Review

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Sterile osteomyelitis: a cardinal sign of autoinflammation

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Abstract

Autoinflammatory bone disorders (ABDs) are characterized by sterile bone inflammation stemming from dysregulated innate immune responses. This review focuses on the occurrence of sterile osteomyelitis in ABDs and related diseases, notably chronic nonbacterial osteomyelitis (CNO) and its sporadic and monogenic forms, such as deficiency of the interleukin-1 (IL-1) receptor antagonist, Majeed syndrome, CNO related to *FBLIM1* mutation, and pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA syndrome). Additionally, other autoinflammatory disorders (AIDs) are discussed, including classical periodic fever syndromes (e.g., familial Mediterranean fever, cryopyrin-associated periodic syndromes), monogenic rare AIDs (such as hyperostosis-hyperphosphatemia syndrome, H syndrome, interferonopathies, and Singleton-Merten's syndrome), polygenic AIDs with bone involvement (e.g., Schnitzler's syndrome, systemic juvenile idiopathic arthritis, adult-onset Still's disease, and calcium pyrophosphate deposition disease), and bone dysplastic syndromes. Sterile osteomyelitis emerges as a cardinal sign of autoinflammation, aiding clinicians in both diagnosis and management of ABDs. Treatment typically involves tumor necrosis factor inhibitors or IL-1 antagonists.

Key words: innate immunity, osteomyelitis, chronic recurrent multifocal osteomyelitis.

Introduction

Autoinflammatory disorders (AIDs) result from the dysregulation of innate immune cells, such as macrophages and neutrophils, leading to episodes of seemingly unprovoked inflammation without the typical autoimmunity features, such as high-titer autoantibodies or antigen-specific T cells [1–4]. These episodes can affect multiple organ systems, with certain organs being more susceptible to autoinflammation [1].

Fever and panniculitis are recognized as cardinal features of AIDs. Periodic fever syndromes, such as familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), were among the first AIDs described [3, 5, 6]. However, not all AIDs present with fever, and bone involvement has emerged as a significant feature in a growing spectrum of these disorders [2, 3]. Traditionally, osteomyelitis was defined as bone inflammation secondary to infection, either acute or chronic, caused by hematogenous or non-hematogenous bacterial propagation. However, in autoinflammatory bone disorders (ABDs), sterile bone inflammation is the hallmark of the condition [4, 7, 8]. This review aims to describe the occurrence of sterile osteomyelitis in ABDs and related diseases, focusing on systemic AIDs. For this purpose, a narrative semi-systematic review was conducted, and the literature was searched using combinations of key words such as "autoinflammatory disorders", "osteomyelitis", and "innate immune system" in the Medline and EMBASE databases. Relevant references from the selected articles were also considered. We specifically focused on systemic AID associated with sterile osteomyelitis, excluding organ-specific disorders such as cherubism, osteoporosis, periodontitis, and wear debris osteolysis, as well as septic osteomyelitis and arthritis.

Bone and the innate immune system

Bone mass and quality are regulated by coordinated actions of osteoblasts and osteoclasts [9]. In CNO,

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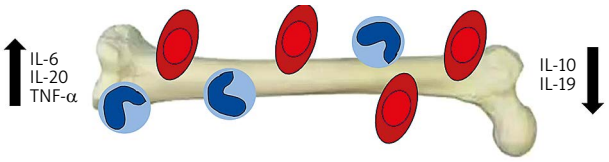

Fig. 1. The imbalance between anti-inflammatory and pro-inflammatory cytokines in CNO.
IL – interleukin, TNF – tumor necrosis factor.

an imbalance between pro-inflammatory and anti-inflammatory cytokines has been documented, as illustrated in Figure 1. The imbalance between prointerleukin-1β (IL-1β) can stimulate the production of receptor activator of nuclear factor κB ligand (RANKL), either directly or indirectly, through various cell types, including mesenchymal cells, synoviocytes, and T cells. This is mediated by the regulation of other pro-inflammatory cytokines such as IL-6, IL-17, and TNF-α [8, 9]. In synergy with RANKL, these cytokines promote osteoclast differentiation while inhibiting osteoblast differentiation and osteogenesis [8, 9]. Additionally, IL-1β can stimulate its own synthesis through pores formed by gasdermin D [9]. Toll-like receptors (TLR) also play a role in modulating osteoclastogenesis [8].

Inflammasomes, macromolecular complexes nucleated by NOD-like receptor pyrin domain containing 3 (NLRP3) and related proteins that activate IL-1β, play a crucial role in the pathogenesis of both sterile and non-sterile inflammatory osteolysis [9, 10]. While these mediators are essential in acute inflammation for maintaining bone integrity by suppressing bone formation and enhancing bone resorption, chronic inflammation ultimately leads to bone damage [9].

Autoinflammatory bone disorders arise from bone infiltration by immune cells, osteoclast differentiation, and activation, leading to osteolysis and bone remodeling [4]. Table I illustrates the different pathogenic mechanisms of bone involvement in systemic AIDs.

Sterile osteomyelitis and autoinflammatory disorders

Chronic osteomyelitis is a hallmark feature of ABDs, including sporadic CNO, pyogenic arthritis, pyoderma gangrenosum, acne (PAPA), and deficiency of the IL-1 receptor antagonist (DIRA) [11]. Autoinflammatory bone disorders are characterized by the absence of bacterial involvement [12]. Sterile osteomyelitis may be asymptomatic, but it often manifests as focal bone pain, accompanied by warmth, swelling, and tenderness to palpation [13]. Patients may also experience nocturnal pain and asymmetric pain, along with objective swelling and/or limited joint range of motion [13, 14]. Involvement of the mandible, spine, and pelvis can lead to decreased jaw opening, back pain, and dysfunction in urination and defecation, respectively [13].

