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Autoinflammatory Bone Diseases

Fatih Haşlak, Nergis Akay, Ümit Gül, Aybüke Günalp, Elif Kılıç Könte, Sezgin Şahin, Özgür Kasapçopur

Department of Pediatric Rheumatology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye

Autoinflammatory bone diseases (AIBDs) constitute a recently identified subset of autoinflammatory diseases. These conditions are characterized by an exaggerated inflammatory response in the bones without any apparent etiology. Inflammatory bone lesions associated with AIBDs exhibit chronic inflammation, are typically culture-negative, and do not exhibit discernible microorganisms on histopathological examination. The most common and representative AIBD is chronic non-bacterial osteomyelitis (CNO), which is also known as chronic recurrent multifocal osteomyelitis. Another variant of CNO, which is typically observed in older teenagers or adults, is known as synovitis, acne, hyperostosis, pustulosis, osteitis syndrome. This condition is distinguished by its notable skin manifestations. Advancements in genetic research have led to the identification of three novel monogenic subtypes within the category of AIBDs. These include Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum, and acne syndrome, and interleukin-1 receptor antagonist deficiency syndrome. Another monogenic AIBD, called cherubism, affects only the maxilla and mandible. Data on the diagnosis and treatment of these rare diseases are extremely limited. However, if not diagnosed and treated promptly, it can result in significant complications, including severe disability and mortality. Thus, it is imperative to maintain a high level of clinical awareness of these diseases. These rare diagnoses should be considered in patients with musculoskeletal complaints in whom no specific etiology can be identified or in patients with systemic manifestations such as cutaneous and gastrointestinal symptoms or fever. In such patients, the diagnostic process, which encompasses imaging and genetic studies, should be initiated promptly.

INTRODUCTION

Autoinflammatory diseases (AIDs) constitute a group of disorders that typically arise from congenital dysfunction or dysregulation of the immune system, affecting multiple organ systems and causing significant morbidity and mortality. AIDs are distinct from the more widely recognized concept of autoimmune diseases owing to its fundamental characteristics such as the absence of autoantibodies. In AIDs, there is uncontrolled activation of innate immune system components, including macrophages, neutrophils, or monocytes, rather than the activation of acquired immune elements, which is observed in autoimmune diseases. Although the concept of AIDs emerged subsequent to the description of familial Mediterranean fever, the spectrum of disorders is rapidly expanding due to recent advancements in molecular sciences and genetics.[1,2]

Autoinflammatory bone diseases (AIBDs) are a recently identified subset within AIDs. AIBDs are characterized by an exaggerated inflammatory response in the bones without an apparent etiology. Inflammatory bone lesions associated with these diseases exhibit chronic inflammation, are typically culture-negative, and do not exhibit discernible microorganisms on histopathological examination.[3-5]

In AIBDs, recurring sterile osteomyelitis is frequently associated with inflammatory symptoms that affect the skin and gastrointestinal system. The most common and representative AIBD is chronic non-bacterial osteomyelitis (CNO), which is also known as chronic recurrent multifocal osteomyelitis (CRMO).[6,7] CNO has gained widespread acceptance as a more inclusive descriptor, because not all patients exhibit multiple bone lesions or experience repeated occurrences. Furthermore, CNO is employed as an umbrella term encompassing all AIBDs.[7]

Patients with CNO exhibit highly heterogeneous clinical manifestations. Consequently, novel subtypes of this disease have been recently identified via advanced genetic investigations. This review article provides a comprehensive and holistic overview of these lesser-known and recently differentiated groups of disorders.

Corresponding author: Özgür Kasapçopur, Department of Pediatric Rheumatology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye

e-mail: ozgurkasapcopur@hotmail.com

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ORCID iDs of the authors: F.H. 0000-0002-6963-9668; N.A. 0000-0001-6102-4055; Ü.G. 0000-0002-1282-8273; A.G. 0000-0003-0137-0460; E.K.K. 0000-0002-8174-5308; S.Ş. 0000-0002-5365-3457; Ö.K. 0000-0002-1125-7720.

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CLASSIFICATON

Following the initial recognition of CNO, researchers have documented various syndromic cases. A subset of these patients exhibit distinctive cutaneous manifestations, hematologic abnormalities, and systemic symptoms such as episodes of high fever.

