO. The interpretation of DWI findings can be difficult because of the heterogeneous bone marrow signals in children. However, it may also be useful for differentiating malignant lesions (12,13). In our experience,

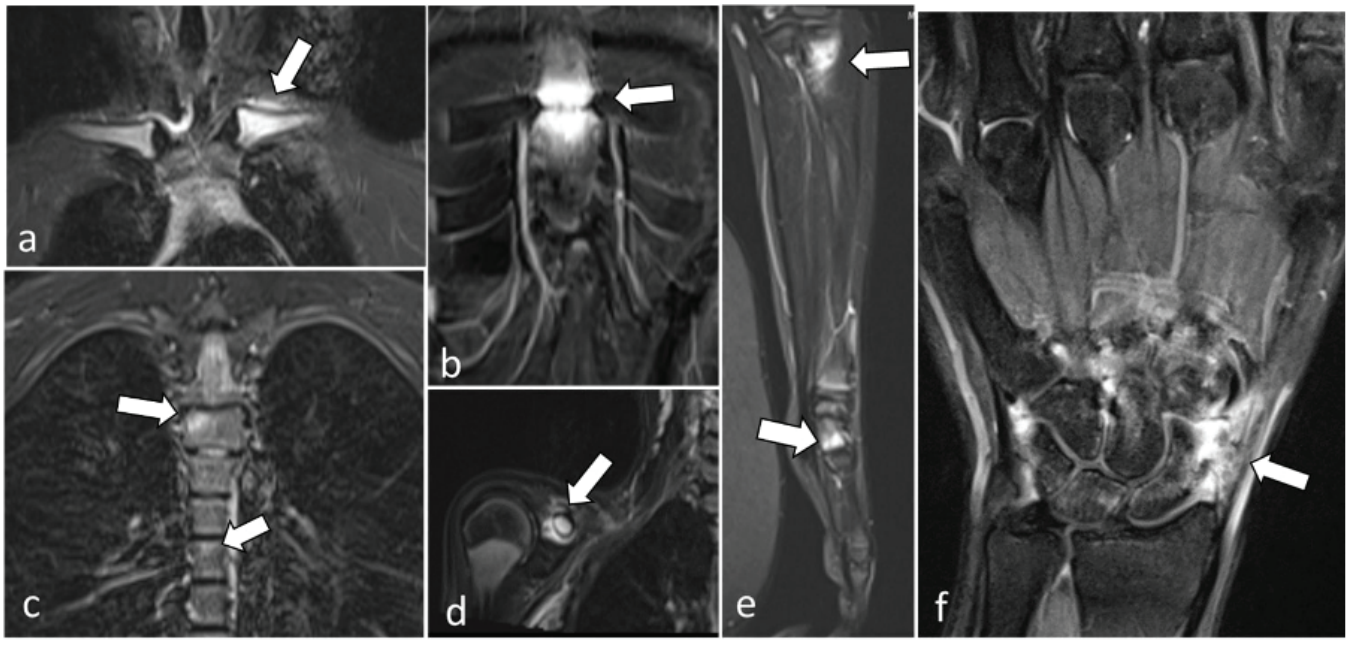

Figure 2. Whole-body magnetic resonance images of a 15-year-old male with axial skeleton and upper extremity involvement. Coronal STIR images show findings of osteitis in the metaphyseal areas adjacent to the physis line in the left clavicle (a), sternum (b), vertebrae (c), coracoid process (d), ulna (e) and carpal bones (e, f)
STIR: Short tau inversion recovery

Table 2. Distribution of the affected bones on magnetic resonance imaging

Affected bones	n (%)
Upper extremity	7 (20)
Humerus	6 (17.1)
Radius	3 (8. 6)
Ulna	1 (2.9)
Carpal/metacarpal bones	4 (11.4)
Lower extremity	**33 (94. 2)**
Femur	23 (65.7)
Tibia	30 (85.7)
Fibula	2 (5.7)
Tarsal/metatarsal bones	23 (65. 7)
Axial skeleton	**18 (51. 4)**
Mandibula	1 (2.9)
Clavicle	8 (22.8)
Scapula/coracoid process	8 (22.8)
Sternum	6 (17.1)
Vertebra	6 (17.1)
Pelvic bones	17 (48.6)

Table 3. Distribution of patients with arthritis

Joints with arthritis	n (%)
Sacroiliitis	14 (40%)
Knee	6 (17.1%)
Sternoclavicular	5 (14.2%)
Ankle	4 (11.4%)
Temporomandibular	2 (5.7%)
Hip	2 (5.7%)
Tarsometatarsal	1 (2.8%)
Talonavicular	1 (2.8%)
Talocalcaneal	1 (2.8%)

it is easier to exclude possible hematological pathologies by adding T1W sequences to STIR images if the patient is scanned without anesthesia and can tolerate a long duration. Hematological malignancies such as leukemia and lymphoma may be confused with CRMO because they may present with abnormal bone marrow. However, in these diseases, rather than edema, focal or extensive bone marrow replacement is observed (14). T1W images are also very useful in differentiating pathologies from the normal red marrow in children (Figure 3). In our patient group, bone marrow blastic infiltration in two patients who could be considered completely normal when coronal STIR images were examined, could be understood from coronal T1W images. The diffuse bone marrow signal reduction in T1W images suggested hematological malignant involvement, and these patients were quickly diagnosed with ALL by bone marrow biopsy.