Chronic nonbacterial osteomyelitis and related disorders

Chronic nonbacterial osteomyelitis, also known as pustulotic arthro-osteitis, sclerosing osteitis, or chronic recurrent multifocal osteomyelitis (CRMO) in cases of multifocal disease, was first reported by Giedion in 1972 as a subacute and chronic, symmetrical osteomyelitis [15–17]. It is characterized by the hyperproduction of pro-inflammatory cytokines such as IL-1β, IL-17a, IL-18, and TNF-α, which in turn activate osteoclasts [13, 14, 18]. Chronic nonbacterial osteomyelitis was originally described within the spondyloarthropathy spectrum due to its association with enthesitis, which is thought to be the starting point of osteitis [19]. It is worth mentioning related syndromes, such as SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome, which includes sterile osteomyelitis with skin manifestations typically observed in adults. This syndrome may represent a slightly different phenotype of CNO. Diffuse sclerosing osteomyelitis of the mandible, often diagnosed by dentists and oral surgeons, is another related condi-

Table I. Systemic bone autoinflammatory disorders and their pathogenesis

Bone loss	
Acro-osteolysis	Gout, SMS, SAVI
Bone erosions	CINCA, Gout, PAPA, SAVI, JIA
Low bone mineral density	CINCA
Increased bone formation (hyperostosis, increase of bone mineral density and/or osteosclerosis)	CED, DIRA, GHD, HHS, H syndrome, SAPHO, SPENCD, SS
Non-infectious osteomyelitis	DIRA, MS, MVK, SAPHO, JIA
Other bone lesions	CINCA, SPENCD

CED – Camurati-Engelmann disease, CINCA – chronic infantile neurologic, cutaneous and articular, DIRA – deficiency of the IL-1 receptor antagonist, GHD – Ghosal hematodiaphyseal dysplasia, HHS – hyperostosis-hyperphosphatemia syndrome, MS – Majeed syndrome, MVK – mevalonate kinase deficiency, PAPA – pyogenic arthritis, pyoderma gangrenosum, and acne, SAPHO – synovitis, acne, pustulosis, hyperostosis, osteitis syndrome, SAVI – STING-associated vasculopathy with onset in infancy, SPENCD – spondyloenchondrodysplasia, SMS – Singleton-Mertens's, SS – Schnitzler's syndrome.

tion [11, 13, 20, 21]. The prevalence of CNO has been estimated at 1–2 per million, with an incidence ranging from 0.4 to 2 per 100,000 children [14–16, 19]. Higher disease incidences have been reported in Central and Northern Europe, where it is almost as common as infectious osteomyelitis, likely due to increased awareness and diagnostic practices [17, 22]. Chronic nonbacterial osteomyelitis exhibits a female-to-male ratio of approximately 2 : 1 and primarily affects children and adolescents, with an average peak of onset around nine to ten years of age; however, onset in adulthood is also observed [13, 23–25]. The familial clustering of CNO cases and its association with TNF-α-mediated disorders such as juvenile spondylarthritis, psoriatic arthritis, and inflammatory bowel disease (referred to as "enteropathic CNO") suggests a genetic component in its etiology [13, 18, 26–28]. Although CNO was originally described as an autosomal recessive disorder, reports of affected siblings, concordant monozygotic twins, and parent-child duos indicate a complex genetic inheritance pattern. The proposed susceptibility locus on chromosome 18q21.3-18q22, however, requires further validation [3, 29]. Mutations in genes such as filamin-binding LIM protein 1 (*FBLIM1*), FGR, and mixed lineage kinase domain-like (*MLKL*) have been implicated in the pathogenesis of CNO [14]. Infectious agents, including *Cutibacterium* acnes, have been suggested as potential pathogens (by triggering autoinflammation in genetically predisposed individuals), particularly in patients with skin manifestations, despite CNO being sterile by definition [30–32]. Mechanisms such as FoxO1 downregulation may allow these microorganisms to evade innate immunity, maintaining a latent state in bone cells [30–32]. The pathogenesis of CNO involves an imbalance between decreased production of anti-inflammatory cytokines, such as IL-10 and IL-19, and increased production of pro-inflammatory cytokines, including IL-1 and TNF-α, along with the dysregulation of neutrophils and neutrophil proteases. Although the role of IL-1β may be independent of inflammasome activation, it remains an important mediator in the disease [2, 11, 14, 15, 25]. Non-syndromic CNO is the most prevalent form of ABD [2, 11]. Clinically, it presents with a heterogenous array of symptoms, typically characterized by the insidious onset of severe bone pain, which often worsens at night. Concurrent symptoms such as fever, malaise, weight loss, and soft tissue swelling around large joints are frequently observed. Involvement of other organ systems, including the skin (manifesting as palmoplantar pustulosis, psoriasis, or pyoderma gangrenosum), lungs, eyes, and gastrointestinal tract, may also occur [2, 11, 16, 24, 25]. Approximately 30% of cases involve adjacent joints, presenting with synovial thickening, exudate, and/or cartilage damage, while paraosseous inflammation may extend to adjacent vessels and/or peripheral nerves [11, 22]. Chronic nonbacterial osteomyelitis exhibits diverse phenotypes, with some cases affecting only the skeleton and following a milder course, while others show extra-skeletal involvement [33]. Three distinct disease patterns have been recognized: those that resolve within six months, those with multifocal lesions and multiple recurrences, and those with persistent symptoms [30]. Notably, a subset of patients with CNO affecting the jaw may experience a later onset of the disease [15]. Laboratory investigations in CNO typically show normal blood cell counts, although leukocytosis may occur in up to 20% of patients [13, 17]. Inflammatory markers such as fibrinogen, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are variably elevated in 40 to 80% of patients, with moderate increases observed [13, 14, 17, 19, 24, 25]. Additionally, alterations in lactate dehydrogenase, alkaline phosphatase, uric acid, and albumin levels may be observed, with low albumin levels potentially indicating "enteropathic CNO" [12]. In contrast to infectious osteomyelitis, bacterial cultures from bones or blood in CNO typically yield negative results [34]. Elevated levels of IL-6 and TNF-α may be found, and antinuclear antibodies are positive in more than one-third of patients [16, 25, 35]. While specific biomarkers for CNO are not yet available, bone biomarkers such as bone-specific alkaline phosphatase and tartrate-resistant acid phosphatase 5b may be elevated. Persistently high levels of soluble IL-2 receptor (sIL-2R), IL-12, and monocyte chemoattractant protein-1 (MCP-1) may serve as potential markers for treatment response [12, 36, 37]. Radiographic imaging plays a crucial role in the diagnosis of CNO, with radiographs typically being the first imaging modality used, despite their low sensitivity. Radiographs identify less than 15% of lesions detected by magnetic resonance imaging (MRI) [13, 14, 17]. Characteristic radiographic findings in CNO include lytic lesions (in more than 50% of patients), sclerotic lesions, or mixed lesions indicative of disorganized bone formation or destruction [13, 17, 19]. While lesions can affect virtually any bone, they are commonly found in the metaphysis of long bones in the lower extremities, often accompanied by progressing hyperostosis and/or sclerosis, which are typically visible on radiographs [2, 13]. Long bone lesions are particularly frequent in children and are consistently associated with bone marrow edema [15]. The tibia, fibula, pelvis, proximal femur, clavicle, and calcaneus are among common sites of involvement, with the clavicles being a notable location. When the medial third of clavicles is affected, it is highly suggestive of CNO, particularly in the presence of psoriasis vulgaris and/or palmoplantar pustulosis [11, 19, 26, 30].

