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RESEARCH ARTICLE

Clinical Characteristics and Short-term Outcomes of Paediatric Patients with Chronic Recurrent Multifocal Osteomyelitis

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ABSTRACT

Objective: Chronic recurrent multifocal osteomyelitis (CRMO) is the most common autoinflammatory disease of the bone characterized by pain and inflammatory lesions without an infectious agent. The aim of this study is to evaluate the clinical, laboratory, and imaging features and treatments of paediatric patients with CRMO followed in our pediatric rheumatology clinic.

Material and Methods: Medical records of ten patients diagnosed with CRMO according to Bristol diagnostic criteria between January 2018 and June 2021 were retrospectively reviewed.

Results: The mean age at diagnosis was 9.3 years, and eight of the patients were male. One patient had concomitant psoriasis, two patients had familial Mediterranean fever and one patient had a history of immunoglobulin A vasculitis. Half of the patients had a moderate acute phase reactant elevation. The most frequently involved bones were the lower extremity bones. While localized magnetic resonance imaging (MRI) was the most commonly used imaging modality in the diagnosis of CRMO, silent bone lesions (15%) were detected only by the whole-body MRI. Non-steroidal anti-inflammatory drug (NSAID) was given to all patients. As second-line therapy, methotrexate and pamidronate were employed on seven and five patients respectively. Three of the patients received anti-TNF treatment (etanercept and infliximab) as the third-line therapy. Imaging with whole-body MRI is important due to clinically silent bone lesions, especially in the course of CRMO.

Conclusion: Concomitant familial Mediterranean fever was not rare in cases with CRMO and treatment of CRMO might be challenging due to the need for anti-TNF treatment in a considerable number of patients.

Keywords: Bone, Chronic Recurrent Multifocal Osteomyelitis, Familial Mediterranean Fever, Pamidronate, Whole Body Imaging

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, autoinflammatory disease of the bone. Although it can be seen at any age, it is especially seen in the childhood age group (1). In 1972, Giedion and colleagues reported subacute and chronic osteomyelitis in four patients for the first time (2). The term chronic recurrent multifocal osteomyelitis was used for the recurrent nature of the disease in 1978 by Bjorksten (3).

The prevalence and incidence of CRMO, which is a very rare disease, is approximately one in a million and constitutes 2-5% of all osteomyelitis (4). The actual incidence of the disease is thought to be higher (5,6).

Neutrophils, macrophages, monocytes, and related cytokines are thought to take part in the emergence of the pathological process in CRMO (7). Patients are often presented with pain in the affected extremity, most commonly involving the metaphysis of the long bones, pelvic bones, vertebrae, and shoulder girdle (1). Bone lesions range from asymptomatic, mild inflammatory lesions to extensive inflammation with sclerotic or lytic lesions (7). Diseases affecting the skin (palmoplantar pustulosis, psoriasis) and gastrointestinal system (ulcerative colitis, Crohn's disease) may be seen in association with CRMO.

The aim of this study is to compare the demographic characteristics, clinical, laboratory and imaging findings and treatments of the patients with CRMO.

MATERIAL AND METHOD

Patients, diagnosed with CRMO under the age of 18, according to Bristol diagnostic criteria (8) between January 2018 and November 2021 were retrospectively analyzed. Age at diagnosis, gender, initial symptoms, delay in diagnosis, presence of other accompanying diseases, laboratory results, findings of direct radiographs, magnetic resonance imaging (MRI) and Tc-

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99m bone scintigraphy imaging, and histopathological features of bone biopsy and treatments of the patients were extracted from medical files.

The agents used in the treatment were evaluated under three steps. Non-steroidal anti-inflammatory drug (NSAID) was the first-line drugs. Methotrexate and pamidronate were classified as second-line therapy and anti-TNF drugs were classified as third-line therapy. Treatments were planned according to the clinical and imaging findings of the patients. Data was presented as frequency with percentage, mean with standard deviation, or median with interquartile range according to the distribution. Statistical Package for the Social Sciences (SPSS) version 23 (IBM) was used for statistical analysis. The study was carried out with the approval of Karadeniz Technical University Ethics Committee. Informed consent was obtained from the participants.

RESULTS

Of the ten patients included in this study, the mean age at diagnosis was 9.3 years ranging from four to fourteen years. Eight of the patients were male with a male-to-female ratio of four. The median time of diagnostic delay was 3.5 months and patients were followed for a median of 15 months. The first complaint in all patients was localized pain, additional swelling was observed in three patients, and one patient presented with a fever. Two patients were previously treated with antibiotics for osteomyelitis (Table 1).

