

Skeletal and Joint Manifestations of Primary Immunodeficiency Diseases

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Abstract

Primary Immunodeficiencies (PIDs) occur due to inherited disorders in the innate or adaptive immune systems, or combinations of disorders in both. The underlying disorder may be attributed to decreased levels, decreased function, or complete nonfunction of immune components. There are 200 different PIDs and more than 270 genes have been described that are associated with or cause PIDs. These PIDs have recently been re-classified into nine different categories using the International Union of Immunological Societies (IUIS) classification of Primary Immunodeficiencies. This review highlights the different manifestations, including infectious as well as noninfectious etiologies that may occur in the skeletal system of patients with primary Immunodeficiencies.

Keywords: Primary immunodeficiency; Arthritis; Osteopenia; Osteomyelitis; Bone findings; Skeletal findings; Bone anomalies; Joint findings

Introduction

Primary Immune deficiencies (PIDs) are inherited disorders that qualitatively or quantitatively affect components of the innate and adaptive immune systems. The pulmonary [1], dermatological [2], gastrointestinal [3], rheumatological [4], autoimmune [5], and hematological/oncological [6,7] manifestations of PIDs have been reviewed. However, skeletal manifestations of PIDs have not been reviewed. There are 200 different PIDs and more than 270 genes have been described that are associated with or cause PIDs. Registry data has been used in epidemiological studies to gauge PID prevalence: 5.38/100,000 in France, 5.6/100,000 in Australia, USA 86.3/100,000 inhabitants [8]. Bousfiha and colleagues [9] calculated the number of PID cases based on the prevalence estimates which ranges from 390,546 using the Australian model, 6 million using the USA model while PID registries and Jeffrey Modell Centers list 27,243-60,000 cases. These PIDs have recently been re-classified into nine different categories. PID treatment ranges from immunoglobulin replacement therapy to hematopoietic stem cell transplant [10]. We present a comprehensive review of skeletal and joint manifestations in PIDs according to the most recent classifications.

Methods

The information offered in this article is based upon PubMed (Medline) and Scopus search engines for the search terms of each individual disease state and one of the following: arthritis, skeletal, musculoskeletal, osteoporosis, osteopenia, or osteomyelitis. The inclusion criteria included Humans and English as the language.

Results

Skeletal and joint abnormalities in nine different categories are shown in the Tables 1-9. Skeletal abnormalities are discussed in detail.

Discussion

Patients with certain types of primary immunodeficiencies display a number of musculoskeletal changes. In patients with primary immunodeficiencies, septic arthritis due to pyogenic bacteria or mycoplasmal arthritis is the most common osteoarticular manifestation. In certain PIDs, chronic, non-infectious arthritis resembling rheumatoid arthritis may occur. In this paper we have extensively reviewed musculoskeletal and osteoarticular changes in PIDs and presented them under most recent IUIS primary immunodeficiency classification.

In SCID, a number of patients developing osteomyelitis following BCG vaccination have been reported [11]. A T-B+NK+ SCID patient developed *Mycobacteria marinum* arthritis and osteomyelitis [12]. Reticular dysgenesis is associated with bone anomalies of square shaped scapular tips and cupped costochondral junctions [13]. Characteristic skeletal changes of anterior rib junction, metaphyseal changes, and scapular squaring have been reported in SCID due to adenosine deaminase deficiency [14,15]. Chronic adenoviral arthritis and microcephaly have been reported in Cernunnos deficiency [16].

