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ORIGINAL PAPER

Clinical characteristics and treatment outcomes of chronic recurrent multifocal osteomyelitis in the population of children from central Poland – observations of one center

Wiktoria Pysiewicz, Julia Niedźwiecka, Justyna Roszkiewicz, Elżbieta Smolewska

Department of Paediatric Cardiology and Rheumatology, Medical University of Lodz, Lodz, Poland

ABSTRACT

Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare autoinflammatory disease that occurs predominantly in the paediatric population. The disease causes recurrent flares of inflammatory bone pain and typically affects multiple bones. The aim of the study was to evaluate demographic and laboratory data, the overall clinical picture and treatment responses among children and adolescents with this disease entity from central Poland.

Material and methods: A total of 25 children diagnosed with CRMO between 2016 and 2022 at the Department of Paediatric Cardiology and Rheumatology at the Medical University of Łódź were enrolled in the study. A comprehensive, retrospective review of the clinical, laboratory and radiological data was conducted.

Results: The median age of onset of the disease was 12 years (range 4–17). The vast majority of patients (68%) were female. The incidence rate of CRMO in central Poland was found to be approximately 1.7/100 000 children/year. 60% of the patients had more than one lesion at the disease onset and male patients were more likely to present with multifocal disease. The most frequently affected bones were tibia (52%) and femur (36%). The mean inflammatory marker values were within normal limits, while the osteocalcin concentration in all of the patients was elevated over the normal range (median concentration 92.4 ng/ml (IQR: 62.6–116.45)). Most of the patients (68%) underwent a whole-body magnetic resonance imaging (MRI) scan that revealed abnormal bone activity of the affected structures. The patients were successfully treated with non-steroidal anti-inflammatory drugs (56%), methotrexate (44%), sulfasalazine (64%) and bisphosphonates (32%).

Conclusions: Although awareness of CRMO is increasing among clinicians, data from the Polish population is still limited. This study analysed the clinical features, laboratory tests, imaging methods and treatment outcomes. Whole-body MRI has been identified as a relevant screening tool for the diagnosis of CRMO. Further research on CRMO is needed in order to increase awareness and consequently reduce the time to diagnosis.

KEY WORDS:

autoinflammation, chronic recurrent multifocal osteomyelitis, non-bacterial osteomyelitis.

INTRODUCTION

Chronic non-bacterial osteomyelitis is a non-infectious autoinflammatory bone disease that mostly occurs in the paediatric population. The term was first introduced by Giedion *et al.* in 1972 [1] to describe children with symmetric, inflammatory bone lesions. Later in 1978, Björkstén *et al.* [2] referred to it as chronic recurrent multifocal osteomyelitis (CRMO) to emphasise the chronic character and severity of the disease. Chronic non-bacterial osteomyelitis is a broader term covering a wide clinical spectrum, ranging from mild and

ADDRESS FOR CORRESPONDENCE:

Justyna Roszkiewicz, MD, PhD, Department of Paediatric Cardiology and Rheumatology, Medical University of Lodz, 36/50 Sporna St., 91-738 Lodz, Poland, phone/fax: 48 42 6177700, e-mail: justyna.roszkiewicz@umed.lodz.pl

short-lasting bone lesions to a multifocal and chronic form with a more severe course. Therefore, more severe and chronic cases are referred to as CRMO [3].

The epidemiological data on CRMO is limited. Most case series studies published have enrolled relatively small numbers of patients. However, they consistently report the ratio of female patients to male patients to be approximately 2 : 1 and mean age of onset being 9–11 years [3–6]. Data on the incidence of CRMO vary in different regions and are considered to be underestimated. In Germany the annual incidence was estimated at 0.4 per 100,000 children/year, while in the UK at 0.65 per 100,000 children/year [7, 8]. The current prevalence of CRMO in Poland is yet unknown.

Although throughout the last decade the awareness of CRMO has significantly increased, data on CRMO from the Polish population is still limited. Despite the presence of diagnostic criteria established by Bristol and Jansson [9, 10], no specific disease marker has been identified, making the diagnostic process challenging and leading to limited data on that disease. Our aim was to evaluate demographic and laboratory data, the overall clinical picture and treatment standards in order to contribute to the understanding of this heterogeneous disease entity.