Advancements in genetic research have led to the identification of three novel monogenic subtypes within the category of AIBDs. These are Majeed syndrome (*LPIN2* gene mutation), pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome (*PSTPIP1* gene alterations), and interleukin-1 receptor antagonist deficiency (DIRA) syndrome (*IL1RN* gene mutations).[8,9] Another monogenic AIBD called cherubism, which involves the maxilla and mandible, occurs due to *SH3BP2* gene mutations.[10]

In most patients with AIBDs, the genetic etiology has not yet been fully elucidated. Synovitis, acne, hyperostosis, pustulosis, osteitis (SAPHO) syndrome, which is characterized by prominent cutaneous manifestations, was previously considered to occur exclusively in adults. However, pediatric cases of SAPHO syndrome have been reported in recent years.[11] Patients without any of the mentioned syndromes have been classified as non-syndromic CNO in this article. The genetic, epidemiological and immunological differences between the AIBD subtypes are elucidated in Figure 1.

EPIDEMIOLOGY

The actual incidence and prevalence of AIBDs remain undetermined, which may be attributed to the rarity of these conditions and insufficient awareness among clinicians. DIRA syndrome is predominantly observed in the neonatal period, whereas Majeed syndrome manifests during infancy, particularly within the first 2 years of life.[7,8] Cherubism typically presents between 2 and 7 years of age, while PAPA syndrome presents between 2 and 8 years of age.[12,13] Non-syndromic CNO is generally observed at a mean age of 9 to 10 years, and SAPHO syndrome primarily affects adults.[14,15]

The incidence of DIRA syndrome and Majeed syndrome in males and females is approximately equal.[16,17] PAPA syndrome and cherubism exhibit a slightly higher prevalence in males, whereas non-syndromic CNO and SAPHO syndrome develop more frequently in females (Figure 1).[13,18-20]

PATHOGENESIS

In AIBDs, dysregulated inflammation that is triggered via various pathways in different subtypes constitutes the primary cause of tissue deterioration. These pathways will be elucidated subsequently in this article. However, the final stage of the disease remains almost identical across all the types. In individuals with a genetic predisposition, an imbalance in cytokine production

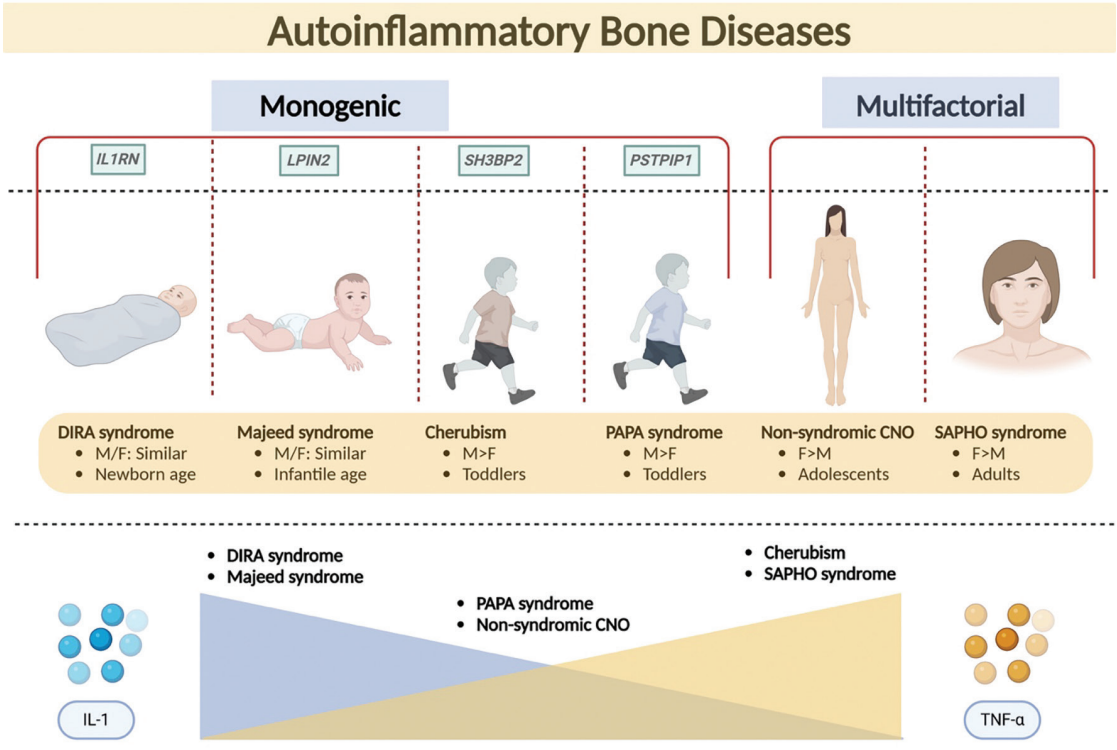

FIG. 1. Genetic, epidemiological, and immunological profiles of autoinflammatory bone diseases.