In Wiskott- Aldrich syndrome, 29% of patients have aseptic arthritis [17-20]. Ataxia Telangiectasia has been associated with rickets where all three members of a family had rickets [21]. Ataxia Telangiectasia-like syndrome has been associated with microcephaly in 40% of patients [22]. Nijmegen-Breakage syndrome (a rare DNA repair disorder characterized by microcephaly, immunodeficiency, and predisposition to

Diseases	Bone/Joint Findings	Reference #
T-B+ SCID	Osteomyelitis	[11]
T-B- SCID		
a. RAG2 deficiency	Osteomyelitis	[159]
b. Reticular Dysgenesis AK2 deficiency	Bone anomalies: - scapular tip squaring - costochondral junction cupping	[13]
c. Cernunnos Deficiency	Septic Arthritis	[16]
d. DNA Ligase IV deficiency	Bone anomalies: - Microcephaly - Severe growth failure	[160,161]
e. Adenosine Deaminase Deficiency	Bone anomalies: - Chondro-osseus dysplasia	[14-15]
f. MHC Class I deficiency	Osteomyelitis	[162]
g. MHC Class II deficiency	Bone Anomalies: - Dolichocephaly - low implanted thumb	[163]

Diseases	Bone/Joint Findings	Reference #
Congenital Thrombocytopenia		
a. Wiskott-Aldrich Syndrome	Aseptic Arthritis Arthralgia	[17-20]
DNA Repair Defects		
a. Ataxia-Telangiectasia	Aseptic Arthritis Rickets	[21]
b. Ataxia- Telangiectasia Like Disease	Microcephaly	[22]
c. Nijmegen Breakage Syndrome	Bone anomalies: - hip dysplasia - rib dysplasia - sacral genesis - clinodactyly - polydactyly - microcephaly - scoliosis - absent thumbs - Juvenile Idiopathic Arthritis	[23-26]
d. Bloom Syndrome	Bone anomalies: - dolichocephaly - short stature	[27]
e. Immunodeficiency with centromeric Instability And Facial Anomalies (ICF)	Bone anomalies: - syndactyly - Juvenile Idiopathic Arthritis	[28-30]
f. MCM4 deficiency	Short Stature	[164]
Thymic Defects with additional congenital anomalies		
a. DiGeorge Syndrome	Bone Anomalies Juvenile Idiopathic Arthritis	[31,32]
Immune-Osseus Dysplasias:		
a. Cartilage Hair Hypoplasia	Aseptic Arthritis Bone anomalies: - Metaphyseal chondrodysplasia - genu varum - metaphyseal flaring - brachydactyly - macrocephaly - lordosis	[33,34]

b.	Schimke Syndrome	Aseptic Arthritis Bone anomalies: - epiphyseal dysplasia - metaphyseal dysplasia - platyspondyly - vertebral anomalies - lordosis	[35,36]
Hyper IgE Syndrome			
a.	AD-HIES (Job's Syndrome)	Bone anomalies: - scoliosis - recurrent fractures - Septic Arthritis - Osteomyelitis	[37,39,40-46]
b.	DOCK8 deficiency	Lupus Arthritis Scoliosis Fractures	[47,48]
Dyskeratosis Congenital (DKC)			
a.	XL-DKC	Bone anomalies: - phalangeal absorption - fractures - avascular necrosis	[49,158]
b.	AR-DKC due to RTEL deficiency	Microcephaly	[50]
c.	AD-DKC due to TERT deficiency	Bone anomaly Scoliosis Osteoporosis	[51]
Comel - Netherton Syndrome		Bone anomalies: - epiphyseal osteosclerosis - rickets	[52,53]
ORA-I Deficiency		Bone anomaly: club foot	[54]
STAT 5b deficiency		Juvenile Idiopathic Arthritis	[87]
Hepatic Veno-Occlusive Disease with immunodeficiency (VODI)		Microcephaly	[55]
FILS Syndrome		Bone Anomaly: macrocephaly	[56]

Table 3: Predominantly Antibody Deficiency.