Accompanied rheumatic disease was present in two of the patients. While both two patients had a diagnosis of familial Mediterranean fever (FMF) one patient had concomitant psoriasis as well. In addition, one patient had a previous diagnosis of immunoglobulin A vasculitis but was not active at the onset of CRMO. The family history of rheumatic disease was observed in half of the patients. While psoriasis in first-degree relatives was seen in two of our patients, three patients had a history of FMF or psoriasis in second-degree relatives. Laboratory investigations revealed normal blood count indices in all patients. The median erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 20 mm/h and 6.1 mg/L, respectively. ESR and CRP values were found to be elevated in six of the patients. While antinuclear antibody (ANA) was positive in three of the patients, HLA B-27 was negative in nine patients (Table 1).

Direct radiography of the symptomatic localizations was employed on all patients but did not reveal any pathological findings. In further examination, a localized MRI was performed on the symptomatic areas for the diagnosis of osteomyelitis. At the onset of the disease, whole-body MRI was performed on four patients, and bone scintigraphy was scanned in six patients. In the follow-up period, a whole-body MRI was performed on eight of the patients. A total of 110 bone involvements were observed by radiological investigation. The most commonly involved bones were the lower extremity bones, followed by the axial bones and the upper extremity bones. Clinically silent lesions were observed in 17 of 110 involvement (15%) and detected only with whole-body MRI. Bone scintigraphy did not reveal any additional information for the CRMO involvement compared to localized MRI. Sites of CRMO involvement according to the localizations are presented in Table 2. Bone biopsy was performed in three patients and fibrotic tissues with mild active chronic inflammatory cell infiltration were seen in and around the tissue samples. Also, no microorganism was grown in the tissue cultures.

Non-steroidal anti-inflammatory drugs were the most common medication used to treat CRMO, but remission of the disease was not achieved in any of the patients with NSAID treatment alone. Methotrexate was given to seven patients and pamidronate to five patients as a second-line therapy. Three of the patients received anti-TNF therapy (third-line therapy), etanercept for two patients, and infliximab for one patient (Table 3).

Table 1: Demographic and clinical features of the patients with chronic recurrent multifocal osteomyelitis

Features	Results
Male n (%)	8 (80)
Age at diagnosis (years) mean±SD	9.3±3.2
Delay in diagnosis (month) mean±SD	4.5±3.1
Follow-up duration (month) mean±SD	21±9.9
Previous antibiotheraphy n (%)	2 (20%)
Familial Mediterranean fever n (%)	2 (20%)
Family history of rheumatic disease n (%)	5 (50%)
Clinical findings	
Pain n (%)	10 (100%)
Swelling n (%)	4 (40%)
Fever n (%)	1 (10%)
Laboratory findings	
Erythrocyte sedimentation rate (mm/h) median (IQR)	21 (6.0-25.5)
C-reactive protein (mg/L) median (IQR)	6.1 (0.9-11)
Positive HLA B27 n (%)	0
Positive ANA n (%)	3 (30)
Bone biopsy, n (%)	3 (30)
Imaging modality	
Whole-body MRI n (%)	8 (80%)
Bone scintigraphy n (%)	6 (60%)
Localized MRI n (%)	10 (100%)

Table 2: Distribution of 110 bone lesions in patients with chronic recurrent multifocal osteomyelitis

Locations	Results, n (%)
Lower extremity	64 (70.4%)
Vertebrae	24 (16.2%)
Radius-ulna	10 (7.0%)
Humerus	9 (3.5%)
Clavicula	4 (2.8%)

Table 3: Medications used in treatment of patients with chronic recurrent multifocal osteomyelitis

1st line treatments	Number (percentage)
NSAID	10 (100%)
Systemic steroid	5 (50%)
2nd line treatments	
MTX	7 (70%)
Pamidronate	5 (50%)
3rd line treatments	
Etanercept	2 (20%)
İnfliximab	1 (10%)

Response to the treatments was favourable in all patients. Pain and swelling recovered in all patients among six patients with increased acute phase reactants, only two remained elevated after treatments. In all patients' treatment response was evaluated with whole-body MRI, and a significant decrease in the number of bone involvements was observed in 9 patients. The median number of bone involvements before treatments was 13 (IQR: 10-22), and after treatments was 5 (IQR: 1-11).

DISCUSSION

In our study, the mean age at diagnosis was 9.3 years, and the disease was found to be more common in males. Male predominance in our study differs from the literature. It has been reported that the disease is two to four times more common in females than males (9, 10). But case series consisting of exclusively male patients and equal males and females were also reported (11,12). This difference can be explained by the small number of patients. The disease is rarely observed in children younger than three years of age, and complaints often begin between the ages of 7-9. The mean age at diagnosis is 9-10 years, and the mean time from the onset of symptoms to diagnosis has been reported to be between 3 and 21 months (6,9,13). In our study, the median time delay to the diagnosis was three and a half months and that might be due to the increased awareness of the disease by clinicians.

