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Case report

CHRONIC NON-INFECTIVE OSTEOMYELITIS OF THE LEFT CLAVICLE IN A 12-YEAR-OLD BOY: A CASE STUDY

Gjeorgjieva Janev Olivera[1], Pecanova Blagica[2], Karanfilovski Vlatko[3], Damjanovska Krstikj Ljubinka[4], Krstevska Balkanov Svetlana[1]

[1]University Clinic for Hematology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[2]General Hospital Strumica, Strumica, Republic of North Macedonia
[3]University Clinic for Nephrology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[4]University Clinic for Rheumatology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
e-mail: olivera.gjeorgjieva@gmail.com

Abstract

Chronic nonbacterial osteomyelitis (CNO) or chronic recurrent multifocal osteomyelitis (CRMO) is a rare idiopathic condition characterized by foci of sterile bone inflammation and prolonged, self-limiting and recurrent course. We describe a case of a 12-year-old boy with several months lasting pain and aggravated morphological abnormality of the left clavicle. Based on computer tomography scan and magnetic resonance imaging, the patient was initially highly suspected of having a neoplastic process. However, open biopsy and pathohistological examination of the resected specimen showed chronic inflammatory components with fibrosis, with no signs of neoplastic disease which set the final diagnosis of unifocal CNO of the left clavicle. Although the clavicle is considered a typical site of CNO, isolated involvement of the clavicle without recurrences, as in our patient, is rarely reported and could delay the diagnosis. The patient was treated with Naproxen (15 mg/kg/day) and experienced complete resolution of the symptoms after few months of treatment. During the two years of follow-up, the patient did not have new flares of the disease. CNO is diagnosis of exclusion, and a high level of suspicion is paramount in atypical cases to avoid unnecessary biopsies and repeated antibiotic regimens.

Keywords: chronic recurrent multifocal osteomyelitis, autoinflammation, children, noninfective osteomyelitis

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disease characterized by periodic exacerbations and remissions of sterile osteomyelitis[1]. CRMO predominantly affects young and adolescent females and has been reported mainly on the metaphysis and diaphysis of the long bones[1-3]. The clavicle is involved in approximately 25% of cases, usually as part of multifocal CRMO[4]. Typical lesions appear to be chronic, unifocal or multifocal with symmetrical distribution[1]. The disease is autoimmune and shares similar immune mechanisms with SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis) syndrome in adults[3]. The clinical presentation usually involves pain and tenderness

localized in the affected bone, which is swollen; the skin above the affected site might appear reddish in color and warm on palpation. The disease might be accompanied by fever or other extra-skeletal conditions including psoriasis, inflammatory bowel diseases, severe acne, Sweet syndrome, Wegener's granulomatosis and Takayasu's arteritis[5]. The clinical presentation, laboratory tests and radiographic appearance of the disease are non-specific, and it should be differed from variety of infective, benign or malignant bone lesions. The diagnosis is one of exclusion, and biopsy is needed in the majority of cases[5].

Materials and methods

We present a rare case of unifocal CRMO of the left clavicle in a 12-year-old boy. Etiological, clinical, radiological and histopathological features to facilitate diagnosis and treatment of this disease are discussed in this study. Written informed consent was kindly obtained from the patient's parents for publication of the case described in this report. The institution's ethical committee approved the publication of this rare condition.

Case report

In July 2020, a 12-year-old Caucasian boy presented to the hospital with a several-month history of painful swelling in the middle part of the left clavicle. The patient was previously healthy, without history of recent trauma or any other precipitating factors for the pain. At the physical examination, the patient had local pain during rest, and painful and severely decreased range of active and passive motion of the left shoulder. The patient was afebrile and there were no foci of active infection or skin lesions elsewhere in the body. His initial blood tests revealed only slight increase of erythrocyte sedimentation rate - 41 mm/hr (reference values bellow 20 mm/hr), a higher level of osteocalcin - 33 ng/ml (reference range: 8-32 ng/ml) and an elevated alkaline phosphatase - 363 IU/L (reference range: 44-147 IU/L).

