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Journal of Orthopedics & Bone Disorders
ISSN: 2577-297X

Overview on Auto inflammatory Bone Disorders: From Pathogenesis to Clinical Manifestations

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Mini Review

Volume 3 Issue 3

Received Date: June 13, 2019

Published Date: June 24, 2019

DOI: 10.23880/jobd-16000185

Chronic Recurrent Multifocal Osteomyelitis (CRMO)

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a rare disease occurring in childhood. It is characterized by insidious onset and variable clinical manifestations that may mimic infections or malignancies [1]. Since CRMO may be neither multifocal nor recurrent, some authors suggest replacing it with the term chronic nonbacterial osteomyelitis (CNO) that includes different disorders with sterile bone inflammation [2]. Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome (SAPHO) is the adult form of CRMO with prominent skin manifestations [3]. CRMO is frequently associated with other inflammatory diseases such as psoriasis and inflammatory bowel disease [4]. CRMO pathogenesis is largely unknown; however, an unbalance towards proinflammatory cytokines has been demonstrated [5,6]. Recently a South Asian child with CRMO and psoriasis has been found harboring an autosomal recessive mutation of FBLIM1 gene [7].

Clinical manifestations may include systemic features such as low-grade fever, pain, slight malaise and fatigue [8]. Bone lesions are often multifocal, mostly in long bones; whereas spinal involvement may lead to severe complications. Laboratory tests are unspecific showing a mild elevation inflammatory markers. Conventional radiography can show the presence of osteolytic lesions typical of advanced disease, whereas early bone lesions may be detected by whole-body MRI (STIR sequences) [9]. Since CRMO is a diagnosis of exclusion, bone biopsies are useful to exclude malignancies showing unspecific inflammatory infiltrate. Recently, very high IL-6 serum levels (≥ 17 ng/ml) have been detected in CRMO patients along with low levels of the eosinophil attracting chemokine (CCL11/eotaxin) (< 110 ng/ml). The combination of both biomarkers has been proposed to discriminate patients with inflammatory diseases from healthy controls [10].

The treatment of CRMO is based on nonsteroidal antiinflammatory drugs (NSAIDs) that represent first-line therapy [1]. NSAIDs lead to pain control and prevention of bone lesions in a large portion of patients [1]. Bisphosphonates are used especially for spinal lesions in the absence of systemic features. Moreover, a trial on pamidronate in CRMO patients is now ongoing (NCT02594878). TNF-α inhibitors are commonly used when first-line therapies fail. The role of TNF-α in osteoclastogenesis and bone resorption is well known, thus anti-TNFα agents are very useful in these patients [11].

Childhood Arthritis and Rheumatology Research Alliance (CARRA) have recently issued a consensus treatment plan for CRMO. After NSAIDs failure (defined as the persistence of symptoms following at least 4 weeks of continuous treatment) one of the following treatments is recommended: methotrexate or sulfasalazine, anti-TNFα agents with or without methotrexate, and bisphosphonates [12].

Deficiency of IL-1 Receptor Antagonist (DIRA)

Patients with deficiency of IL-1 receptor antagonist (DIRA) show both skin and bone involvement along with systemic inflammation. Recessive mutation of IL1RN gene causes loss of IL-1β and IL-1α physiological inhibition

[13]. Pustular lesions appear within the first months of life and are associated with inflammatory markers rising; later on DIRA patients develop osteitis and periostitis [13]. Bone lesions show neutrophilic infiltrate at biopsies. Widening of the anterior rib ends and periostitis of long bones are classically described in these patients [13,14]. The exogenous IL-1 receptor antagonist, anakinra, is able to neutralize both IL-1α and IL-1β and is successfully employed in DIRA patients [13.]

Majeed Syndrome

Majeed syndrome, characterized by sterile osteomyelitis, dyserythropoietic anemia and neutrophilic dermatosis. It is a monogenic bone autoinflammatory disease due to loss of function mutation of LPIN2 inherited in an autosomal recessive pattern. The protein LIPIN2 is involved in lipid metabolism [15]. Disease onset is within 2 years of age and is usually associated with fever attacks and growth disturbances along with joint contractures. Some Majeed patients do not show skin manifestations. The efficacy of IL-1 blocking agents has indirectly confirmed the pathogenesis of Majeed syndrome [16].

Cherubism

Cherubism is due to heterozygous mutations of SH3 binding protein 2 (SH3BP2) gene with variable penetrance and phenotypic manifestation within the same family. Furthermore, de novo mutations are also described [17]. SH3BP2 plays a key role in osteoclast activation fostering bone resorption [18]. These patients show osteolytic lesions of mandibles very early in life; the following fibrotic tissue deposition and bone remodeling give to patients with cherubism the typical aspect with puffy cheeks [19]. Ribs may be the other location of disease [19]. Cherubism treatment is based on case reports in which adalimumab and bisphosphonates have been both used [20, 21].

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