Skull involvement is rare in CNO [8, 17]. Increased signal intensity on short tau inversion recovery (STIR) sequences and decreased signal intensity on T1-weighed images are characteristic MRI findings that indicate an active lesion in CNO [13, 38]. Whole-body MRI (WB-MRI) is considered the preferred diagnostic tool for evaluating CNO and has been investigated as a means of assessing disease activity [28, 39, 40]. The ChRonic nonbacterial Osteomyelitis MRI Scoring (CROMRIS) system has been developed and studied to assess disease activity by evaluating several MRI features (e.g., bone edema, cortical disruption, soft tissue involvement) [40, 41]. Bone scintigraphy is another imaging modality used to detect affected skeletal regions in CNO, particularly those with osteoblastic or erosive changes. The "bull's head" sign in the sternocostoclavicular and manubriosternal joint is characteristic of SAPHO syndrome. However, bone scintigraphy is less sensitive and less innocuous than MRI, potentially missing symmetric metaphyseal involvement [13, 14, 38]. Bone biopsies are often necessary to exclude other diagnoses such as intraosseous lymphoma, infections, Langerhans cell histiocytosis, or fibrous dysplasia. A clinical scoring system has been proposed to help determine whether a bone biopsy is warranted [14, 25, 30, 42]. Notably, skull involvement in CNO is considered malignant until proven otherwise in a bone biopsy [11]. Histologically, bone lesions in CNO exhibit nonspecific osteitis, characterized by neutrophils in the early stages, along with multinucleated giant cells, osteoclastic bone resorption, and scattered granulomatous foci. In later stages, fibrosis, lymphocytes, plasma cells, monocytes, and macrophages may be observed [2, 3, 19]. Mast cell infiltrates may also be present [12]. Multifocal disease in CNO typically affects the femur and/or tibia, including the tibio-appendicular multifocal pattern, and less commonly involves the pelvis and/or spine. In contrast, unifocal disease is more frequently observed in the clavicle, although it occurs in only 10–20% of patients [13, 24, 30]. Low bone mineral density (BMD) is often observed in patients with CNO [36]. Diagnostic delay is common in CNO, with estimates ranging from one to two years from the onset of symptoms [14, 17]. Chronic nonbacterial osteomyelitis is typically diagnosed through a process of exclusion, considering both imaging and histological data. Although there are no pathognomonic features, a combination of chronic relapsing-remitting bone pain, radiologically proven osteomyelitis, hyperostosis, sclerosis, increased isotope uptake on bone scintigraphy, and skin manifestations are suggestive of the condition, especially when

Table II. Proposed criteria for the diagnosis of chronic nonbacterial osteomyelitis

Jansson et al. [42]	Bristol criteria
Major criteria	Mandatory criteria
– Radiologically proven osteolytic/sclerotic bone lesion	– Typical clinical findings (bone pain +/– significant local or systemic features of inflammation or infection)
– Multifocal bone lesions	– Typical radiologic findings (plain X-ray showing combination of lytic areas, sclerosis, and new bone formation, or preferably STIR MRI showing bone marrow edema +/- bone expansion, lytic areas, and periosteal reaction)
– PPP or psoriasis	Facultative criteria
– Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis	– More than one bone involved (or clavicle alone)
Minor criteria	Without significantly raised CRP (< 30 mg/l)
– Normal blood count and good health condition	– Unifocal disease (other than clavicle), or CRP 30 mg/l, with bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis or sclerosis) with no bacterial growth whilst not on antibiotic therapy
– CRP and ESR less than 2 times the upper limit	Diagnosis: Both mandatory criteria plus one facultative criterion
– Observation time more than 6 months	
– Hyperostosis	
– Association with other autoimmune disorders apart from PPP or psoriasis	
– Grade 1 or 2 relatives with autoimmune or autoinflammatory diseases, or with CNO	
Diagnosis: 2 major criteria or 1 major plus 3 minor criteria	

CRP – C-reactive protein, CNO – chronic nonbacterial osteomyelitis, ESR – erythrocyte sedimentation rate, PPP – palmoplantar pustulosis or psoriasis, STIR MRI – short tau inversion recovery magnetic resonance imaging.

the lower limbs and clavicles are involved [24, 38, 39, 43]. Proposed diagnostic criteria for CNO/CRMO have not been validated in prospective studies, but they often include the presence of bone pain, characteristic imaging findings, and multifocal pattern (unifocal disease usually requires a negative bone biopsy), as shown in Table II [13, 15, 17, 44, 45]. Treatment for CNO is generally empiric [4]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as first-line treatment, with 40–80% of patients experiencing pain relief after 12 months. However, only about one quarter of patients are expected to be free of active lesions on MRI, and lesions can be asymptomatic in at least half of patients. Additionally, there is limited evidence supporting the effectiveness of NSAIDs in adults [13, 15, 17, 46]. Nonsteroidal antiinflammatory drugs may be particularly beneficial in cases of CNO with peripheral and/or clavicle involvement [17, 30]. Bisphosphonates, glucocorticosteroids (GCs), sulfasalazine, methotrexate, and colchicine are alternative treatment options when NSAIDs fail. The choice of treatment may depend on individual patient factors and disease severity [16, 23, 24]. Antibiotics are generally not expected to alleviate symptoms of CNO, as the condition is sterile by definition. However, there have been reports suggesting a possible anti-inflammatory effect of azithromycin, which improved clinical and radiological manifestations of CNO in a case series [14, 30]. In terms of biologic treatments, the ARC/CARRA (Childhood Arthritis and Rheumatology Research Alliance) treatment plan designates TNF-α inhibitors as the first biologic option when immunosuppressants fail, and these agents may be particularly helpful when marked inflammation is present [13, 19]. Additionally, IL-1 inhibitors and biologics targeting the IL-17/IL-23 axis have been used in CNO and SAPHO when TNF blockers are ineffective, while JAK inhibitors have also shown promising results in some cases [14, 47]. In contrast to infectious osteomyelitis, surgery is generally not considered useful for the treatment of CNO, although it may be performed before a solid diagnosis is established, particularly in cases where the jaw is affected [15]. Inflammatory markers are typically regarded as unhelpful for monitoring disease activity, although they often normalize during inactive periods [17, 39]. Chronic nonbacterial osteomyelitis usually follows a protracted course with several painful relapses in most patients, and more than 90% of children are expected to develop multifocal lesions [13, 24]. Remission has been documented in about 40% of patients after one to five years of follow-up, but flares occur in more than half of the patients [17]. Complications are expected in 25–50% of patients with CNO, including bone deformities, chronic spondyloarthropathy, leg hypertrophy or asymmetries, joint angulations, vertebral fractures, and growth failure [11, 13, 30]. Monophasic disease generally carries a much better prognosis [11].