M, male; F, female; DIRA, interleukin-1 receptor antagonist deficiency syndrome; IL, interleukin; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; CNO, chronic non-bacterial osteomyelitis; SAPHO syndrome, synovitis, acne, hyperostosis, pustulosis, osteitis syndrome; TNF-α, tumor necrosis factor-alpha.

from peripheral monocytes develops either spontaneously, as an aberrant reaction to pathogens, or via undetermined mechanisms.[21]

In patients with AIBDs, the production of antiinflammatory cytokines such as interleukin-10 (IL-10) and IL-19 decreases, whereas that of proinflammatory cytokines and chemokines such as IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), IL-8, interferon gamma-inducible protein-10 (IP-10), membrane cofactor protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, and MIP-1β increases.[22-26] This uncontrolled inflammation enhances the interaction between the receptor activator of nuclear factor-κB (RANK) and its ligand RANKL on osteoclast precursor cell surfaces. Consequently, osteoclast activation and differentiation are promoted, resulting in bone tissue damage (Figure 2).[27-29]

Although all subtypes of AIBD exhibit shared pathogenetic pathways and are characterized by the uncontrolled mixture of certain proinflammatory cytokines, there are some minor differences between them. While TNF-α plays a pivotal role in SAPHO syndrome and cherubism, DIRA syndrome and Majeed syndrome are predominantly driven by elevated IL-1 levels.[8,30-33] In contrast, PAPA syndrome and non-syndromic CNO exhibit a more balanced distribution of TNF-α and IL-1 levels (Figure 1).[26,34,35]

DIAGNOSIS

The key to diagnosing AIBDs is demonstrating sterile bone inflammation via screening methods and a biopsy, while simultaneously ruling out malignant and infectious etiologies. Currently, no biochemical diagnostic test exists for AIBDs. Laboratory tests are primarily performed to exclude other diagnoses. The results of the complete blood count parameters typically remain within normal range. However, some patients may exhibit microcytic anemia due to chronic disease. Human leukocyte antigen-B27 (HLA-B27) and low titers of antinuclear antibodies may be infrequently detected. Levels of markers such as lactate dehydrogenase, uric acid, calcium, phosphorus, and alkaline phosphatase typically remain within the normal ranges.[36] Acute phase reactants, such as C-reactive protein and erythrocyte sedimentation rate, are generally elevated even when patients are asymptomatic, indicating subclinical inflammation. However, these markers may be significantly increased during exacerbations.[37-39]

Plain radiography is commonly used for the initial screening of painful bone conditions, identification of radiolucent, osteolytic, and sclerotic lesions, and determination of differential diagnoses on the basis of lesion morphology and location. However, X-rays