MATERIAL AND METHODS

Patients under the age of 18 years hospitalised in the Department of Paediatric Cardiology and Rheumatology at the Medical University of Łódź between 2016 and 2022 diagnosed with CRMO were enrolled in the study. Retrospective analysis of their medical histories has been conducted including clinical characteristics such as age, sex, age at onset of symptoms, delay in diagnosis, symptoms, affected bones and treatment used. The results of the following laboratory tests were analysed: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count, serum calcium, vitamin D_3 and osteocalcin concentration. Osteocalcin concentration was measured using the electrochemiluminescence immunoassay, vitamin D_3 using the clinical laboratory improvement amendment method. Bone mineral density was assessed by dual-energy X-ray absorptiometry (DEXA), using the Horizon Wi device (S/N 200800).

RESULTS

GENERAL

There were 25 patients diagnosed with CRMO between 2016 and 2022. The median age of onset was 12 years (range 4–17). Over half of the patients – 68% (n = 17) – were female. The incidence rate of CRMO was assessed as 1.7/100 000 children, based on our findings and the population of children in the Łódź Voivodeship in 2022 [11].

CLINICAL PRESENTATION

In all cases, the predominant symptom reported by patients was pain at the site of inflammation. Additionally, swelling was observed in 11 patients (44%) and limited mobility was reported in 7 patients (28%). 60% of the patients had more than one lesion at the disease onset (median of 2, range 1–7). Male patients were more likely to present with multifocal disease (7/8, 87.5%) in comparison with female patients (8/17, 47%). The most frequently affected bones were tibia (52%) and femur (36%). Additionally, two of the patients presented with symptoms of synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (SAPHO).

LABORATORY TESTS

The analysed laboratory test results revealed inflammatory marker values within normal limits in the majority of patients: with median ESR 12 mm/h (IQR: 5–25) (normal range < 15 mm/h) and 8 (32%) patients presented elevated ESR value; median CRP was 1.15 mg/l (IQR: 0.4–3.55) (normal range 0–5.0 mg/l) with 4 patients (16%) exceeding the normal value. Mean leukocyte count was 6360 ±1620 cells/µl and did not exceed the normal range in any of the patients and median vitamin D concentration was at the border of normal range, reaching the median of 30.7 ng/ml (IQR: 25.9–40.4) (normal range 30–50 ng/ml), whereas calcium concentration was within normal limits (9.66 ±0.48 mg/l, with the normal range 8–11 mg/dl). In all of the patients osteocalcin concentration was elevated over the normal value for the age, with the median concentration of 92.40 ng/ml (IQR: 62.6–116.45) (normal range 6–25 ng/ml). No patient was ANA positive and only one patient had HLA-B27 antigen. The discussed data together with clinical characteristics is presented in Table 1.

IMAGING METHODS

Seventeen patients (68%) underwent a whole-body magnetic resonance imaging (MRI) scan that showed abnormal bone activity of the affected structures. Three of the patients (12%) had bone scintigraphy and four of them (16%) underwent a bone biopsy. Moreover, sixteen of the patients (64%) underwent bone densitometry, from which eleven revealed a Z-score value below –1, indicating low mineral density of the affected bones (Figures 1, 2).

TREATMENT

The treatment consisted of non-steroidal anti-inflammatory drugs (NSAIDs) (n = 14, 56%) used as the first-line treatment and followed by disease-modifying anti-rheumatic drugs – methotrexate (n = 11, 44%) and

TABLE 1. Clinical and laboratory characteristics of children with chronic recurrent multifocal osteomyelitis