The patient was previously seen by orthopedic surgeon, who initiated computer tomography (CT) scan of the left clavicle and administered a non-steroidal anti-inflammatory drug (Ibuprofen) to the patient to relief the pain. The CT showed an osteolytic zone in the distal part of the left clavicle with propagation towards the middle part (Figure 1). The sternoclavicular joint and bone cortex were intact. Reactive sclerosis around the joint was present, with rich periosteal reaction along the whole circumference of the clavicle. Reactive lymph nodes of 5 mm were detectable in the surrounding tissues. The differential diagnoses included: osteitis, inflammatory osteofibrous dysplasia, aggressive osteoblastoma, Ewing sarcoma. For the definitive diagnosis, biopsy and magnetic resonance imaging (MRI) were advised. The latter MRI showed a similar reading as the CT scan with a most probable diagnosis of Ewing sarcoma. A two-phase bone scintigraphy with Tc-99m methylene diphosphonate (MDP) was arranged, where the static scintigram showed pathological accumulation with relatively high intensity, which spread out of the contours of the bone, affecting the medial part of the middle third of the clavicle. The rest of the skeleton was unaffected. Serology for Brucella, Salmonella, Tularemia and Mycobacterium tuberculosis were negative.

The patient had been taking Naproxen for 2 months and was feeling well until the end of December 2020, when he stopped taking the drug for personal reasons (felt better), after which the pain and swelling returned to the same site of the left clavicle, but this time, the pain was spreading to his back. At that point, a whole-body MRI was recommended by a rheumatology specialist, which was performed in January 2021 (Figures 2, 3, 4 and 5).

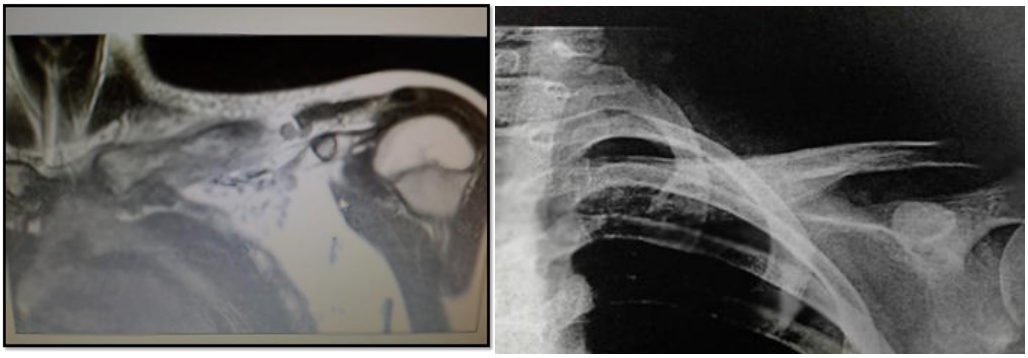

Fig. 1. CT showed osteolytic zone in the distal part of the left clavicle with propagation towards the middle part. The sternoclavicular joint and bone cortex were intact. Reactive sclerosis around the joint was present, with rich periosteal reaction along the whole circumference of the clavicle. Reactive lymph nodes of 5 mm were also detectable.