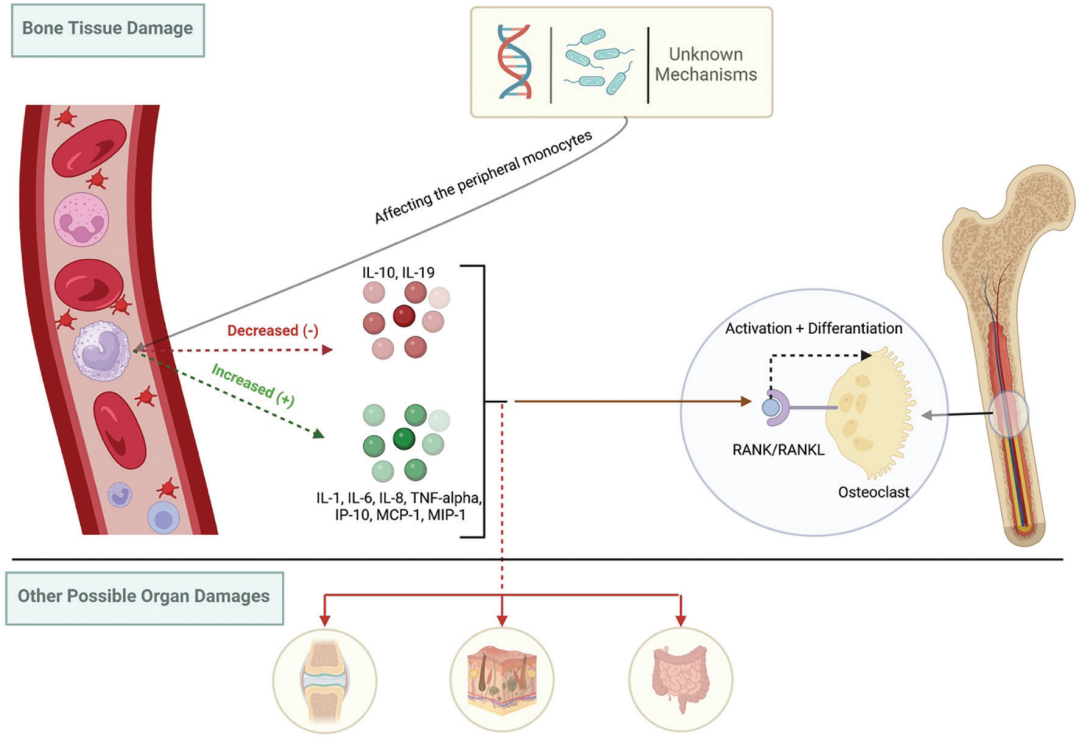

FIG. 2. Pathogenesis of autoinflammatory bone diseases (Specific genetic mutations, infections, and other unknown mechanisms can alter the cytokine profiles released by peripheral monocytes. The elevation of proinflammatory cytokines and chemokines, in conjunction with a reduction in anti-inflammatory cytokines, enhance the interactions between RANK and RANKL on osteoclast surfaces. This phenomenon leads to the initiation of osteoclast activation and differentiation, resulting in bone tissue damage. Furthermore, in a group of patients, this process may affect joints, skin, and intestinal tissues).

IL, interleukin; TNF-α, tumor necrosis factor-alpha; IP-10, interferon gamma inducible protein; MCP, membrane cofactor protein; MIP, macrophage inflammatory protein; RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand.

may not reliably detect early-stage conditions. Therefore, magnetic resonance imaging (MRI) of the affected areas or whole-body MRI is preferred for lesion assessment.[40] MRI employs coronal short tau inversion recovery (STIR) sequences to visualize bone lesions, with STIR and T1-weighted sequences providing detailed information regarding vertebral lesions and bone marrow changes. Furthermore, MRI may reveal periosteal and soft tissue reactions, articular involvement (particularly of the sacroiliac joint), spinal involvement, reduced intervertebral space, and pathological vertebral fractures.[41-43]

When MRI is unavailable, bone scintigraphy may be performed.[19,44] Bone biopsy should be considered in patients who present with a solitary lesion, cytopenia, or markedly elevated inflammatory markers to exclude infections and malignancy.[26]

DISEASE SUBTYPES

Non-syndromic CNO

Despite the widespread use of CNO or CRMO as an umbrella term for all AIBDs, in this article we have classified patients with AIBDs who do not meet the criteria for the other five subtypes as patients with non-syndromic CNO. The condition was initially described as a symmetrical multifocal osteomyelitis with subacute or chronic manifestations. However, with the accumulation of extensive knowledge, it became apparent that its clinical presentation could significantly vary. We can know recognize the condition's diverse spectrum, encompassing unifocal to multifocal involvement, and ranging from self-resolving cases to cases with chronic or recurrent patterns.[35,45] The Bristol criteria for the diagnosis of CNO or CRMO are listed in Table 2.[46]

TABLE 1. Bristol Criteria for the Diagnosis of Non-syndromic Chronic Non-bacterial Osteomyelitis or Chronic Recurrent Multifocal Osteomyelitis.

Bristol criteria for the diagnosis of CNO/CRMO[46]

Both are mandatory:

- The presence of typical clinical findings (bone pain +/- localized swelling without significant local or systemic features of inflammation or infection),
- The presence of typical radiological findings (plain X-ray: *showing combination of lytic areas, sclerosis* and *new bone formation* or preferably STIR MRI: *showing bone marrow oedema +/- bone expansion, lytic areas* and *periosteal reaction*).

One of two is mandatory:

- More than one bone (or clavicle alone) without significantly raised CRP (CRP < 30 g/l),
- If unifocal disease (other than clavicle), or CRP > 30 g/l, with bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis or sclerosis) with no bacterial growth whilst not on antibiotic therapy.

CNO, chronic non-bacterial osteomyelitis; CRMO, chronic recurrent multifocal osteomyelitis; STIR, short tau inversion recovery, MRI, magnetic resonance imaging; CRP, C-reactive protein.

TABLE 2. Diagnostic Criteria for SAPHO Syndrome.