Characteristics	Our patients
Sex, *n* (%)	
Male	8 (32)
Female	17 (68)
Mean age (years)	11
Time to diagnosis (months) (mean ± SD)	9 ±20
Affected bones, *n* (%)	
Tibia	13 (52)
Femur	9 (36)
Ilium	6 (24)
Metatarsus	6 (24)
Talus	6 (24)
Clavicle	5 (20)
Humerus	3 (12)
Ribs	3 (12)
Calcaneus	2 (8)
Fibula	2 (8)
Sacrum	2 (8)
Spine	2 (8)
Ulna	2 (8)
Mandible	1 (4)
Phalanges	1 (4)
Sternum	1 (4)
Inflammatory markers	
ESR [mm/h] (median, IQR)	12.0 (5–25)
CRP [mg/l] (median, QR)	1.15 (0.4–3.55)
WBC [cells/µl] (mean ± SD)	6360 ±1620
Osteocalcin [ng/ml] (median, IQR)	92.40 (62.6–116.45)
Calcium-phosphate metabolism markers	
Calcium [mg/dl] (mean ± SD)	9.66 ±0.48
Vitamin D [ng/ml] (median, IQR)	30.7 (25.9–40.4)

CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, WBC – white blood cells
Normal values of the parameters: Calcium (8–11 mg/dl), CRP (0.08–3.1 mg/l), ESR (< 10 mm/h), Osteocalcin (6– 25 ng/ml), Vitamin D (30–50 ng/ml), WBC (4000–10000 cells/µl)
Values are presented as mean ± SD or median ± IQR, depending on data distribution.

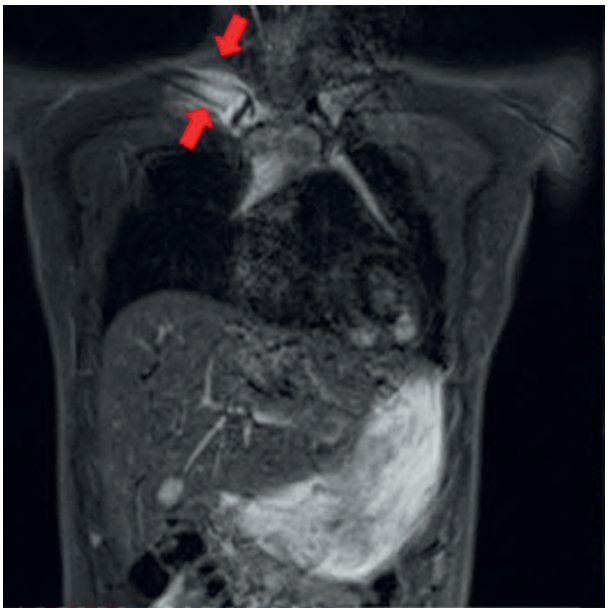

FIGURE 1. Magnetic resonance imaging scan demonstrating clavicular involvement in the inflammatory process associated with chronic recurrent multifocal osteomyelitis

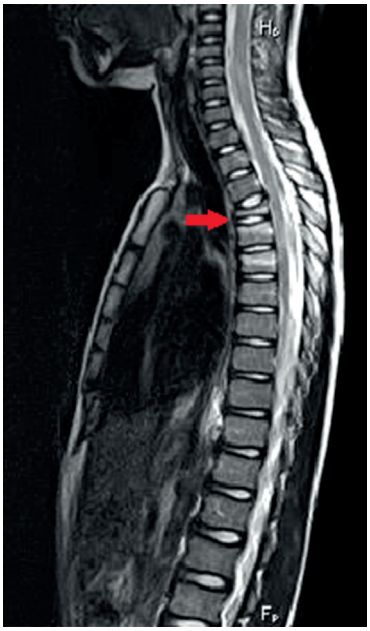

FIGURE 2. Magnetic resonance imaging scan of a 12-year-old boy demonstrating inflammatory changes within the vertebral column (marked with arrows)

sulfasalazine (n = 16, 64%). Methotrexate was administered in the standard dosing of 10–15 mg/m² BSA either orally or subcutaneously, based on the patient's preference and presence of methotrexate treatment side effects. Sulfasalazine was administered orally at a dose of 20–30 mg/kg. In patients non-responding to standard treatment regimen bisphosphonates were introduced as a third-line treatment (n = 8, 32%), leading to disease remission and normalisation of osteocalcin concentration. None of the patients was treated with biologic disease-modifying anti-rheumatic drugs. Bisphosphonates used in the study included pamidronate sodium, given at a dose of 1 mg/kg for 3 consecutive days every 4 months. Bisphosphonates were used for a course of 2 years, while synthetic disease-modifying anti-rheumatic drugs (methotrexate and sulfasalazine) were used for a minimum of 2 years. The exact duration of drug administration cannot be precisely measured, as the majority of patients included in the study are still undergoing treatment. The criteria for remission included the improvement of clinical symptoms together with the normalization of inflammatory marker values.