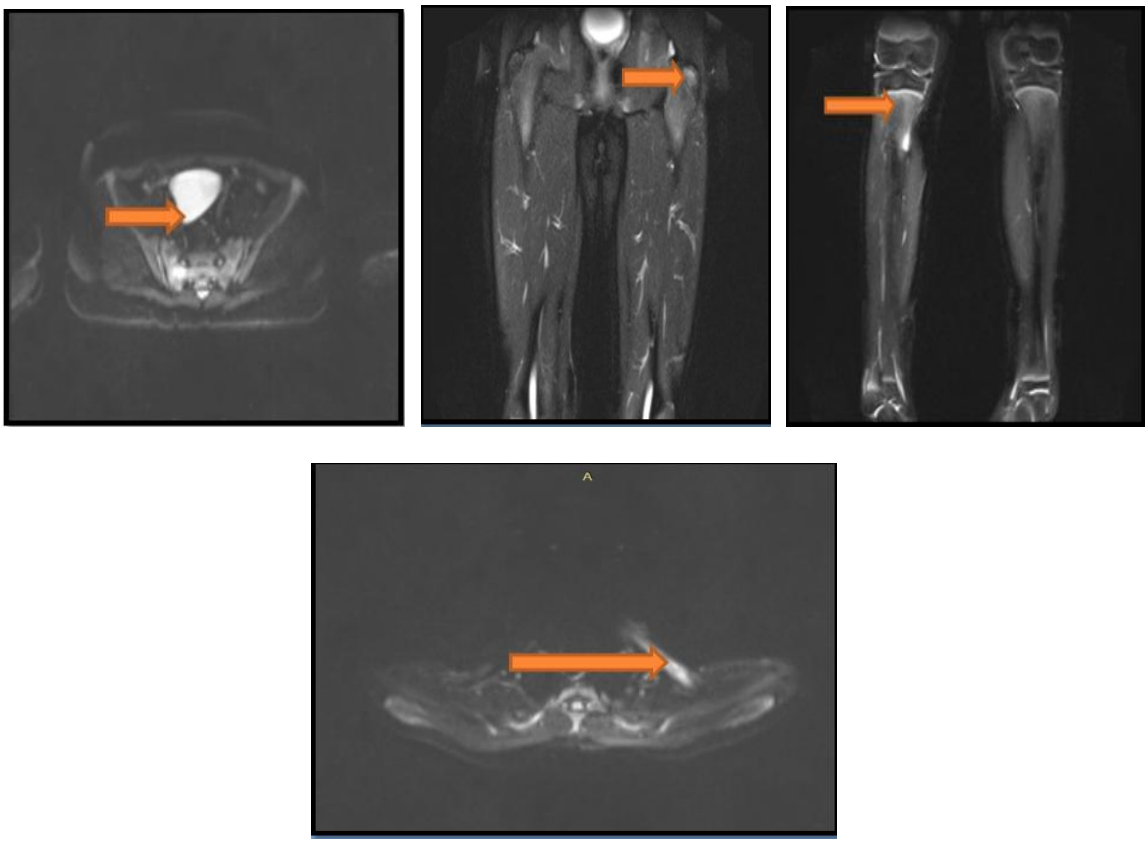

Fig. 2 - 5. Whole-body MRI demonstrated bone marrow edema in the left clavicle, predominantly in the lateral (acromial) part, with signs of residual activity. Additional chronic lesions with bone edema were observed in the right sacral lateral mass (S2 level) and in the left greater trochanter, consistent with multifocal but inactive foci of chronic osteomyelitis.

To set the definitive diagnosis, an open biopsy of the involved bone was done. The pathohistological examination showed extensive new bone formation with medullar fibrosis, and minor chronic inflammatory components which morphologically corresponded to residuals of older chronic osteomyelitis. There was no evidence of neoplastic process in the resected specimen. The overall morphological picture set the diagnosis of chronic non-infective osteomyelitis (CNO). Anti-inflammatory treatment with Naproxen was started and the symptoms slowly disappeared.

MRI showed edema of the left clavicle, predominantly at lateral (acromial) part. It was described as a preexisting lesion, which was more discreet on previous imaging tests. There was restriction in diffusion on this localization as well as in the middle third of the left clavicle. The process of remodeling of the medial (sternal) part of the left clavicle was evident. However, according to diffusion, it seemed that there was still some metabolic activity in that region.

A lesion was visible on T2 FS imaging in the right lateral sacral mass at S2, showing edema but no significant diffusion restriction, suggesting a possible chronic phase. Similar findings were seen in the left trochanter major, with edema on T2 FS and ADC maps but no restriction, indicating a similar phase.

The patient was given non-steroidal anti-inflammatory medications, which were continued for 6 months, and then the doses were gradually tapered. The symptoms improved and the patient functioned normally throughout the everyday activities.

Another control MRI was done next year, in January 2022 (Figure 6). It showed persistent osseous edema on the left clavicle in the medial and sternal part, which was reduced in comparison with previous year's MRI. There was no cortical involvement, but reactive lymph glands on the neck were still present. At the level of trochanter major: a lesion with surrounding edema and restricted diffusion with discrete extension to the metaphysis was noted, described as chronically active localization of the disease with signs of resolution. On the lateral malleolus of the fibula, there was also a chronic lesion, which did not involve the cortex. On the proximal meta-diaphysis on the right tibia, a non-ossifying fibroma was noted.