Diagnostic criteria presented by Kahn and Khan[58]	**Diagnostic criteria modified by Kahn and Khan[58]**	**Diagnostic criteria presented by Benhamou et al.[60,61]**
The presence of any of the following three clinical pictures is sufficient for the diagnosis: 1. Chronic recurrent multifocal osteomyelitis (usually sterile, may have spinal involvement, may or may not have skin manifestations), 2. Acute, subacute or chronic arthritis with palmoplantar pustulosis, pustular psoriasis or severe acne, 3. Palmoplantar pustulosis, pustular psoriasis, psoriasis vulgaris or any sterile (or with the presence of *Propionobacterium acnes*) osteitis with severe acne (a single localization is sufficient, including spondylodiscitis).	Absence of exclusion criteria and the presence of one of the following five clinical conditions are sufficient for diagnosis: 1. Bone/joint involvement with palmoplantar pustulosis and psoriasis vulgaris, 2. Bone/joint involvement with severe acne, 3. Isolated sterile (except *Propionobacterium acnes*) hyperostosis/osteitis (adults), 4. Chronic recurrent multifocal osteomyelitis (children), 5. Bone/joint involvement with chronic bowel diseases. **Exclusion criteria:** - Infectious osteitis, - Bone tumors, - Non-inflammatory dense lesions of bone.	Absence of exclusion criteria and the presence of one of the following four clinical conditions are sufficient for diagnosis: 1. Osteoarticular manifestations with severe acne, 2. Osteoarticular manifestations with palmoplantar pustulosis, 3. Hyperostosis (with or without dermatosis), 4. Chronic recurrent multifocal osteomyelitis involving axial or peripheral skeleton (with or without dermatosis). **Exclusion criteria:** - Septic osteomyelitis, - Infectious chest wall arthritis, - Infectious palmoplantar pustulosis, - Palmoplantar keratoderma, - Diffuse idiopathic skeletal hyperostosis, - Osteoarticular manifestations of retinoid therapy.

SAPHO, synovitis, acne, hyperostosis, pustulosis, osteitis.

Although the precise pathogenesis remains unclear, certain microbial infections, including those caused by *Propionibacterium acnes*, *Mycoplasma*, and *Staphylococcus* species, have been implicated as potential triggers of inflammation.[47-49] Impaired activation of mitogen-activated protein kinases, extracellular signal-regulated kinase (ERK) 1, and ERK2 in monocytes is a key mechanism underlying the dysregulated production of cytokines. This reduced activation is associated with attenuated phosphorylation and nuclear translocation of the transcription factor specificity protein-1 (Sp-1).[50] Consequently, Sp-1 recruitment to the promoter regions of IL-10 and IL-19 is diminished, suppressing their transcription.[50,51] ERK1/2-mediated phosphorylation of histone H3 at serine 10 (H3S10), an essential epigenetic modification that facilitates chromatin accessibility, is also impaired in non-syndromic CNO.[51,52]

Disruptions in transcriptional regulation are accompanied by altered DNA methylation patterns. Increased DNA methylation at the IL-19 promoter region and reduced methylation at the IL-20 promoter region further contribute to the imbalance in cytokine expression.[24,50,51,53,54] This imbalance promotes enhanced activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and RANK/RANKL signaling.[24,27,28]

CNO primarily manifests as nocturnal bone pain. Patients may not experience tenderness, swelling, warmth, or fever. The condition typically affects the metaphyseal regions of long bones, with varying patterns of involvement that can be either multifocal or unifocal and symmetric or asymmetric. Although CNO lesions can develop in any bone, they are most frequently observed in the clavicle, vertebrae, and pelvis. CNO may also present with non-osseous manifestations, including articular complications (such as oligoarthritis, polyarthritis, or spondyloarthritis), dermatological manifestations (such as psoriasis, pustular rashes, or severe acne), and gastrointestinal complications (such as inflammatory bowel disease).[14,19,46] A seven-year-old male patient with CNO presented to our department with right arm and right clavicular involvement (Figure 3a-c). Another patient, a sixteen-year-old female with CNO, presented with bilateral clavicular involvement, with predominant involvement of the right clavicle (Figure 3d, e).

Non-steroidal antiinflammatory drugs (NSAID) are considered the preferred first-line treatment for patients with CNO without spinal lesions. In patients in whom remission cannot be achieved with NSAIDs or in patients with spinal lesions, steroids, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine, and biologic agents (e.g., anti-TNF agents) are often required. Bisphosphonates (e.g., pamidronate and zoledronic acid) are promising treatment options that facilitate the control of osteoclast activity via the suppression of proinflammatory cytokine expression. Anti-IL-1 and anti-IL-6 agents, which play critical roles in the final stage of the inflammatory pathway, are less effective than other therapeutic approaches.

