

Impact of immunostimulation on autoinflammatory disease. CRMO case presentation and literature review: A case report

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Abstract. Chronic recurrent multifocal osteomyelitis (CRMO) is a rare bone condition included in the spectrum of autoinflammatory pediatric rheumatological diseases. In the present case report, a 9-year-old female patient with a personal history of psoriasis since the age of 5 presented with left clavicle pain persisting for ~2 months. Following thorough anamnesis and investigations carried out, a diagnosis of CRMO was established. The present case report discusses a rare pediatric autoinflammatory pathology with autoimmune implications, emphasizing the role of immunostimulation/immune dysfunction. It is possible that immunostimulation with *Propionibacterium acnes* (also known as *Cutibacterium acnes*) for psoriasis management may underlie the development of autoinflammatory-destructive bone lesions. Establishing causal relationships between immunological, bacterial and autoinflammatory factors was challenging during the patient's evaluation in our service.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) represents the most severe manifestation of chronic non-bacterial osteomyelitis (CNO), constituting a rare autoinflammatory bone disorder (1). CRMO predominantly affects the metaphysis of long bones, pelvis, clavicle and spine (2). This rare condition is part of the spectrum of autoinflammatory rheumatological

diseases together with Majeeed syndrome, IL-1 receptor antagonist deficiency (DIRA), IL-36 receptor deficiency (DITRA) and *Pyoderma gangrenosum* (PAPA). CRMO is also known by various names such as SAPHO (synovitis, acne, pustulosis, hyperostosis and osteomyelitis) or non-bacterial osteomyelitis (NBO), both referring to the same disease entity (3). Described first in 1972 by Giedion *et al* (4), CRMO predominantly affects female children, with an average onset age of 10 years. The worldwide prevalence is estimated at 1-9 cases per million, with ~480 cases documented in the Eurofever registry (5). In total, ~50% patients experience persistent chronic disease, and ~20% of patients with CRMO experience recurrences. Because CRMO is a diagnosis of exclusion and can mimic other inflammatory bone conditions, the condition is considered to be underdiagnosed. Several cases occur associated with other autoinflammatory and autoimmune diseases, such as skin disorders, peripheral arthritis, inflammatory bowel disease, and granulomatosis with polyangiitis. Association with several autoinflammatory conditions can be detected in ~1/3 of patients with CRMO (6).

CRMO presents with an insidious onset and polymorphic clinical manifestations that can mimic infections or malignancies. Bone pain is the most common initial symptom, often accompanied by tenderness at the affected site, with or without swelling. Nocturnal bone pain can be misinterpreted as growing pains (7). Mild febrile conditions, asthenia and fatigue occur in <5% of patients. Laboratory analyses typically reveal elevated inflammatory markers, including elevated erythrocyte sedimentation rate (ESR) in 59% of patients, elevated C-reactive protein (CRP) in 49%, elevated leukocyte count in 14%, and elevated serum amyloid A in 12%. No relevant increases are observed in immunoglobulin levels. Additionally, HLA-B27 is present in 7.9% of individuals, and 38% of tested patients have elevated ANA titers (5).

CRMO diagnosis often involves a process of exclusion, occasionally requiring a bone biopsy. Diagnostic criteria, such as the Jansson and Bristol criteria, aid in establishing a diagnosis. In the Jansson classification, meeting two major criteria or one major and three minor criteria is necessary. Major criteria include radiologically demonstrated osteolytic/osteosclerotic

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bone lesions, multifocality of bone lesions, palmoplantar dermatosis (psoriasis-pustulosis), and sterile bone biopsy with signs of inflammation, fibrosis, or sclerosis. Minor criteria consist of normal blood count and favorable general health, increased CRP and ESR, symptom duration of more than half a year, hyperostosis, and positive family history with first or second-degree relatives diagnosed with any autoimmune disease (8). Within the Bristol system, diagnostic criteria encompass characteristic clinical presentations (such as localized bone pain with or without localized swelling, without signs of infection). Typical radiological observations include plain X-ray findings (showing a combination of lytic areas, sclerosis, and new bone formation), or preferably STIR magnetic resonance imaging (MRI) findings, which may include bone marrow edema, bone expansion, lytic areas, and periosteal reaction (9). Furthermore, diagnosis requires fulfillment of one of the subsequent criteria: (i) Involvement of >1 bone (or clavicle only) without significantly elevated C-reactive protein (CRP <30 g/l); and (ii) unifocal lesion (other than clavicle) or CRP >30 g/l, with bone biopsy demonstrating inflammatory changes (such as plasma cells, osteoclasts, fibrosis, or sclerosis) without bacterial growth while not under antibiotic therapy (8).