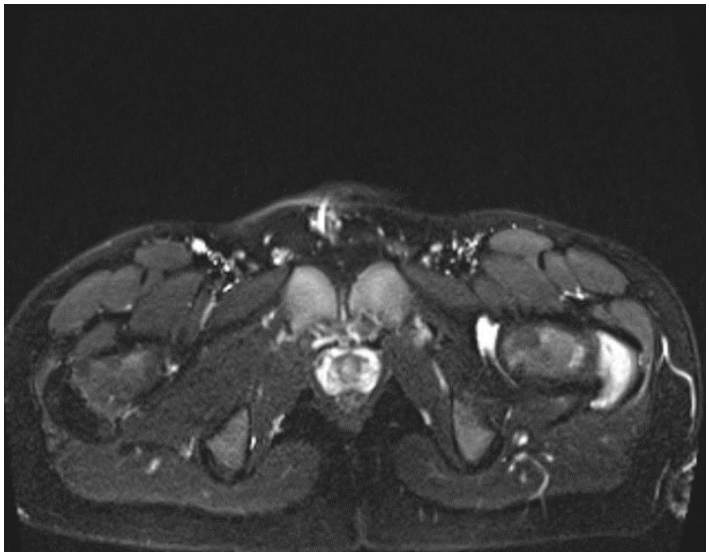

Fig. 6. Whole-body MRI from January 2022 showed regression of the clavicular lesion with reduced edema, persistence of a chronically active but resolving focus at the left greater trochanter, and additional inactive lesions on the fibula and on the right tibia (non-ossifying fibroma).

The patient was regularly followed up in the subsequent year and showed no signs of progression or relapse that needed further treatment. The last whole-body MRI was done in April 2023 and compared to the previous MRI from January 2022, the changes on the left clavicle, trochanter major and right tibia were without signs of progression. New focal lesions were not detected (Figures 7, 8 and 9*).*

The patient has been treatment-free after the initial therapy, which lasted approximately one year (July 2020-July 2021), and is a rare example of a disease not often seen but can be effectively controlled when properly diagnosed.

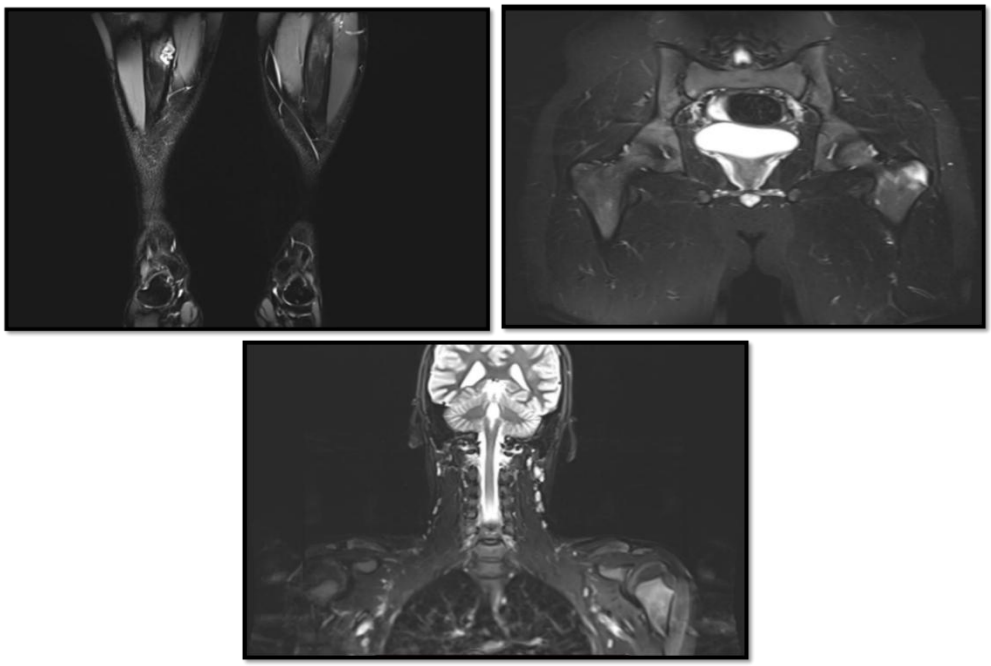

Fig. 7-9. Whole-body MRI from April 2023 showed the changes on the left clavicle, trochanter major and right tibia were without signs of progression. New focal lesions were not detected

Discussion

CRMO is a challenging diagnosis, and it is believed that the symptoms persist up to 18 months before obtaining the right diagnosis[1-6]. Bristol criteria based on clinical, radiological and histological findings could help to establish an early diagnosis of CRMO and to start appropriate treatment[6]. In case of an unifocal disease, as it was in our case, biopsy might be crucial to rule out infectious or neoplastic diseases and should be performed in all ambiguous cases[7].

The main pathophysiological pathway that is incriminated against the occurrence of bone lesions in CRMO has not been fully elucidated. Severe autoimmune deregulations have been noted, as misbalanced immune response regarding IL10 (anti-inflammatory)/IL6 and TNF (pro-inflammatory) cytokines, as well as homozygous mutations in *PSTPIP2* (Proline-Serine-Threonine Phosphatase Interacting Protein 2) gene, but neither of these mechanisms is strictly proven to be the cause of the condition[8]. The condition might be sporadic or a manifestation of some monogenic autoinflammatory syndromes such as Majeed syndrome, Deficiency of Interleukin 1 Receptor Antagonist and SAPHO syndrome[5].