Although there is no consensus on the duration of treatments, the chronic nature of the condition typically necessitates continuing therapy for 6-12 months after clinical and radiological signs of improvement are observed.[44,55-57]

SAPHO syndrome

Although SAPHO syndrome has been documented in some children, it predominantly affects adults, particularly females aged 30-50 years. The prevalence of SAPHO syndrome remains undetermined. However, it is hypothesized to be significantly more common than reported due to misdiagnosis, misclassification, limited awareness of the condition, and challenges in differential diagnosis.[15] The criteria for the diagnosis of SAPHO syndrome are listed in Table 2.[58-61]

Due to clinical similarities, SAPHO is considered the "late stage" or adult form of CNO. Furthermore, although autoinflammation due to innate immune system disorders is predominant in both conditions, skin and nail changes are more frequently seen in SAPHO syndrome. These changes develop over time due to the activation of acquired immune mechanisms and pathological activation of effector T-lymphocytes.[35,62] However, there may not be a genetic link between SAPHO syndrome and CNO. Mutations in the *FBLIM1* gene, which is thought to be linked to CNO susceptibility, have not been associated with the occurrence of SAPHO syndrome.[63]

Although the pathogenesis of SAPHO syndrome is not yet fully understood, infectious, genetic, immunological, and environmental factors are thought to play a role in its development. HLA-B27 positivity has been found in up to 30% of patients with SAPHO syndrome. Furthermore, there is a relationship between the copy numbers of some variations in *ADAM5*, *CSF2RA*, *MEGF6*, and *NOD2* and susceptibility to SAPHO syndrome. Immunoglobulin G4 levels are elevated in approximately one-fourth of the patients with SAPHO syndrome, and it is correlated with disease activity. Furthermore, the levels of TNF-α, which plays a role in the development of osteitis, and those of IL-6 and IL-23 are frequently elevated in patients with SAPHO syndrome, especially during the active periods of the disease.[30]

SAPHO syndrome primarily affects the bones, joints, and skin. However, not all patients may exhibit all clinical manifestations, and the severity and frequency of symptoms may vary. Some individuals may present with mild symptoms, whereas others may experience a more severe disease course. Symptoms may manifest in a single or multiple anatomical regions, and they may occur continuously or episodically, with periods of exacerbation and remission.[64]

Bone and joint manifestations, such as osteitis, hyperostosis, and synovitis, are the primary clinical features of SAPHO syndrome that manifest in all patients regardless of skin involvement.[65] Common manifestations of SAPHO syndrome include inflammation of the anterior chest wall, mandible, long bones, and pelvic bones, spondylitis, sacroiliitis, peripheral joint arthritis, and enthesitis.[66,67] Anterior wall involvement, seen in about 65-90% of patients, characteristically affects the sternocostal, sternoclavicular, and osteoclavicular joints.[30,68]

Skin lesions, seen in 60-90% of patients, can manifest before, during, or after the development of bone and joint symptoms. Skin lesions are generally more severe and resistant to treatment than bone and joint symptoms, and they may flare independently.[66,69] The most

common skin manifestations are psoriasis and cystic acne, whereas palmoplantar pustulosis, Sneddon-Wilkinson syndrome, Sweet's syndrome, and pyoderma gangrenosum are rare.[68] A sixteen-year-old male patient with SAPHO syndrome presented to us with predominantly cystic acne (Figure 3f).

Extraosseous manifestations such as inflammatory bowel disease and palmoplantar pustulosis are more common and tubular bone metaphyseal involvement is rarer in SAPHO syndrome than in non-syndromic CNO.[70] In SAPHO syndrome, venous thrombosis, osteoporosis, hypertrophic pachymeningitis, pulmonary involvement, and secondary malignancies may be seen in addition to bone, joint, and skin findings.[71] Systemic findings of fever, although rare, have been reported in childhood.[72]

Despite the lack of an optimal treatment regimen, NSAIDs, corticosteroids, bisphosphonates, and DMARDs such as methotrexate, sulfasalazine, leflunomide, azathioprine, and cyclosporine are used.[11] TNF-α blockers such as etanercept, infliximab, and adalimumab have demonstrated significant clinical improvement in 90% of the patients. Furthermore, the IL-17 antagonist secukinumab, IL-12/23 inhibitor ustekinumab, and JAK inhibitors have proven beneficial in the treatment of SAPHO syndrome. Anti-IL-1 agents such as anakinra and canakinumab exhibit more limited effects on skin manifestations than on bone manifestations.[64]

DIRA syndrome

DIRA syndrome is a rare monogenic autoinflammatory disorder that develops due to loss-of-function mutations in the *IL1RN* gene. DIRA syndrome is characterized by systemic inflammation, pustular rash, sterile osteomyelitis, oral mucosal alterations, and elevated levels of acute phase reactants due to the unregulated release of IL-1*a* and IL-1*b*, particularly during the neonatal period.[8]

The skin manifestations of DIRA syndrome can range from occasional pustular lesions to severe widespread pustular dermatosis that resembles ichthyosis. In the advanced stages of the disease, nail disorders such as onychomadesis may develop. Skin biopsies typically reveal corneal pustules, acanthosis, and hyperkeratosis.