Diseases	Bone/Joint Findings	Reference #
BTK Deficiency	Aseptic Arthritis Septic Arthritis Aseptic Osteomyelitis Septic Osteomyelitis	[57-61]
μ heavy chain deficiency	Aseptic Arthritis	[62,165]
λ5 deficiency	Aseptic Arthritis	[63]
Thymoma with immunodeficiency (Good Syndrome)	Aseptic Arthritis Septic Arthritis	[64,65]
Common Variable Immunodeficiency	Septic Arthritis Rheumatoid Arthritis Septic Osteomyelitis	[66-70,166]
ICOS deficiency	Rheumatoid Arthritis	[71,72]
TWEAK Deficiency	Osteomyelitis	[73]
Warts, Hypogammaglobulinemia, infection, Myelokathexis Syndrome (WHIM)	Osteomyelitis	[74]
CD40L deficiency	Osteomyelitis, Unspecified	[75]
AID Deficiency	Aseptic Arthritis	[76,77]
Isolated IgG Subclass deficiency	Septic Arthritis Osteomyelitis	[78]
IgA with IgG subclass deficiency	Rheumatoid Arthritis	[79]
PRKC δ	Bone Anomalies: -microcephaly -polysyndactyly	[80]
Selective IgA Deficiency	Juvenile Idiopathic Arthritis Rheumatoid Arthritis Osteomyelitis	[81-84]

Diseases	Bone/Joint Findings	Reference #
UNC13D/MUNC 13-4 Deficiency	Juvenile Idiopathic Arthritis	[85]
IPEX (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)	Arthritis	[86]
APCED (Autoimmune polyendocrinopathy candidiasis ectodermal dysplasia)	Short Stature Juvenile Rheumatoid Arthritis Osteopenia/Osteoporosis	[88]
ITCH Deficiency (Human <i>ITCH</i> E3 ubiquitin ligase deficiency)	Arthritis	[89]
Autoimmune Lymphoproliferative Syndrome		
a. ALPS-FAS	Osteopenia	[90]
b. ALPS-FASL (TNFR)	Arthritis/Arthralgia	[91]
Immune Dysregulation with Colitis		
a. IL-10 R α deficiency	Arthritis/Arthralgias	[92]
b. IL-10 R β deficiency	Aseptic Arthritis	[92]
Type 1 Interferonopathies		
a. TREX1 deficiency, Aicardi-Goutieres Syndrome	Bone Anomaly: hypoplastic digit(s)	[167]
b. SAMHD1 deficiency	Aseptic Arthritis Microcephaly	[93,94]
c. Spondyloenchondrodysplasia with immune dysregulation	Bone Anomalies: -metaphyseal changes -vertebral changes -platyspondyly	[95]

Diseases	Bone/Joint Findings	Reference #
1. Defects of Neutrophil Differentiation		
	Short Stature Osteopenia	
a. Glycogen storage disease 1b	Osteomyelitis	[96]
b. Cyclic Neutropenia	Osteomyelitis	[97]
Defects of Motility		
a. Leukocyte Adhesion Deficiency Type 1	Septic Osteomyelitis	[98,99]
b. Leukocyte Adhesion Deficiency Type 2	Bone Anomalies: - short limbs - overriding toes - microcephaly	[100]
c. Leukocyte adhesion deficiency Type 3	Osteomyelitis	[157]
d. Shwachman-Diamond Syndrome	Bone anomalies: - metaphyseal abnormalities - growth plate thickening - secondary ossification centers - coxa valga - stress fractures - Osteopenia	[101-103]
Defects of Respiratory Burst		
a. X-linked chronic granulomatous disease (CGD)	Septic Arthritis Osteomyelitis	[104-110,168]
b. Autosomal recessive CGD-p22 phox deficiency	Septic Osteomyelitis	[111]
c. Autosomal Recessive CGD- p47 phox deficiency	Juvenile Idiopathic Arthritis	[114]
d. Autosomal Recessive CDG p-67 phox deficiency	Septic Osteomyelitis	[112,113]
Mendelian susceptibility to mycobacterial disease (MSMD)		
a. IL12 and IL23 Receptor β 1 chain deficiency	Septic Arthritis Osteomyelitis	[115]
b. GATA2 deficiency	Arthritis	[169]