Subgroup classification of CRMO based on the distribution of bone lesions has been proposed, including the 'tibio-appendicular multifocal model' and the 'clavicular-spinal pauci-focal model', although these remain purely descriptive (3).

Most patients with CRMO likely possess a genetic predisposition that, on its own, may not be sufficiently strong enough to induce the disease without the influence of additional factors. One of the environmental factors that can influence or determine this disease is *Cutibacterium acnes* (*C. acnes*), previously known as *Propionibacterium acnes* or *Corynebacterium parvum*. *C. acnes*, the primary bacteria implicated in acne, naturally resides in the sebaceous glands of all individuals, where it contributes to the balance of the skin microbiome. As a saprophytic bacterium, it feeds on decaying organic matter such as sebum.

Each person possesses a unique microbiome profile. Typically, sebaceous skin is predominantly inhabited by *Cutibacteria spp.* (formally known as *Propionibacteria*), *Staphylococci spp.*, β -*Proteobacteria* and *Corynebacteria spp.*, while dry skin is characterized by an abundance of β -*Proteobacteria*, *Corynebacteria spp.*, *Flavobacteriales* and *Cutibacterium spp.* This diverse microbial community is vital for maintaining skin health, as it helps establish and modulate skin immunity and host defense by producing antimicrobial peptides (10). A decrease in the abundance of *C. acnes* is often associated with various skin conditions, including acne, atopic dermatitis, rosacea and psoriasis. *C. acnes* and the diversity of its clonal population actively contribute to the skin's normal physiological functions by modulating lipid metabolism and mitigating oxidative stress (11). In patients with psoriasis, itching can cause skin wounds, allowing certain bacteria to penetrate deep into the dermis or even enter the peripheral blood, where they stimulate both innate and adaptive immune responses. A decrease in *Corynebacterium spp.*, *Lactobacillus spp.*, *Burkholderia spp.* and *Propionibacterium acnes* were observed in the skin of patients with psoriasis lesions compared with healthy skin (12).

Case presentation

The patient is a 9-year-old female with a personal history of psoriasis since the age of 5. Family history reveals two sisters with psoriasis. In December 2023, she was hospitalized due to a left shoulder injury sustained two months prior, resulting in pain and limited mobility. Orthopedic consultation suggested a possible clavicle fracture in the healing process, leading to immobilization in a plaster cast. However, symptoms persisted after cast removal, with added swelling, pain and functional impairment, prompting admission to the 'Louis Turcanu' Children's Emergency Clinical Hospital in Timisoara for further investigation.

On admission, clinical examination revealed a swollen, hardened area with intense pain on palpation and marked functional impairment at the left clavicle (Figs. 1 and 2). Additionally, discomfort while walking was noted, attributed to hip pain.

Laboratory investigations showed normal blood count, liver and kidney function, with slightly increased inflammatory markers: CRP=4.97 mg/l (normal values 0-5 mg/l) and ESR=32 mm/h (normal values 0-13 mm/h). Procalcitonin, HLA-B27, and antinuclear anti-nuclear antibodies (ANA) were negative. An X-ray of the left clavicle revealed changes in its shape and bone structure, along with an exaggerated periosteal reaction in the middle third. Additionally, the coxo-femoral X-ray of the left femur exhibited morphological and structural changes in the intertrochanteric region, characterized by widening of the femoral neck and the area with a mixed osteolytic and osteosclerotic pattern, predominantly osteosclerotic. The 'frog-leg' incidence highlights linear opacity parallel to the femoral neck (Figs. 3 and 4).