DISCUSSION

Chronic recurrent multifocal osteomyelitis is an autoinflammatory disease which is characterized by an imbalance between pro- and anti-inflammatory cytokine expression. The disease is associated with inflammatory bone lesions and osteolysis. The predominant clinical manifestations of this condition include recurrent inflammatory bone flares, most commonly affecting multiple bones.

Despite the growing awareness of the disease among clinicians, there was no data on its incidence in the population of Polish children. Our study is a first case series study among children with CRMO in central Poland. Compared with previous reports, over half of our patients were female, which is in accordance with large European cohort studies [3–5, 7]. However, the median age at onset being 12 years in our study was slightly higher than in other studies [3–7, 12], suggesting a significant delay in disease diagnosis, as CRMO is still not well recognised in our country.

Based on our study, the incidence rate of CRMO is approximately 1.7 per 100,000 children/year. This is slightly higher than the annual incidence estimated in Germany or in the UK, being 0.4 and 0.65 per 100,000 children/year, respectively [7, 8]. Our data however, might be more inaccurate because of a smaller sample size.

The most frequently affected bones were tibia and femur, which is comparable with other studies [4, 6, 12–14]. However, in our study multifocal lesions were less frequent than in other case series studies, yet still affecting more than a half of our patients [12–14]. Our data show that male patients are more likely to have multifocal lesions, which is in line with large cohort studies from France and the United Kingdom [5, 8].

Patients enrolled in our study had no family history and no ANA positivity. Only one patient presented positive HLA-B27. Although the relation between CRMO and HLA-B27 positivity is unclear, there is ongoing research associating carriage of HLA-B27 with greater risk of developing CRMO, especially in male patients [15]. Similar to other studies that describe some extra-osseous involvement in CRMO [5, 8, 14], we observed skin lesions in two of our patients who presented with SAPHO.

Most common imaging tests used in diagnostics of CRMO include X-ray, computed tomography (CT), MRI, bone scintigraphy and DEXA scans. X-ray was used as a screening test, while bone scintigraphy was a first-choice diagnosing method in older cases. Currently, due to its widespread availability, whole body MRI scan is used for both diagnosis and assessment of the therapy effects. In contrast to older studies [12, 13], a great number of our patients underwent a whole-body MRI. This is in accordance with large cohort studies that described in recent years the common use of this imaging method [6, 8]. An extensive research conducted in the United Kingdom and Republic of Ireland suggests that the increasing availability of whole-body MRI might be leading to a shorter time to establishing final diagnosis [8]. Another large case study conducted in the north-western United States associates the better access of whole-body MRI with a greater detection of CRMO, particularly with multiple bone lesions [15]. Moreover, magnetic resonance is considered to be more sensitive than other imaging methods at identifying asymptomatic lesions, which is crucial in diagnosing early CRMO [16].

The treatment used in our patient was comparable to the treatment described in the literature with NSAIDs used as a first-line treatment and followed by steroids, methotrexate, sulfasalazine and bisphosphonates.

Chronic recurrent multifocal osteomyelitis is a rare disease which results in low awareness of this disorder among clinicians. Due to the lack of unequivocal clinical features or laboratory findings, many patients face a significant diagnostic delay.

STUDY LIMITATIONS

As in the single-centre analysis of a rare disease entity, the main study limitation is a relatively small sample size. Moreover, as the patients from the region may be treated in different paediatric rheumatology units, the disease frequency might be underestimated.

CONCLUSIONS

Given its non-specific clinical presentation and low disease prevalence, awareness of CRMO among clinicians and patients remains limited. It is essential to consider this condition in the differential diagnosis of paediatric patients presenting with bone pain. While standard laboratory parameters may often remain within normal limits, elevated osteocalcin concentration could serve as a potential biomarker supporting the diagnostic process. Whole-body MRI remains the imaging method of choice, both for establishing the diagnosis and for evaluating treatment response.

DISCLOSURES

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2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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