Bone involvement often presents as sterile osteomyelitis, which is characterized by enlarged ribs and clavicles or multiple lytic lesions in long bones. Fever patterns vary in DIRA syndrome, with some patients experiencing prolonged high temperatures, while others remain afebrile. Less common complications of the syndrome include interstitial pulmonary disease, atlantoaxial subluxation, positive pathergy test results, enlarged liver and spleen, eye inflammation, respiratory distress, portal vein thrombosis, and vasculitis in the central nervous system.[73,74] Systemic inflammatory response syndrome or interstitial lung disease may be associated with mortality.[3]

Although the symptoms of DIRA syndrome typically manifest in the neonatal period, they have been detected during the intrauterine period or in school-going children.[74,75] Anakinra, kanakinumab, and rilonacept have been found to be highly effective in the treatment of the disease.[14] However, a significant clinical benefit has also been reported with anti-TNF agents such as adalimumab or etanercept.[74]

Majeed syndrome

Majeed syndrome is an extremely rare autosomal recessive AID caused by a loss-of-function mutation in the *LPIN2* gene, which encodes phosphatidic acid phosphatase. This enzyme catalyzes the conversion of phosphatidic acid to diacylglycerol, which is a critical step in lipid metabolism. Lipin-2 is one of the lipin family proteins (lipin-1, lipin-2, and lipin-3) that play a central role in lipid metabolism. Lipin-2 plays a significant role in the activation of the NLRP3 inflammasome and the regulation of IL-1 production in macrophages via various mechanisms. Consequently, Majeed syndrome is characterized by an uncontrolled IL-1 response.[33,76]

In the majority of patients, symptoms manifest within the first 2 years of life. In addition, to the typical CNO findings, Majeed syndrome is characterized by the presence of congenital dyserythropoietic anemia and inflammatory cutaneous manifestations such as neutrophilic dermatosis or Sweet syndrome. Furthermore, growth retardation and splenomegaly or a paravertebral mass secondary to congenital dyserythropoietic anemia may be observed. Periodic fever may be present in some patients, and the levels of acute phase reactants are typically elevated during these episodes.[7] These patients may also experience neonatal jaundice and neutropenia.[77,78] Furthermore, proinflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α are known to be increased in patients with Majeed syndrome. MRI is the gold standard imaging method for identifying lesions related to bone inflammation.[79] An 8-year-old male patient who presented to us with leg pain was diagnosed with Majeed syndrome after an MRI of the lower extremity was obtained (Figure 3g).

Various medications, including NSAIDs, corticosteroids, bisphosphonates, anti-TNF agents, and anti-IL-1 medications, have been effective in the treatment of Majeed syndrome. For patients who are refractive to standard treatments, bone marrow transplantation and gene therapies may be considered as alternative options.[8]

PAPA syndrome

PAPA syndrome is a rare autosomal dominant inherited disorder that develops due to a mutation in the proline-serine-threonine phosphatase interacting protein 1 (*PSTPIP1*) gene.[9] This mutation results in excessive phosphorylation of the encoded protein, which enhances its capacity to bind to pyrin. This interaction subsequently leads to the aberrant regulation of IL-1β production.[70]

Recurrent and sterile inflammation of the joints, bones, and skin constitutes the hallmark of PAPA syndrome. Severe cystic acne, pyoderma gangrenosum, psoriasis, and pathergy positivity are the most common skin findings of the condition.[73,80] Although no standardized treatment protocol exists for PAPA syndrome, NSAIDs, corticosteroids, anti-TNF agents, and anti-IL-1 medications are efficacious, particularly for the management of arthritis and osteomyelitis.[8]