Considering the absence of infectious history, fever, or weight loss, along with the discrepancy in inflammatory factors and multifocal radiological lesions, further imaging and biopsy were pursued. Subsequently, a scintigraphic examination was performed revealing intense hyper uptake of contrast substance at the left clavicle (sternal extremity, body of the clavicle) with an uneven distribution indicative of thickening of the bone outline. Similarly, heightened contrast substance capture was observed at the trochanteric region of the left femur, particularly at the greater trochanter (Fig. 5).

The histopathological result of the sampled formation describes spongy bone tissue with areas of necrosis and edema, congested vascular structures, infiltration of lymphocytes and plasma cells consistent with non-specific chronic inflammation, medullary fibrosis and osteonecrosis.

Given the autoimmune and autoinflammatory nature of the patient's condition, attention was directed towards understanding the underlying pathophysiological mechanisms. Thus, it was found out from the patient's history that she had been receiving off-label immunostimulation therapy for psoriasis since the age of 5. The treatment involved injection with *C. acnes*, one weekly injection. A favorable evolution of skin lesions was initially observed but with multiple relapses during the years when it stops.

Non-steroidal anti-inflammatory therapy (Naproxen 7.5 mg/kg/day) was chosen as the first-line therapeutic approach, resulting in an initial improvement, pain and swelling decreased, arm mobility returned and hip discomfort resolved.



Figure 1. Swollen left clavicle area, vicious position at the level of the left shoulder. Injury after clavicular biopsy. Psoriasis anterior chest elements.



Figure 2. Lesions of pre- and retro-auricular psoriasis.

From a biological point of view, an initial decrease in ESR was observed. After 3 months, the painful symptomatology accompanied by swelling and functional impotence reappeared. The patient was clinically reevaluated, against the background of active psoriasis and reactivated autoinflammatory pathology; it was decided to initiate treatment with subcutaneously injected Methotrexate 15 mg/m²/weekly. Subsequently, the evolution was slowly favorable both clinically and biologically with the improvement of painful symptoms, and the reduction of bone swelling. Psoriatic lesions were substantially reduced. Biological investigations did not detect inflammatory signs.

A total of ~2 months after initiation of disease-modifying antirheumatic drugs (DMARDs) treatment, the patient presented with fever, odynophagia and left otalgia. A pharyngeal swab was performed, which tested positive for Group A beta-hemolytic *Streptococcus*. An ENT evaluation was conducted, diagnosing muco-purulent otitis, for which a 7-day antibiotic treatment was initiated. For hearing disturbances,



Figure 3. Pelvic X-ray showing morphological and structural changes of the trochanter.



Figure 4. Clavicle X-ray observing changes in shape and bone structure.

an ENT consultation was performed after antibiotic treatment finished, diagnosing chronic hypertrophic tonsillitis and hypertrophic adenoid vegetation. An audiogram (Fig. 6) confirmed bilateral hypoacusis.

A subsequent computed tomography scan (Fig. 7) revealed complete bilateral opacification of the mastoid cells, dense material in the left middle ear, and marked hypertrophy of lymphoid tissue in the nasopharynx, leading to lumen obstruction. The findings suggested bilateral mastoiditis, left middle ear otitis with a possible cholesteatoma, and proximal nasopharyngeal lumen obstruction due to hypertrophic adenoid tissue. Additionally, chronic inflammatory changes were observed in the right sphenoidal and ethmoid-maxillary regions.