Chronic nonbacterial osteomyelitis is primarily a sporadic condition; however, there are monogenic forms associated with specific gene mutations, including DIRA, Majeed syndrome (MS), CRMO related to *FBLIM1* mutation, and possibly PAPA [2, 18, 21, 48]. In addition to these monogenic forms, genomic expression profiling has implicated other immune-related genes, such as *IRF5*, *OAS3*, and *HLA-A*, as well as ribosomal-related genes, in the pathogenesis of CRMO [49]. There are also other syndromic forms of CNO not discussed here, including cherubism, hypophosphatasia, and primary hypertrophic osteoarthropathy, which may present with bone manifestations [11].

Deficiency of the IL-1 receptor antagonist is an autosomal recessive AID caused by mutations in the *IL1RN* gene, which encodes the IL-1 receptor antagonist (IL-1Ra) [4, 13]. The absence of functional IL-1Ra leads to uncontrolled IL-1 signaling, resulting in a systemic inflammatory response syndrome (SIRS) and subsequent osteoclast activation [23, 27, 30]. Patients with DIRA typically present with severe inflammation involving both the skin and bones, often manifesting in the first few months of life (the pustular skin rash usually appears within the first weeks), and include multifocal sterile osteomyelitis, osteopenia with lytic bone lesions, periostitis, widened ribs, and an erythrodermic pustular rash [23, 27, 30, 50, 51]. While sterile osteomyelitis may be limited to specific areas, extensive bone involvement is more common in DIRA, often affecting the distal ribs and long bones [1, 4, 30]. Patients may also experience joint swelling and pain, aphthous ulcers, hepatomegaly, central nervous system (CNS) vasculitis, respiratory distress with interstitial lung disease, venous thrombi, and failure to thrive. Laboratory findings often include anemia, leukocytosis, thrombocytosis, and elevated ESR and CRP levels [4, 50, 51]. Radiographic features include multifocal osteolytic lesions, widening of the anterior rib ends, and periosteal elevation of long bones [27, 30]. Bone biopsy may reveal purulent, culture-negative osteomyelitis with sclerosis and fibrosis [30]. Diagnosis is typically based on clinical grounds and confirmed by genetic testing of the *IL1RN* gene [4, 51]. Treatment with IL-1 blockade is considered lifesaving, and disease manifestations often show significant improvement with these agents. However, responses may vary, particularly in patients carrying certain genetic mutations, such as the 175kb genomic deletion [4, 13, 27]. Mortality remains a concern, occurring in approximately 30% of infants in the early months, primarily due to SIRS, interstitial lung disease, and organ failure [1, 27].

Majeed syndrome is a rare autosomal-recessive disorder classified as a NLRP3 inflammasomopathy, caused by mutations in the *LPIN2* gene [13, 23]. The loss of lipin-2 activity likely results in an abnormal response of the innate immune system to fatty acids, leading to the hyperproduction of proinflammatory cytokines and dysfunctional oxidative stress in macrophages [2, 12, 29]. Majeed syndrome presents as an early form of CRMO, typically accompanied by severe dyserythropoietic anemia during the first two years of life. Although the anemia is usually hypochromic and microcytic, it can range from mild to transfusion-dependent. Milder phenotypes have been associated with older ages at onset [2, 3, 21, 23, 50]. Psoriasis and Sweet's syndrome may also be present, though they are often transient [2, 6, 13, 30]. While the classic triad of early-onset CRMO, severe congenital dyserythropoietic anemia, and neutrophilic dermatosis occurs in less than 10–25% of patients, phenotypic variability is common [6, 21]. In MS, symptoms tend to be persistent, with only infrequent, brief remissions [3]. Microcytic anemia and elevated inflammatory markers are present in about 90% of patients, but other manifestations, such as neutropenia, hepatosplenomegaly, and transient cholestatic jaundice, occur in a minority [6]. Patients typically present with lytic radiolucent and sclerotic bone lesions affecting the metaphysis of long bones, although hyperostosis may also occur in clavicular lesions [2, 50]. Histologically, the bone inflammation observed in MS resembles that seen in CRMO and DIRA, while bone marrow aspiration typically demonstrates erythroid hyperplasia with bi- or multinuclearity [2, 6]. The mainstay of treatment for MS includes NSAIDs and physical therapy, but short courses of GCs, methotrexate, or pamidronate may also be beneficial in managing symptoms [2, 21]. However, patients with MS typically show only moderate responses to NSAIDs, GCs, and TNF inhibitors, while dyserythropoietic anemia does not improve with these treatments [4, 27]. Interleukin-1 inhibitors have shown promise in the treatment of MS, although their effect on hemoglobin levels may be less pronounced compared to other symptoms. It remains unclear whether this is due to a reversal of the dyserythropoiesis or better control of chronic inflammation [2, 13]. Complications of persistent inflammation in MS can include joint deformities, contractures, muscle atrophy, and growth delay [6, 30].

Homozygous mutations in the *FBLIM1* gene, which encodes the anti-inflammatory filamin-binding LIM protein (FBLP-1), have been described in sporadic cases of CNO [2, 13]. FBLP-1, also known migfilin, plays a critical role in balancing bone remodeling processes [13, 21, 48]. Mutations in FBLIM1 lead to loss of FBLP-1 function and increased activation of RANKL, a key mediator of bone resorption [14]. In addition to its role in bone remodeling, FBLP-1 has been implicated in IL-10-mediated autoinflammatory responses in macrophages. This suggests that dysfunction of FBLIM1 may contribute to the dysregulation of the immune system, leading to the development of sterile osteomyelitis and CNO in affected individuals [13, 21, 48]. Moreover, cases of CRMO associated with *FBLIM1* mutations have been reported to occur concurrently with psoriasis, indicating a potential link between *FBLIM1* mutations and inflammatory skin conditions [21]. These findings highlight the importance of FBLP-1 in maintaining immune homeostasis and bone health. Further research into the molecular mechanisms underlying *FBLIM1* mutations may provide deeper insights into the pathogenesis of CNO.