CNO is a spectrum of conditions with huge variety in number of affected bones and recurrences during the disease.

At presentation, our patient had a several-month history of swelling in the middle part of the left clavicle with local pain and a severely reduced range of active and passive motion of the left shoulder. This was his first reported episode.

In a cohort of 30 children with CNO, Girschik *et al.* found that nine patients had an unifocal lesion with no relapses, three unifocal lesions with relapses, nine multifocal lesions without relapses, and nine multifocal lesions with relapses. Clavicular lesion as a part of unifocal or multifocal disease was noted in eleven out of thirty patients (37%) [9]. Only one patient in this cohort had unifocal non-recurrent lesion of the clavicle, as in our case. The condition typically starts to develop on the clavicle or the metaphysis and epiphysis of the tibia or humerus. The spinal vertebrae and calcaneus are also frequently involved[10-12]. Arthritis of

the joints adjacent to the bone lesion is reported in more than 80% of patients[9]. Skin lesions such as palmoplantar pustulosis, psoriasis and acneiform processes might be also present[10-12].

Clavicle is considered a typical site of CNO, but isolated clavicular affection without recurrences, as in our patient, is rarely reported and could delay the diagnosis. The CNO diagnosis is of exclusion, based on the clinical, laboratory and radiological findings[4]. The blood tests are nonspecific and usually show only modest elevation of inflammations parameters and leukocytosis in most cases [4]. Radiological features in the early phases might be normal. As the disease progresses, plain X-rays show features similar to bacterial osteomyelitis, including osteolysis, sclerosis and new bone formation. Some lesions have periosteal reactions or soft tissue swelling; others have lytic areas and mimic bone tumors[10]. Therefore, always when available, a whole-body MRI (WB-MRI) is recommended, not only for diagnosing and distinguishing the condition from other diseases, but also for measuring disease activity and the therapy efficacy. Biopsy of the bone lesion is not often required but could be necessary in unclear cases to exclude infectious osteomyelitis or malignant bone tumor[10-13]. The differential diagnosis of CNO includes infectious osteomyelitis, malignancy (osteosarcoma, Ewing's sarcoma, non-Hodgkin lymphoma), benign bone lesion (as osteoid osteoma) and Langerhans cells histiocytosis[9-13].

Regarding therapy, NSAIL is considered as a first line therapy. Indomethacin and Naproxen have been described as effective both in primary lesions and for relapses[10, 11, 14]. Naproxen is considered an excellent and sufficient treatment option for unifocal and multifocal non-recurrent CNO[4]. Corticosteroid therapy is a second line treatment (oral Prednisolone, Hydrocortisone, i.v. Methylprednisolone)[15,16]. Disease modifying agents such as Methotrexate or Azathioprine are ineffective as single-line agents[10]. Recently, bisphosphonate therapy, and particularly intravenous Pamidronate, has been proposed as a treatment for patients with CRMO who do not improve with nonsteroidal anti-inflammatory treatment[14]. Biological therapies such as Infliximab, Etanercept, Anakinra and Adalimumab are described in several case reports over the past years as possible therapeutic agents in patients with a low response to the previously mentioned therapeutic options[13-17]. The main aim of the whole treatment, regardless of which therapeutic option is chosen, is to minimize interruptions in normal bone growth in childhood and allow a normal function to the near localized joints[17].

Our patient was treated only with Naproxen (15 mg/kg/ day) and experienced complete resolution of the symptoms after 12 months of treatment. During the two-year follow-up, the patient did not have new disease flares. According to the literature, the course of the disease varies among patients, with alternating relapses and remissions until puberty. There is a possible evolution into atypical spondyloarthropathy, although further studies are required to define this whole entity[16,17].

Conclusion

Although CNO usually occurs in a multifocal recurrent pattern, our case illustrates that this disease can arise in a single location without recurrences. These atypical forms of disease often lead to delays in referral and diagnosis, prolonged courses of antibiotics and unnecessary radiation exposure from multiple plain radiographs or bone scans. Clinicians should be aware of atypical forms of CNO to achieve timely diagnosis and to avoid unnecessary invasive diagnostic and therapeutic procedures.

Conflict of interest statement. None declared.

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