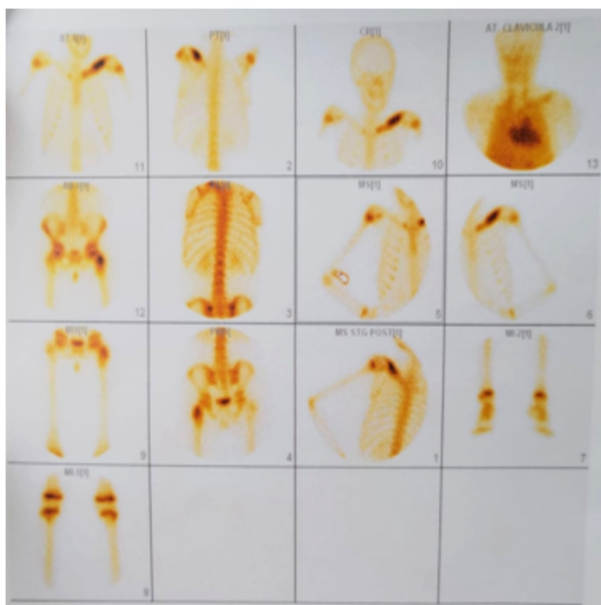


Figure 5. The scintigraphy image shows increased uptake in the clavicle and femur regions.

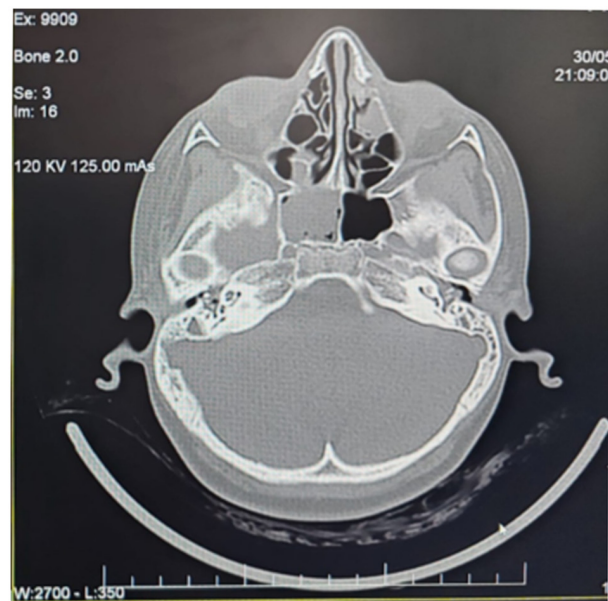


Figure 7. Axial computed tomography scan of the skull base.

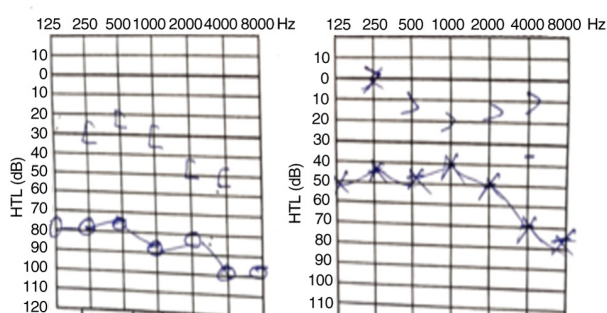


Figure 6. Mixed hearing loss, moderate left ear (right panel), severe right ear (left panel).

Discussion

Although the precise mechanism of CRMO remains incompletely understood, it has been included in the family of autoinflammatory diseases because, primarily due to the predominant involvement of autoinflammatory bone. This condition is characterized by an imbalance of cytokines, patients often exhibiting decreased production of anti-inflammatory cytokines such as interleukins (IL)-9, -10 and -18, and increased levels of pro-inflammatory cytokines including IL-1 β , IL-6 and tumor necrosis factor- α (TNF- α) (9,13). Notably, monocytes from patients with CRMO exhibit impaired immune regulatory IL-10 in response to Toll-like receptor stimulation (14), which is partially attributed to reduced activation of mitogen-activated protein kinases, ERK1 and 2, resulting in deficient expression of anti-inflammatory cytokines (15). However, the disease-causing mutations in one or more genes remain unknown (16).

There is controversy about whether *Cutibacterium* plays a role in the etiology of CRMO. It has been postulated that this bacterium could trigger chronic inflammation in genetically

predisposed patients. Dysregulation of IL-1 is important in the pathogenesis of autoinflammatory bone diseases. When healthy individuals are exposed to *C. acnes* stimulation, there is an increase in caspase-1 activity in neutrophils, which is associated with the production of IL-1 β and IL-18. Additionally, *in vitro* studies have demonstrated that *C. acnes* stimulation results in elevated production of IL-8 and TNF- α by monocytes, keratinocytes and dendritic cells (DCs) (17). Surgical interventions, particularly orthopedic device implantation, may inadvertently promote infection (18). It is worth mentioning that 2 years ago our patient underwent surgery to remove a foreign body (needle) that had become lodged in the bone at the level of the tibial plateau, an event that occurred as a play accident. These types of infections are associated with bacteremia, endocarditis, systemic inflammation, and even bone destruction, underscoring the potential role of bacterial infections in CRMO pathogenesis (19).