The PAPA syndrome is an autosomal dominant AID caused by gain-of-function (*GOF*) mutations in the *PSTPIP1* (proline, serine, threonine, phosphatase interactive protein) gene, also known as CD2 binding protein 1 (*CD2BP1*). These mutations lead to hyperphosphorylation of the mutated protein, which in turn increases its binding affinity for pyrin. This interaction triggers the activation of pro-caspase 1 activation, resulting in excessive production of IL-1β [2, 4, 29]. Clinically, PAPA syndrome typically manifests in childhood with recurrent episodes of sterile pyogenic erosive arthritis, which often progresses to bone destruction and ankylosis. Neutrophilic skin lesions, including pyoderma gangrenosum and cystic acne, usually appear during puberty [1, 2, 50]. Other potential manifestations include aphthous stomatitis, irritable bowel syndrome, pathergy, and pancytopenia [4]. Diagnosis is primarily based on clinical features, with genetic testing used to confirm the presence of *PSTPIP1* mutations [4]. Treatment options for PAPA syndrome include high-dose GCs, IL-1β antagonists, and TNF inhibitors. The response to these treatments can vary between individuals [2, 52]. Tumor necrosis factor inhibitors are generally more effective for managing skin involvement, while IL-1 antagonists tend to offer better relief for arthritis. However, some patients receiving high doses of IL-1 inhibitors may experience disease flares, potentially due to IL-18-driven inflammation [1, 4]. In cases of severe erosive arthritis, joint replacement therapy may be necessary to address joint damage and improve quality of life [4].

Other autoinflammatory disorders and related disorders

Monogenic disorders

Familial Mediterranean fever is caused by activating mutations in the *MEFV* gene, which encodes pyrin. These mutations trigger the activation of caspase-1,

leading to the increased production of proinflammatory cytokines, particularly IL-1β [5, 9]. Familial Mediterranean fever is most commonly observed in populations of Middle Eastern descent [1, 53]. Clinically, FMF is characterized by recurrent episodes of fever, typically lasting several hours to three days, accompanied by symptoms such as serositis, erysipeloid rashes, and arthritis, which often affects the large joints of the lower limbs [1, 50]. Patients may also experience low bone mass, along with cartilage and bone erosions [9]. During attacks, inflammatory markers are often markedly elevated [53]. Familial Mediterranean fever is characterized by high levels of IL-1β, IL-6, IL-8, and IL-12 [9]. The condition frequently coexists with CNO, suggesting a potential association between the two disorders [54]. In fact, an increased frequency of MEFV mutations has been observed in CNO patients, with such mutations often correlating with a more severe phenotype [55]. The diagnosis of FMF is typically based on clinical diagnostic criteria, such as the Tel Hashomer, Livneh, and Turkish pediatric criteria, which consider clinical symptoms, family history, and response to colchicine. The Eurofever/PRINTO group has proposed additional classification criteria that also incorporate genetic testing results [53]. Treatment for FMF usually involves daily colchicine, which leads to complete remission in approximately three-quarters of patients [50, 56]. For those who are unresponsive to or intolerant of colchicine, IL-1 antagonists have been found to be effective in improving disease outcomes [1, 50, 52]. Anti-TNF agents may also be beneficial, particularly for patients with significant articular involvement [1]. If left untreated, chronic elevation of the acute phase reactant serum amyloid A can lead to the development of amyloidosis [1]. Other complications of FMF include growth retardation, pubertal delay, infertility, serosal scarring, adhesions, musculoskeletal pain, joint deformities, and osteoporosis [53].

Neonatal-onset multisystem inflammatory disease (NOMID, also known as chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome, represents the most severe form of CAPS. It is caused by GOF mutations in the *NLRP3* gene, also referred to as *CIAS1* [5, 9, 29, 51]. Common features of all cryopyrinopathies, such as recurring fever, urticaria, and conjunctivitis, are also present in NOMID. However, NOMID presents with additional severe manifestations, including CNS involvement (e.g., aseptic meningitis and cerebral atrophy), skin rashes, and arthropathies, which may result in bone deformities and epiphyseal abnormalities [1, 9, 50, 51]. Bone involvement in CAPS, particularly in the childhood form, typically includes two distinct types of manifestations: 1) severe patellar hypertrophy, which occurs in 14 to 33% of patients with NOMID, is characterized by abnormal enlargement of the patella, likely due to inflammatory processes affecting the bone; 2) non-specific bone lesions resulting from severe inflammatory polyarthritis, which can lead to various bone abnormalities, though these are not unique to CAPS but may be seen in other inflammatory conditions [2, 29]. The *NLRP3* gene is expressed not only in monocytes and macrophages but also in osteocytes, contributing to the osteitis observed in CAPS, including NOMID [57]. Osteitis has also been described in Muckle-Wells syndrome (MWS), another form of CAPS [58]. Common laboratory finding in NOMID and CAPS include anemia, neutrophilic leukocytosis, thrombocytosis, and elevated acute phase reactants [50, 51]. The treatment for CAPS primarily involves IL-1 inhibitors, which can rapidly resolve inflammatory symptoms [50, 51]. However, while these biologic agents are highly effective in controlling inflammation, they may have limited effects on certain complications, such as hearing loss, mental retardation, and bone dysplasia, and their real-life effectiveness may be lower than what is reported in clinical trials [1, 52]. Although IL-1 antagonists can suppress the inflammatory symptoms associated with CAPS, they may not fully address issues such as bony overgrowth, as IL-1β may not be the primary driver of skeletal manifestations in this condition [2, 9]. In some cases, systemic GCs and NSAIDs can be used for symptomatic relief, especially in managing joint pain or inflammation [1].

Mevalonate kinase deficiency (MKD) is a rare metabolic AID that encompasses both the milder hyper-IgD syndrome (HIDS) and more severe forms such as mevalonic aciduria (MVA) [29, 59]. Mevalonate kinase deficiency is caused by mutations in the *MVK* gene and typically presents at an early age with fever, lymphadenopathy, rash, abdominal pain, and occasionally osteitis, which often affect the long bones, spine, or pelvis [50, 59]. Inflammatory markers are commonly elevated during disease flares, and genetic testing confirms the diagnosis [59]. Elevated urinary mevalonic acid levels are typically found in MVA [50]. Treatment includes NSAIDs for supportive care, while IL-1 inhibitors are highly effective in controlling systemic symptoms and bone inflammation [29, 59]. Glucocorticosteroids and TNF inhibitors may be used in specific cases [29, 52]. Although flares tend to be very frequent, amyloidosis is a rare complication [52].