Table 6: Defects in Innate Immunity.		
Diseases	Bone/Joint Findings	Reference #
Anhidrotic Ectodermal Dysplasia with immunodeficiency		
a. EDA-ID, X Linked	Septic Arthritis Septic Osteomyelitis	[116,117]
b. EDA-ID, Autosomal Dominant	Septic Arthritis Septic Osteomyelitis	[116]
TIR signaling pathway defect		
a. IRAK4 deficiency	Septic Arthritis Septic Osteomyelitis	[118]
b. Myd88 deficiency	Septic Arthritis Septic Osteomyelitis	[119]
Predisposition to fungal diseases		
a. CARD 9 Deficiency	Osteomyelitis	[119,120]

Table 7: Autoinflammatory Diseases.		
Diseases	Bone/Joint Findings	Reference #
Defects affecting the inflammasome		
a. Familial Mediterranean Fever	Aseptic Arthritis Rheumatoid Arthritis Juvenile Idiopathic Arthritis Aseptic Osteonecrosis Osteoporosis	[121-125]
b. Hyper IgD Syndrome	Aseptic Arthritis	[126]
c. Muckle-Wells Syndrome	Aseptic Arthritis	[127,128]
d. Familial Cold Autoinflammatory Syndrome	Arthralgias	[129]
e. Neonatal Onset Multisystem inflammatory disease (NOMID)	Aseptic Arthritis Bone anomalies: - Hyperostosis - Contractures	[130]
Non-inflammasome related conditions		
a. TNFR associated periodic fevers	Arthralgia/Arthritis	[131]
b. Pyogenic sterile arthritis Pyoderma gangrenosum Acne Syndrome	Aseptic Arthritis Aseptic Osteomyelitis Fractures	[132]
c. Blau Syndrome	Aseptic Arthritis	[133]
d. Chronic Recurrent Multifocal Osteomyelitis and congenital dyserythropoietic anemia	Aseptic Osteomyelitis Septic Osteomyelitis	[134]
1. DIRA (deficiency of the Interleukin 1 antagonist)	Bone anomalies: -widened bones -bone ossification	[135,136]
2. Cherubism	Bone anomaly: -jaw resorption Aseptic Osteomyelitis	[137]
3. CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy)	Bone anomalies: -microcephaly -contractures	[138]
4. PLAID (PLCγ2 associated antibody deficiency and immune dysregulation)	Aseptic Arthritis	[170]

Table 8: Complement Deficiencies.		
Diseases	Bone/Joint Findings	Reference#
C1q deficiency	Lupus Arthritis	[139,140]
C1s deficiency	Lupus Arthritis	[141]
C4 deficiency	Lupus Arthritis	[141]

C2 deficiency	Juvenile Idiopathic Arthritis Lupus Arthritis Osteoporosis Septic Arthritis Septic Osteomyelitis	[142-145]
C3 deficiency	Lupus Arthritis Osteomyelitis	[140,142]
C5 deficiency	Lupus Arthritis Septic Arthritis	[146,147]
C6 deficiency	Aseptic Arthritis Septic Arthritis	[148,149]
C7 deficiency	Rheumatoid Arthritis Ankylosing Spondylitis Septic Arthritis	[150,151]
C9 deficiency	Ankylosing Spondylitis	[152]
C1 inhibitor deficiency	Aseptic Arthritis Lupus Arthritis Rheumatoid Arthritis	[153]
Properdin deficiency	Septic Arthritis Septic Osteomyelitis	[154]
Factor I deficiency	Juvenile Idiopathic Arthritis Septic Arthritis	[171]

Table 9: Phenocopies of PID Associated with Somatic Mutations.