Further studies are needed to improve the understanding of the role of skin microbiome in individuals predisposed to autoimmune or autoinflammatory disease. Skin dysbiosis may trigger conventional DCs to secrete IL-23, stimulating Th17 cells to produce IL-17, which in turn promotes keratinocyte hyperproliferation and leukocyte infiltration (20,21). In addition, innate lymphoid type 3 cells (ILC3) can respond to stimulatory cytokines, including IL-1 β , IL-18 and IL-23, and secrete IL-17, IL-22 and IFN- γ . IL-17 stimulates keratinocytes to produce chemokines such as CXCL1, CXCL2, CXL20, IL-6 and IL-8, resulting in leukocyte infiltration. Infiltrating leukocytes can further produce IL-1 β and IL-18 to stimulate ILC3 cells to produce more IL-22 and IL-23, promoting keratinocyte hyperproliferation (22,23).

To establish the diagnosis CRMO, several potential differential diagnoses were eliminated through comprehensive laboratory and imaging investigations. Infections, including bacterial osteomyelitis and tuberculosis, were ruled out due to the absence of recent infection history, lack of active infection signs, negative Quantiferon test results, and normal findings

on chest X-ray without pneumonic foci. Immune deficiency was considered and ultimately dismissed as the patient had no history of severe or recurrent infections requiring hospitalization or antibiotic treatment. Furthermore, immunoglobulin levels (IgM, IgG, IgA) and serum protein electrophoresis were found to be within normal limits. The possibility of malignant hematological tumors such as leukemia or lymphoma was also investigated. Clinical examination revealed no suspicious adenopathy, and biological assessments showed no abnormalities in blood counts or blasts in the peripheral blood smear. Additionally, chest X-ray and ultrasound examinations of the cervical zone and abdominal regions revealed no evidence of malignancy. Malignant bone tumors were ruled out based on findings from scintigraphy examination and bone biopsy results, which did not align with the characteristics of such tumors. Metabolic bone disease was considered and excluded based on laboratory tests that revealed no deficiencies in blood microelements. Lastly, the potential for monogenic autoinflammatory disorders with bone damage, including PAPA, DIRA and Majeed syndromes, was explored (24). However, the onset of pathology did not occur in infancy or early childhood, and there were no accompanying features such as dys-erythropoietic anemia, pustulosis, or joint swelling indicative of these monogenic disorders.

The radiographic evaluation depends on the stage of the disease. Decalcification or osteolysis can be observed in an early stage, whereas advanced stages often manifest with hyperostosis and sclerosis. The periosteal reaction can occur at any stage. Tubular bone lesions are most often located at the metaphysis of long bones but may extend to the diaphysis and occasionally to the epiphysis. Initially, radiographs reveal metaphyseal involvement, with eccentric lytic lesions adjacent to the growth plate, a sclerotic rim separating it from the underlying bone, and a limited periosteal reaction (25). Identification of the multifocal configuration through two-phase bone scintigraphy is crucial for accurate CRMO diagnosis (26). Both bone scintigraphy and MRI have been shown to be useful tools for detecting CRMO lesions. In the evaluation of the axial skeleton (particularly the spine), MRI offers higher spatial resolution compared with planar scintigraphy (27). Fluid-sensitive sequences can visualize bone marrow edema, a typical feature of CRMO. Small bone changes may be detected, and clinical symptoms may emerge as the disease progresses (28). As a modern method of investigation, the magnetic resonance of the whole body has become the method of choice because it does not expose the patient to radiation and offers superior evaluation capability. MRI can also demonstrate marrow edema, periostitis, soft tissue inflammation and joint involvement (29). In our case, scintigraphy was chosen for its utility in confirming the diagnosis at low financial costs.