Concomitant rheumatic diseases were not rare in patients with CRMO (13-16). Palmoplantar pustulosis, psoriasis, and inflammatory bowel disease were frequently encountered in patients with CRMO (13,14). In addition, Concha and colleagues reported rheumatic disease in 21% of their 19 CRMO patients but neither of them had palmoplantar pustulosis, psoriasis, or inflammatory bowel disease (15). Despite only one of our patients having a diagnosis of psoriasis, we thought that these diseases may occur in the follow-up of our cases due to the short follow-up period in this study.

We observed concomitant FMF in two of our patients. Like our results, two studies from Turkey reported FMF in CRMO patients (16,17). While Cicek and colleagues (17) reported FMF in six of the 23 CRMO patients, three of them had concomitant spondyloarthropathy. In another study, Avar-Aydın and colleagues (16) found MEFV mutations in five of the 18 CRMO patients, with sacroiliitis in three of them. But, FMF was associated with the spondyloarthropathy group of diseases (18), and significant overlap exists between CRMO and spondyloarthropathies, and the classification of such patients is controversial, especially in the presence of sacroiliac involvement (9). In addition, diagnosis of spondyloarthropathy was common in long-term follow-up of patients with CRMO (19). Results of the EUROFEVER Registry which included

486 patients with CRMO, signified only positive HLA-B27 as a discriminative feature for spondyloarthropathy (9). Spondyloarthropathy was common in patients with FMF and tended to be less frequently associated with positive HLA-B27 compared to juvenile spondyloarthropathies (20, 21). Thus, large-scale studies had to be conducted to investigate whether CRMO is associated with FMF or whether features were in the spectrum of FMF-related spondyloarthropathy.

There is no laboratory marker specific for the diagnosis of the disease, and inflammatory markers may be moderately elevated (22). In our study, inflammatory markers were elevated in 50% of the patients. Moderate elevation of inflammatory markers was reported in 50-90% of patients with CRMO (10,12,23).

Pain, especially at night, is the main symptom in patients with CRMO due to bone inflammation (7). In our study, pain was the main complaint in all patients, and swelling was present in two patients. The disease can affect all bones except the neurocranium. It usually involves the metaphysis of long bones symmetrically and produces painful lesions (9). Studies have shown that CRMO mostly affects the lower extremity bones with a predilection of metaphysis of the long bones but, axial involvement was not rare (9,10,24). Similarly, we found that lower extremity bones were the most frequent involvement. Also, axial involvement was observed in half of the patients.

Pre-diagnosis antibiotic use could be seen in patients with CRMO. Schnabel-Ursula and colleagues reported previous anti-biotherapy use in 36% of CRMO patients. In addition, it was observed that this rate decreased from 70% between 1998-2007 to 18% between 2008-2015 (13). Previous antibiotic treatment in this study, observed in 20% of our patients, was similar to the reported rates in the literature. As the recognition and awareness of the disease increases, rates of previous antibiotic treatment are expected to decrease.

Sclerotic lesions may be seen on direct radiographs but are frequently normal in the early phases of the disease. MRI is the most sensitive imaging modality for diagnosis, and it can also be used to screen for silent bone lesions (25). Whole-body MRI shows bone marrow edema, periosteal thickening, sclerotic changes, and signal increases in STIR sequence including clinically silent lesions, and is known to be more sensitive than radiography and scintigraphy for the evaluation of the disease severity (25). We also preferred to use whole-body MRI at the onset and through the follow-up period of the disease. However, we performed bone scintigraphy in the follow-up of two patients who could not undergo whole-body MRI due to

different reasons. A study comparing the whole-body MRI with bone scintigraphy reported that MRI was more sensitive than bone scintigraphy for detection of the lesions (26). In accordance with that whole-body MRI was the sole imaging modality that detected the clinically silent involvements in our patients.

Non-steroidal anti-inflammatory drugs such as naproxen and indomethacin are used as the first choice in the treatment of CRMO. Disease-modifying anti-rheumatic drugs (methotrexate, sulfasalazine, and azathioprine) are used in patients whose remission was not achieved by NSAIDs (22). In our study, none of the patients went into remission with NSAID treatment alone. Pamidronate is recommended as second-line therapy for patients with axial involvement or those presenting with sclerosis (22). In studies conducted on the efficacy and safety of pamidronate in the treatment of CRMO, it was stated that short stature due to vertebral loss was prevented as well as rapid clinical response (27-29). In our study, half of the patients were on pamidronate treatment and pamidronate provided dramatic pain relief. Three of our patients required anti-TNF treatment for the refractory disease. Treatment of CRMO with anti-TNF may induce clinical and radiological remission in refractory or severe cases (30,31). However, due to the off-label character and relatively high cost, cytokine blocking strategies should only be considered for refractory cases.

The retrospective nature of the study and a small number of patients were the main limitations. Also, the follow-up period was relatively short for the evaluation of the treatment responses. In addition, an absence of whole-body MRI in some of the patients might limit the detection of the silent disease involvements.

Ethics Committee Approval: This study was approved by the Karadeniz Technical University Ethics Committee.

Informed Consent: Written consent was obtained from the participants.

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