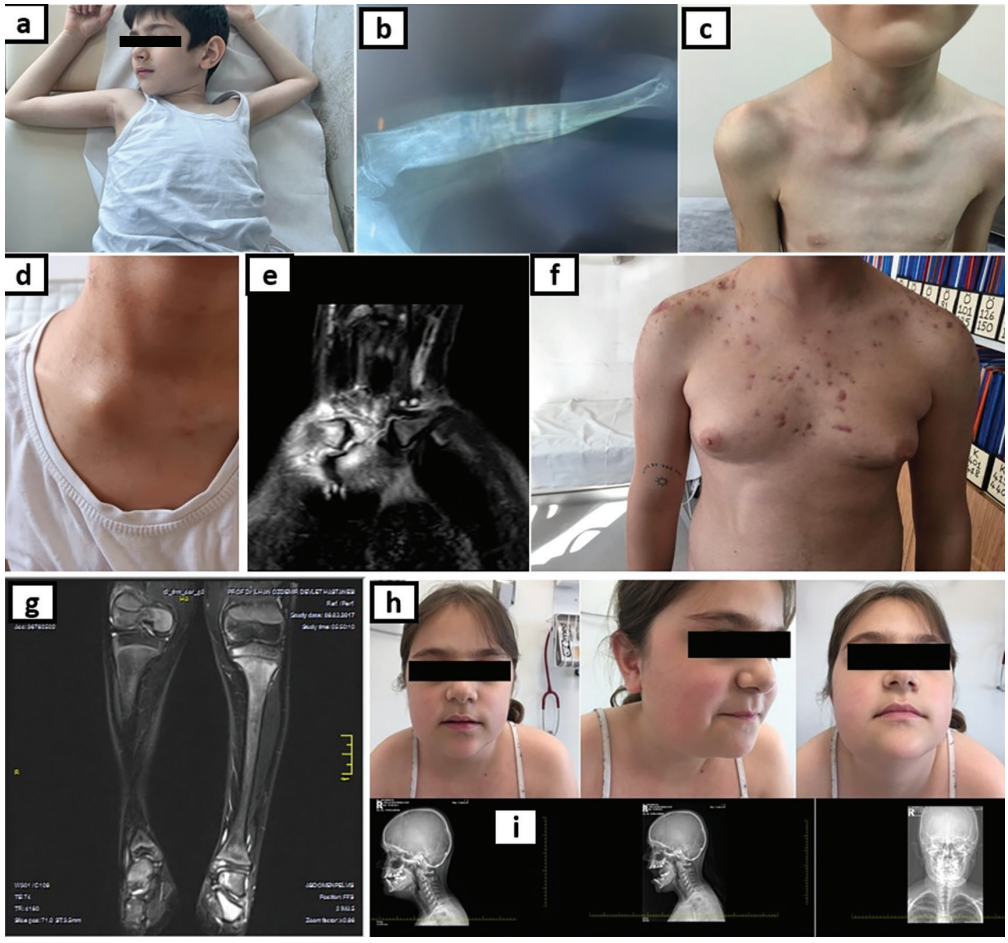

FIG. 3. Clinical and screening findings of our patients with autoinflammatory bone diseases.

Cherubism

Cherubism is a benign self-limiting condition that affects osseous and fibrous tissues, and it is characterized by symmetrical enlargement of the mandible and maxilla. The distinctive feature of cherubism is the bilateral swelling of the lower facial region, which imparts an appearance reminiscent of cherubs depicted in the Renaissance artwork. This disorder is one of the few genetically influenced conditions that results in osteoclastic lesions. Typically, cherubism manifests in pediatric patients aged 2-7 years, with a tendency toward stabilization or regression following puberty. The condition exhibits a male predominance, with a male-to-female ratio of 2:1.[81]

Cherubism may be inherited in an autosomal dominant manner or as a consequence of de novo mutations, resulting in enhanced cellular responses and the formation of hyperactive osteoclasts (giant cells) and TNF-α-producing macrophages. Giant cell granulomas may be observed on histological examination of lesions in patients with cherubism.[31,82] Studies in cherubism-induced mouse models have revealed that TNF-α plays a crucial role in disease progression. Consequently, suppressing TNF-α could inhibit the formation of bone abnormalities that are typically associated with cherubism.[31,32]

Cherubism exhibits unstable progression during growth. Clinical manifestations of cherubism may regress over time or may result in facial deformities and dental malocclusion.[12] Furthermore, in severe cases, upper airway obstruction and even visual disturbances may occur as a consequence of compression.[83,84] Radiological imaging typically reveals soap bubble-like cystic lesions in the affected areas. Cherubism is finally diagnosed on the basis of clinical and radiological findings, histological examination findings, and genetic testing results.[12] A patient presented to us with swelling in both mandibles, more prominently on the right side than on the left side, at the age of 7 years (Figure 3h). She was subsequently diagnosed with cherubism at the age of 9 years (Figure 3i).

Medical treatment of cherubism encompasses immunosuppressive agents, particularly anti-TNF medications and calcitonin. However, their efficacy is limited.[85] In severe cases, corrective surgical intervention may be necessary during the developmental period to achieve satisfactory facial esthetics and function. Nevertheless,

corrective surgery may precipitate adverse reactions such as the rapid regrowth of lesions.[12]

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