The current hearing disorders need to be investigated and possibly correlated with the underlying pathology, not just in the context of infectious issues in the ENT sphere. The term 'autoinflammatory' in autoinflammatory diseases (ADs) refers to the seemingly spontaneous onset of inflammation, in the absence of infectious triggers, autoreactive T lymphocytes and specific autoantibodies. ADs result from dysregulated production of pro-inflammatory cytokines, prominently IL-1, and a delayed termination of the immune response (30). The inflammasomes are large multimeric protein complexes that

regulate the activation of proinflammatory cytokines such as interleukin-1 β and -18, and inflammatory cell death known as pyroptosis. NLRP1, NLRP3, NLRC4, AIM2 and pyrin can induce the formation of inflammasomes. Among these, the NLRP3 inflammasome is the most well-characterized. Previous studies have revealed that variants in the NLRP3 gene can cause genetic diseases, including a systemic inflammatory syndrome called cryopyrin-associated periodic syndrome and non-syndromic neurosensory hearing loss DFNA34 (31). Auto-inflammatory diseases can lead to hearing loss, and evidence suggests that inflammation may play a role in hearing loss associated with other conditions. The inflammasome is a multi-molecular pro-inflammatory protein complex formed in activated macrophages, which may contribute to hearing loss (32). Macrophage-like cells are distributed throughout all cochlear tissues, including the auditory nerve, spiral ganglion, basilar membrane, stria vascularis and spiral ligament. The p.Arg918Gln mutation in NLRP3 can lead to non-syndromic sensorineural hearing loss (33).

Regarding treatment, non-steroidal anti-inflammatories remain the first-line treatment option for most patients. In cases of non-responsiveness to non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, DMARDs, TNF inhibitors and bisphosphonates (such as Pamidronate) may be considered. Since the NSAID action starts after at least 4 weeks of therapy, it is important to maintain the treatment for at least 1 month before declaring therapeutic failure (34). If discovered and treated promptly, CRMO can show a favorable evolution. In the present case, it was recommended starting treatment with injectable Methotrexate after surgery.

The uniqueness of the present case resides in the fact that the pre-existing chronic autoimmune pathology (psoriasis) was treated for a long period with an injectable immune stimulant based on *Propionibacterium Parvum*, which is incriminated in multiple studies as a trigger factor in patients with pre-existing genetic susceptibility. Familial psoriasis (genetic substrate) combined with environmental factors (skin dysmicrobism) may have led to the development of psoriasis since early childhood. The immune dysregulation prompted by psoriasis, along with the immunostimulation with *C. acnes*, may have resulted in the development of bone lesions specific to CRMO.

In conclusion, this case report presents a rare and complex pathology from an etiopathogenic perspective, involving both autoinflammatory and autoimmune elements. It is considered that the genetic predisposition, in combination with bacterial immunostimulation in the context of an autoimmune disease, may contribute to the development of a concurrent autoinflammatory disease. Investigating any potential specific pathogenic relationship between these two conditions would necessitate multicenter studies. Furthermore, there remains a lack of specific biomarkers for CRMO, highlighting the need for further research to identify characteristic patterns of CRMO and optimal methods for monitoring disease progression.

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Availability of data and materials

The data generated in the present study are not publicly available due to ethical restrictions but may be requested from the corresponding author.

Authors' contributions

AIM conceptualized the study, provided resources, wrote the original draft of the manuscript and developed methodology. IJ and MAB validated data. AIM and DMN performed formal analysis, conducted investigation and data curation. DMN and MAB wrote, reviewed and edited the manuscript. OM and IJ confirm the authenticity of all the raw data, supervised the study, and edited language. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted according to the guidelines of the Declaration of Helsinki and was approved (approval no. 3157/07.02.2024) by the Ethics Committee for Research of ‘Louis Turcanu’, Children's Emergency Hospital (Timisoara, Romania).

Patient consent for publication

Consent for publication of data and associated images of the patient was provided by the legal guardian of the minor.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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