Hyperostosis-hyperphosphatemia syndrome (HHS) is a rare genetic disorder caused by mutations in the *GALNT3* gene, which encodes a glycosyl-transferase enzyme involved in regulating phosphate metabolism [2, 60]. The HHS is often considered part of the clinical spectrum of familial tumoral calcinosis, a condition that can also result from mutations in other genes besides *GALNT3* [2]. The underlying pathology of HHS is linked to

the dysfunction of fibroblast growth factor 23 (FGF23), leading to hypophosphatemia, increased tubular reabsorption of phosphate, and elevated levels of 1,25-dihydroxyvitamin D3 [2, 60]. Some individuals with HSS may remain asymptomatic, while others experience disabling calcifications, which can occur in multiple locations, including periarticular areas, eyelids, vascular walls, and the gastrointestinal tract [2]. Patients may also present with recurrent fever, pain, and tenderness over long bones, alongside elevated inflammatory markers, anemia, and thrombocytosis, suggesting an autoinflammatory component to the disease [2, 59]. Radiographic findings are characteristic and typically include diaphysitis, hyperostosis, and periosteal apposition [2, 61]. Treatment options for HHS are limited, but IL-1 inhibitors have shown some effectiveness in managing symptoms associated with the inflammatory component of the disease [2].

The H syndrome is a rare autosomal recessive AID caused by mutations in the *SLC29A3* gene, which is thought to play a role in osteoclast differentiation and function. These mutations result in a diminished number of osteoclasts in affected patients, contributing to the bone manifestations observed in the disease [2]. As a genodermatosis, H syndrome is characterized by hyperpigmentation and hypertrichosis, and a range of systemic features, including deafness, hepatosplenomegaly, hypogonadism, hyperglycemia, heart anomalies, and systemic inflammation with fever and elevated inflammatory markers in some patients [2, 61, 62]. Bone involvement is also a hallmark of H syndrome and may include features such as wide long bones, diaphyseal cortical hyperostosis, metaphyseal flaring, flattened epiphysis, skull thickening of the calvaria, short stature, dysosteosclerosis, hallux valgus, and flexion contractures [2, 62]. Treatment options for H syndrome are limited, but biologic medications such as tocilizumab have been tried with some success in managing the inflammatory symptoms associated with the disorder [2, 62, 63].

Interferonopathies are a group of disorders characterized by upregulation of the type I interferon pathway, which can lead to systemic inflammation and bone involvement. This is thought to occur because type I interferons may inhibit osteoclast differentiation, potentially contributing to skeletal abnormalities seen in these conditions [2]. Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) is a rare AID caused by GOF mutations in the transmembrane protein 173 (*TMEM173*) gene, which encodes STING protein. STING is a transmembrane adaptor molecule involved in sensing cytosolic DNA, which activates the production of type I interferons, leading to chronic inflammation [2, 64]. Clinically, SAVI is characterized by a range of symptoms, including violaceous, scaly skin rashes caused by vasculitis and microthrombotic angiopathy, livedo reticularis, telangiectasias, and Raynaud's phenomenon, interstitial lung disease, systemic inflammation of neonatal onset, and elevated levels of CRP and ESR [2, 50, 51]. Some patients may also have low-titer antineutrophil cytoplasmic antibodies (ANCAs) and antiphospholipid antibodies, suggesting a possible autoimmune component [51]. Bone involvement in SAVI can include bone resorption of the distal phalanges, ulnar deviation, and carpal bone lesions, which are thought to result from chronic joint inflammation [2]. Histopathological analysis of lesional biopsies typically shows leukocytoclastic vasculitis [51]. The increased production of proinflammatory cytokines, particularly type I interferons, is thought to contribute to inflammatory bone loss and the associated bone manifestations in SAVI [2]. Treatment options for SAVI are limited, but Janus kinase 1/2 inhibition has shown efficacy in patients who do not have significant bone involvement, while IL-1 antagonists have been used to manage systemic inflammatory symptoms in some patients, although their effects on bone involvement remains less clear [2, 50, 64].

Singleton-Merten's syndrome (SMS) is a rare autosomal dominant AID caused by GOF mutations in the *IFIH1* gene, which encodes the melanoma differentiation-associated protein 5 (MDA5), a sensor protein involved in detecting viral RNA and triggering immune responses [2]. Clinical manifestations of SMS are broad and can involve multiple systems, including bone abnormalities such as enlarged medullary cavities, osteoporosis, and osteolysis, particularly affecting the distal extremities, aortic and valvular calcifications, recurrent infections, glaucoma, psoriasis, and distinctive facial features [2, 65].

Polygenic autoinflammatory disorders and autoinflammation-related syndromes

Schnitzler's syndrome (SS) is a rare, acquired AID characterized by the presence of monoclonal gammopathy, typically IgM (or rarely IgG), with more than 90% of cases associated with κ-light chain. This gammopathy is often accompanied by a chronic urticarial rash, which is notable for having neutrophilic infiltrates but typically causes little or no itching [66–68]. The median age at onset is around 55 years [69]. The characteristic urticarial rash is often accompanied by recurrent fever, bone and joint pain, headache, fatigue, and lymphadenopathy [1, 68]. Bone pain is a prevalent symptom, affecting nearly 70% of patients, often localized to the pelvic bones and tibia, while bone structural changes such as osteosclerosis or osteopenia are found in over 60% of individuals with SS [68, 70]. The clinical phenotype of SS

bears similarities to other AIDs, particularly CAPS. Some cases of SS have been linked to somatic mutations in the *NLRP3* gene, even though the exact role of these mutations in SS pathogenesis remains uncertain [1, 5]. Elevated inflammatory markers are commonly observed in SS, including ESR, neutrophil count, CRP, IL-6 and IL-18, while inflammatory anemia and thrombocytosis may be present in some patients [68]. The diagnosis is based on clinical criteria, with the Lipsker and Strasbourg criteria being commonly used: the Lipsker criteria emphasize chronic recurrent exanthema and monoclonal gammopathy, while the Strasbourg criteria require evidence of abnormal bone remodeling, in addition to other clinical features [66, 68]. Bone lesions are found in approximately two-thirds of patients with SS. These lesions are typically sclerotic or predominantly sclerotic, and commonly affect the distal femur, proximal tibia, and innominate bones [71]. A ^{99m}Technetium bone scan can be used for screening bone involvement in SS and is helpful in identifying areas of abnormal bone activity, possibly correlating with disease activity. Magnetic resonance imaging may reveal characteristic low T1 and elevated T2 signal abnormalities in the affected bones [66, 71]. Patients with SS may exhibit increased bone density, though the extent of this can vary between individuals [67]. Traditional treatments for SS include NSAIDs, GCs, and immunosuppressants [1]. However, IL-1 inhibitors have shown remarkable efficacy in treating SS, with clinical remission achieved in virtually all patients and complete remission in over 80% of cases. Notably, paraproteins may persist even in patients who achieve remission with IL-1 blockade [67, 69]. The prognosis for SS is generally excellent, especially with appropriate treatment. Survival rates are high, but around 15-20% of patients may develop lymphoproliferative disorders, which can significantly impact prognosis [67, 68]. AA amyloidosis is rare in SS, particularly if patients receive appropriate treatment to control inflammation [69].

Systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD) represent the same clinical entity but with different ages of onset – SJIA typically begins in childhood, while AOSD affects adults [1, 18]. Both are polygenic AIDs, and they share similar pathogenesis, including the upregulation of IL-1 and other proinflammatory cytokines, including IL-1, IL-6, IL-17a, IL-18, TNF-α, and interferon-γ (IFN-γ) [18]. Both SJIA and AOSD present with daily spiking fevers and polyarticular arthritis as hallmark features, and sometimes with an evanescent salmon-colored maculopapular rash, serositis and hepatosplenomegaly [1]. Systemic juvenile idiopathic arthritis has been observed alongside other systemic AIDs, such as TRAPS syndrome and CAPS [18]. Inflammatory markers are typically high, including ferritin, and may be used for monitoring disease activity and response to treatment [72, 73]. In SJIA, inflammatory bone lesions have been described, which resemble those seen in monogenic bone AIDs [18]. Bone edema and erosions have been demonstrated in AOSD, indicating that bone involvement is an important feature of this condition [74]. For AOSD, the International League of Associations for Rheumatology (ILAR) classification criteria are used when symptoms onset occurs before the age of 16 years. These criteria include the presence of arthritis lasting for at least six months, along with other clinical features. On the other hand, Fautrel's criteria and Yamaguchi criteria are among the most widely recognized diagnostic criteria for AOSD [73]. Conventional treatment for both SJIA and AOSD typically includes NSAIDs and GCs to control inflammation and manage symptoms [1]. Interleukin-1 biologics have emerged as effective therapeutic options for SJIA and have shown promise in inducing remission of both the systemic symptoms and bone lesions associated with the condition [9, 18]. Specifically, anakinra, an IL-1 receptor antagonist, has proven effective in treating osteitis and other disease-specific symptoms in AOSD [23]. Both canakinumab and tocilizumab have been approved by the FDA for the treatment of SJIA, further expanding therapeutic options [1]. Macrophage activation syndrome (MAS) is a frequent and potentially life-threatening complication of both SJIA and AOSD and is caused by mutations in the NLRC4 gene that result in overproduction of proinflammatory cytokines, including IL-18 and IL-1β [9, 72, 73]. The NLRC4 inflammasome, activated by nucleotide-derived metabolites and fatty acids, is also upregulated by bone-derived danger-associated molecular patterns (DAMPs) during osteoclastogenesis, possibly exacerbating systemic inflammation and contributing to disease progression [9].

Gout arises from the formation of monosodium urate (MSU) crystals, while calcium pyrophosphate deposition disease (CPPD) is caused by the precipitation of calcium pyrophosphate dihydrate crystals. Additionally, degenerative disorders such as osteoarthritis and Milwaukee shoulder are associated with the deposition of basic calcium phosphate (BCP) crystals [9, 75]. In gout, MSU crystals negatively impact osteoblast viability and function, promoting a shift towards osteocyte activity, bone resorption, and inflammation [75]. *In vitro* studies have demonstrated that BCP crystals can promote osteoclastogenesis in an NLRP3-dependent manner, although their exact role in skeletal pathology remains unclear [9]. Although CPPD crystals are known to have a stronger inflammatory potential than BCP crystals, they are particularly linked to the development of pseudogout flares [76].

Bone dysplasia syndromes

Some bone dysplasia syndromes characterized by hyperostosis and systemic inflammation fall within the spectrum of autoinflammation [2]. Ghosal hematodiaphyseal dysplasia (GHD) is one such condition, caused by mutations in the *TBXAS1* gene, which encodes thromboxane A synthase. Thromboxane A synthase plays a role in platelet aggregation and also modulates BMD [2]. Ghosal hematodiaphyseal dysplasia follows an autosomal recessive inheritance pattern, with a higher prevalence in Middle Eastern and Indian populations [77]. In GHD, reduced expression of *TNFSF11* (which encodes RANKL) and *TNFRSF11B* (which encodes osteoprotegerin) disrupts the balance between these key regulators of osteoclastogenesis. This leads to elevated acute phase reactants, metadiaphyseal dysplasia of long bones, cortical endosteal hyperostosis, and bone marrow fibrosis and/or sclerosis, all of which impair hematopoiesis. As a result, cytopenias, including normochromic normocytic anemia and/or thrombocytopenia, occur in approximately 50% of patients, with pancytopenia being a possible complication [2, 77, 78]. Involvement of the base of the skull is common in GHD [2]. Glucocorticosteroids have shown effectiveness in treating both the skeletal and hematological manifestations of GHD [2, 77]. Camurati-Engelmann's disease (CED) is an autosomal dominant disorder caused by mutations in the *TGFB1* gene, which leads to the premature activation of TGF-β1. This results in hyperostosis, primarily affecting the diaphysis of long bones in a progressive manner, and occasionally involving cranial bones [2, 79, 80]. Also known as progressive diaphyseal dysplasia, CED often presents with neuromuscular symptoms such as proximal muscle weakness, limb pain, and fatigue [77, 80]. Currently, there is no specific treatment for CED, but GCs have shown efficacy in managing pain and radiographic lesions associated with the disease [2]. Glucocorticosteroids not only inhibit osteoblast proliferation and differentiation, but also promote osteoclastogenesis. It appears that bisphosphonates may offer additional therapeutic benefits in managing CED [80].