Additionally, we had the opportunity to evaluate the vertebral columna better in sagittal STIR images. Of the

pathological signal changes, compression fractures, disc and spinal canal pathologies can be better defined. Two patients with spondylodiscitis and one patient with spinal granulocytic sarcoma could be detected by sagittal STIR images in our study.

The average scan time for WBMRI has been reported to be 40 min in previous studies. In our study, the total time of WBMRI varied between 30 and 45 min, depending on the size of the child.

In the literature, the average age of patients at diagnosis of CRMO is 9-11 years, and girls are affected more than boys (2,13,15). In our study group, the mean age at diagnosis was 12 years, and this was more common in boys (65%). It is difficult to determine the onset of the disease because of insidious and subtle symptoms. In a multicenter study of 178 patients, Wipff et al. (16) reported that CRMO was twice as common in the female group, the mean symptom onset year was 9.8 years, the mean age at diagnosis was 16.4 years, and the diagnostic delay time was 17.3 months. These periods decrease over time as the disease becomes more recognizable. In our study, the mean age at diagnosis was 11.8 years, and the mean delay in diagnosis was 17.4 months.

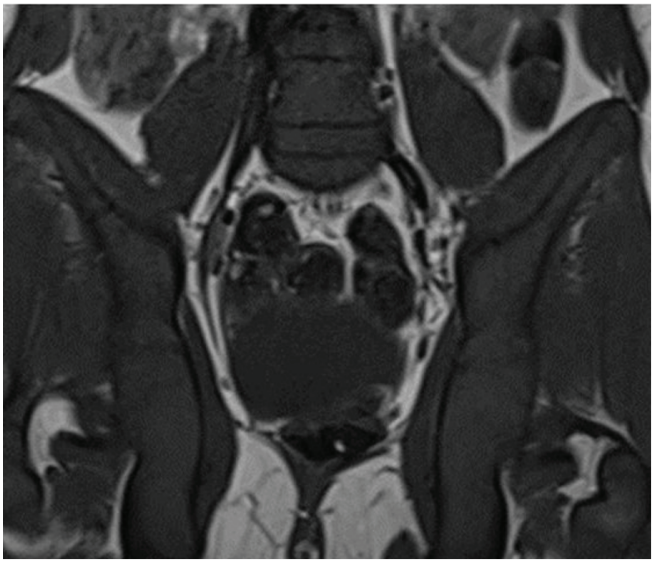

Figure 3. Coronal T1-weighted image of a nine-year-old male patient diagnosed with acute lymphocytic leukemia, showing a markedly decreased T1 signal secondary to the diffuse infiltration of the bone marrow

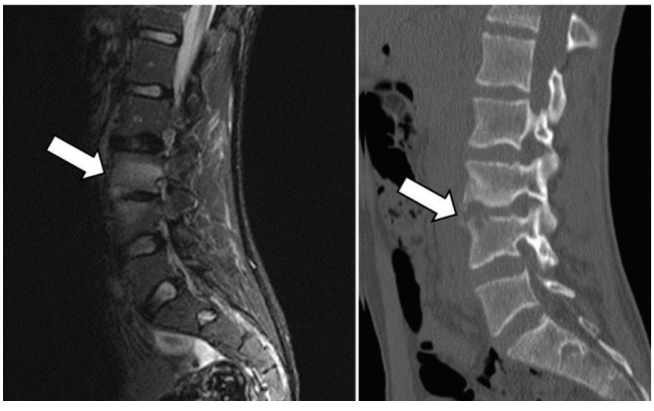

Figure 4. MRI and CT of 17-year-old male patient, inflammatory signal changes are observed in the L3_L4 disc and the vertebral end plateaus facing the disc in sagittal STIR images. There is moderate loss of height in the disc and lytic changes in the bone tissue in the vertebra end plateaus

MRI: Magnetic resonance imaging, CT: Computed tomography, STIR: Short tau inversion recovery

The typical radiological findings of CRMO are multifocality and involvement of the juxtaphyseal/periphyseal areas,

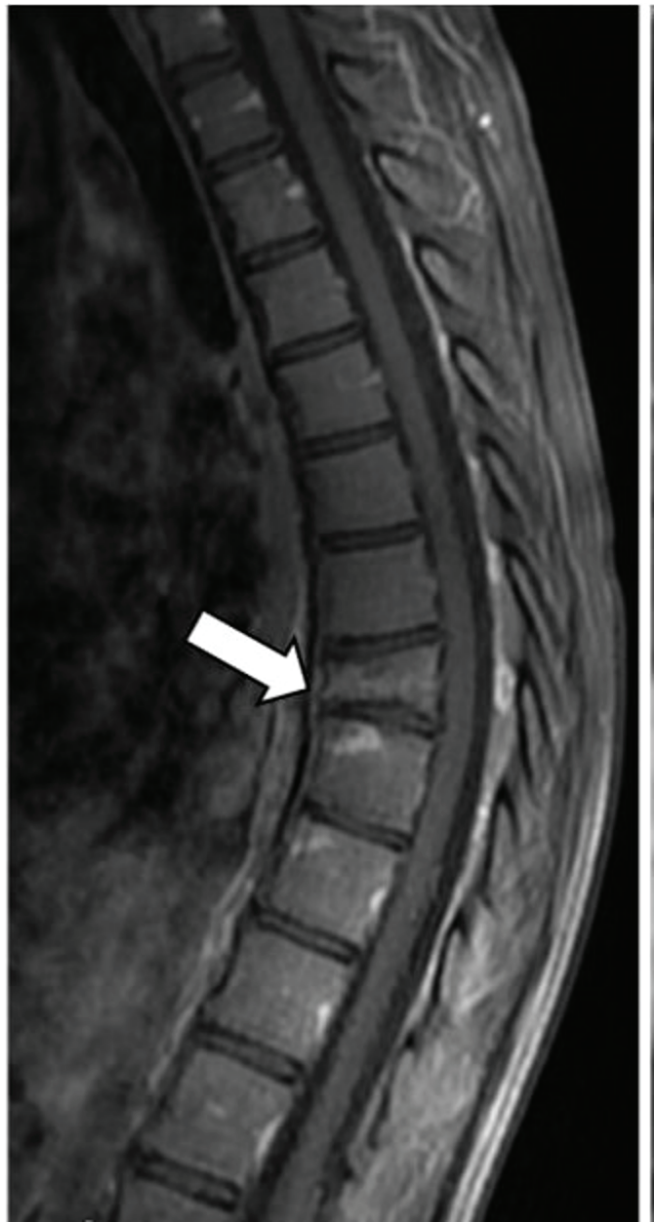

Figure 5. Sagittal STIR images of a 16-year-old girl presenting with a compression fracture in the T8 vertebra and bone marrow edema in the T9 and T10 vertebra corpus superior end plateaus

STIR: Short tau inversion recovery

particularly in the metaphyses. Most bone lesions are located in the tibia, followed by the femur, appendiceal, and axial skeleton (7,17). In our study, the bones of the lower extremities were the most affected body regions, consistent with the literature. In this study, relapse was observed in 28% of the patients during the clinical follow-up. The lower rates of relapse compared with those in the literature may be related to the treatment and follow-up time.

Although CRMO is the most common disease affecting 1/3 of the medial clavicle, clavicular involvement is atypical in bacterial osteomyelitis. In our study, clavicular involvement was present in eight patients (~23%). In some studies, up to 30% of the lesions were reported to be located in the clavicle in patients with CRMO (18).

Spinal involvement is less common than the involvement of long tubular bones, but it can complicate CRMO cases due to pathological fractures. Spinal involvement has recently been recognized as a typical feature of CRMO, with a reported prevalence of up to 30% (16,19,20). In 23 articles, the incidence of spinal involvement in children with CRMO varied between 2% and 43% (21). It can be difficult to differentiate CRMO spinal lesions from bacterial spondylitis or spondylodiscitis. Disc involvement is not expected in CRMO; however, rare cases of CRMO involving the disc have been described (7,20,22). In our study group, spinal vertebral involvement was present in six (17%) patients (Figure 5). Compression fracture complications secondary to thoracic vertebral involvement developed in two of our patients (Figure 2).

Similar to previous studies, multifocal bone lesions were observed in the majority of our patients. The affected bones in the four patients with unifocal involvement were the tarsal bones, fibula, and mandible. Gaal et al. (23) evaluated the data of 22 patients with mandibular involvement who were diagnosed with CRMO and reported that 18 patients had unifocal lesions.

A standard WBMRI protocol was not used in any patient. Biopsy was not undertaken in ten cases due to the typical clinical presentation of CRMO. Since spontaneous remission may occur in patients with CRMO, some patients did not attend their follow-up, and therefore, complete data could not be obtained concerning their treatment and recovery processes.

CONCLUSION

CRMO is a multifocal autoimmune disease that often presents as metaphyseal bone lesions. Recently, CRMO has been increasingly detected using WBMRI. In this study, we discuss the different and overlapping features of our cases in relation to the literature. WBMRI is important for both the diagnosis and follow-up of CRMO with recurrent attacks and multifocal bone involvement. In addition to coronal STIR images, which constitute an essential component of WBMRI, coronal T1W and spinal sagittal STIR images should be included in the evaluation of differential diagnosis of non-bacterial chronic osteomyelitis.

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ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (decision no: 283, date: 30.09.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.T., Concept: S.T., B.S., Design: S.T., Data Collection or Processing: S.T., B.S., Analysis or Interpretation: S.T., B.S., Literature Search: S.T., Writing: S.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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