Spondyloenchondrodysplasia (SPENCD) is classified as an interferonopathy, caused by biallelic mutations in the *ACP5* gene, which encodes tartrate-resistant acid phosphatase. This genetic abnormality leads to elevated serum levels of IFN-α and the upregulation of interferon-stimulated genes, potentially contributing to increased BMD [2, 81]. Clinical manifestations of SPENCD typically include skeletal dysplasia characterized by enchondromas, platyspondyly, and/or metaphyseal dysplasia. These may be accompanied by other features such as short stature, kyphosis, pectus carinatum, and short distal phalanges [2]. Radiographic findings often show radiolucent lesions in the metaphysis and vertebrae [2]. Neurological symptoms may include developmental delay, intracranial calcifications, and spasticity. Additionally, up to 85% of patients exhibit autoimmunity features, such as thrombocytopenic purpura and systemic lupus erythematosus [2, 81]. Immunodeficiency features are common, likely due to the increased susceptibility to viral and bacterial infections [2]. Spondyloenchondrodysplasia with immune dysregulation (SPENCDI) is a specific condition characterized by an immune phenotype alongside skeletal and neurological manifestations [81]. Treatment typically involves GCs and immunosuppressants to manage autoimmune manifestations, although these therapies do not impact bone involvement [2].

Young patients with Blau syndrome (BS) often exhibit bone morphological dysplastic-like changes, such as camptodactyly, biconcave radial epiphysis, carpal dysplasia with carpal crowding, and short plump ulnae [2]. Unlike the sporadic form observed in early-onset sarcoidosis, BS represents the familial form of sarcoidosis [82]. It arises from missense mutations in the NACHT domain of NOD2 (also known as CARD15), which trigger downstream activation of RIP2 kinase and subsequent release of proinflammatory cytokines [1, 2]. Clinical manifestations of BS result from granulomatous infiltration, commonly presenting as dermatitis (erythematous maculopapular rashes and lichenoid papules), arthritis, and uveitis. However, granulomatous liver disease, interstitial lung disease, cranial neuropathies, and large vessel vasculitis may also occur [29, 50, 82]. Laboratory tests often yield normal results [50]. Radiographs typically show morphological changes rather than erosions, with frequent alterations observed in radial, ulnar, and carpal bones [82]. Treatment of BS can be challenging and may involve GCs, methotrexate, cyclosporin, thalidomide, anti-TNF monoclonal antibodies, and anakinra [1, 50, 52].

In VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, not only dysplastic bone marrow but also myelodysplastic syndromes occur in approximately half of patients [83, 84]. The VEXAS syndrome is an acquired AID caused by somatic mutations in the *UBA1* gene, which clinically manifests as severe adult-onset chronic inflammation, with a median age of onset at 67 years. It is often associated with hematological disorders, particularly myelodysplastic syndrome [83]. The VEXAS syndrome can affect potentially all organs, leading to a heterogenous clinical presentation, but typical features include fever, weight loss, and other systemic symptoms, as well as arthralgia and myalgia, ocular inflammation, neutrophilic dermatosis, vasculitis, relapsing chondritis, cytopenias, and pulmonary infiltrates, with a high mortality rate [83, 85]. Treatment with high-dose GCs is often effective, but biologic therapies (such as

anakinra, tocilizumab, JAK inhibitors), azacytidine, abatacept, and allogenic hematopoietic stem cell transplantation have shown promising results [83]. Nevertheless, VEXAS carries a poor prognosis, attributed to both disease-related causes and treatment toxicity [83, 84].

Discussion

Infection represents the leading cause of osteomyelitis [22]. Infection can reach the bone by hematogenous spread, contiguous spread or direct inoculation, while certain medical conditions (e.g., diabetes, peripheral vascular disease, sickle cell anemia) predispose individuals to osteomyelitis. However, several AIDs present with sterile osteomyelitis. Chronic nonbacterial osteomyelitis serves as a common denominator among ABDs, which are rare disorders characterized by recurrent episodes of bone inflammation without any infection or autoimmune cause. These conditions can be categorized based on the pathogenesis of bone involvement [2]. According to the molecular/immunologic mechanisms underlying autoinflammation, most AIDs with bone involvement are classified as IL-1β activation disorders and related inflammasomopathies. These include intrinsic disorders such as MWS and NOMID/CINCA, extrinsic disorders such as FMF, PAPA, CRMO, MS and DIRA, as well as complex disorders such as SS [29]. Recently, proteomic analysis has identified upregulated proteins in patients with acute CNO. Axon guidance appears to be the most enriched category of upregulated proteins in these patients, along with neutrophil degranulation and mitogen-activated protein kinase cascade regulation [86]. These upregulated proteins may be used as biomarkers for CNO diagnosis and activity in the future. However, given that biochemical and histopathological data are often complementary, MRI usually constitutes the reference standard in diagnosing CNO. It is important to note that axial skeletal lesions are more common in adult populations, while children and adolescents frequently exhibit involvement of appendicular skeletal sites [87].

In ancient times, inflammation was described by the classic "quadruple" signs of *calor* (heat), *dolor* (pain), *rubor* (redness), and *tumor* (swelling) [50]. Rudolph Virchow later added loss of function (*functio laesa*) to this list, completing the classic description of inflammation [88]. Alongside these classic signs of autoinflammation, sterile osteomyelitis could also be considered a cardinal feature of autoinflammation. Sterile bone inflammation is also associated with warmth, swelling and focal tenderness at the affected sites [87]. Although signs such as fever (e.g., FMF and CAPS may present with both fever and sterile osteomyelitis) or neutrophilic rashes are common and may overlap across various AIDs, specific signs like panniculitis can help differentiate conditions, such as proteasome-associated AIDs. Specifically, CNO serves as a common denominator among all ABDs, making sterile osteomyelitis a crucial indicator for recognizing this specific subset of AIDs [8].

In an era when serum biomarkers are not widely available, defining clinical subsets within AIDs is critical, particularly when determining appropriate therapeutic approaches. While IL-1 inhibitors are often the most effective biological agents for many AIDs, ABDs (CNO and others) may respond effectively to a variety of biologics, including TNF inhibitors, IL-1 antagonists, or even a combination of both. Therefore, recognizing bone involvement in AIDs is essential for timely diagnosis and initiation of biologic therapies, ensuring better management and outcomes for these complex disorders.

Conclusions

Sterile osteomyelitis occurs in many AIDs, with CNO serving as a common denominator among ABDs. This includes not only CNO and related syndromes, but also monogenic, polygenic, and dysplastic AIDs. Defining clinical subsets within AIDs is crucial, particularly in ABDs, where prompt recognition of bone involvement can guide clinicians to consider early initiation of TNF inhibitors and/or IL-1 antagonists. Such timely intervention may improve outcomes by addressing the underlying inflammation and preventing further bone damage.

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