Diseases	Bone/Joint Findings	Reference #
a. Autoimmune lymphoproliferative Syndrome (ALPS-FAS_	Aseptic Arthritis	[155,156]

malignant lymphomas) is associated with Juvenile Idiopathic Arthritis (JIA)-like clinodactyly, syndactyly, and hip dysplasia [23-26]. In Bloom Syndrome, two patients with dolichocephaly have been reported [27]. In Immunodeficiency with centromeric instability and facial anomalies syndrome, 20% of patients present with juvenile idiopathic arthritis, 12% with dolichocephaly, 6% each had microcephaly or macrocephaly, 7% had cleft palate, and 5% had syndactyly [28-30]. DiGeorge syndrome is associated with juvenile idiopathic arthritis, and 20% with cleft palate and vertebral anomalies [31,32]. A cartilage hair hypoplasia patient was found to have aseptic arthritis [33], while another patient was found to have brachydactyly and femoral bone widening [34]. Aseptic arthritis, platyspondyly, phalangeal anomaly, and clinodactyly have been observed in Schimke syndrome [35,36]. Autosomal dominant Hyper IgE Syndrome, which is caused by mutation of STAT-3, is associated with increased frequency of fractures, 66% hyperextensibility (66%), scoliosis (63%), osteopenia (40%), osteoporosis (20%), aseptic arthritis (8%), and septic arthritis (17%) [37-43]. Osteogenesis imperfecta as well as craniosynostosis has also been reported [44-46]. Autosomal recessive Hyper-IgE Syndrome, which is caused by DOCK8 mutations, presented with

Systemic Lupus Erythematosus (SLE) with purpuric and necrotic skin lesions diffuse arthritis, and glomerulonephritis [47]. Scoliosis and fractures have been reported in some cases [48]. In autosomal recessive Dyskeratosis Congenita (DKC) due to RTEL (regulation of telomere elongation helicase 1) deficiency, one patient had avascular necrosis [49]. In autosomal recessive DKC,

a syndrome characterized by immunodeficiency, bone marrow failure, somatic abnormalities, and cancer predisposition resulting from defective telomere, 80% have microcephaly [50]. In autosomal dominant DKC due to Telomerase Reverse Transcriptase (TERT) deficiency, 26% have osteoporosis/osteopenia and 3% scoliosis [51]. In Comel-Netherton syndrome, two out of three patients were found to have rickets in addition to the ichthyoses, hair shaft defect, and atopy found in patients that have the disease [52,53]. Oral calcium release activated calcium modulator (ORAI-1) deficiency known for autoimmunity, ectodermic dysplasia, and myopathy also had a case report of skeletal findings of clubfoot and defect of posterior arch closing in a patient [54]. Hepatic veno-occlusive disease with immunodeficiency, 33% of patients had microcephaly [55]. In facial dysmorphism, immunodeficiency, live do and short stature (FILS) syndrome, patients have facial dysmorphisms, immunodeficiency, live do and short stature with 9% of patients having macrocephaly [56]. Table 2 has highlighted the specific disease manifestations with the bone findings specific to each disease.

In X-linked Agammaglobulinemia (XLA), a primary immunodeficiency disease caused by mutations in the Bruton's Tyrosine Kinase (BTK) gene, arthritis and osteomyelitis occurs with different frequency; aseptic arthritis (11%), juvenile idiopathic arthritis (17%), septic arthritis (8%), and nonspecific osteomyelitis (3%) [57-60]. Zhu and associates described a patient with XLA and Juvenile Idiopathic Arthritis (JIA) who later developed invasive *Klebsiella pneumonia* polyarticular septic

arthritis [61]. Authors suggested that XLA combined with JIA may contribute to invasive *K. pneumoniae* infection. A single case of aseptic arthritis has been reported with μ heavy chain deficiency and $\lambda 5$ deficiency [62,63]. Thymoma with immunodeficiency (Good syndrome) has a 2% risk of septic arthritis (*Mycoplasma* as implicated species) and one case report of rheumatoid-like arthritis has been reported [64,65]. In a cohort of 243 patients with Common Variable Immunodeficiency (CVID), 2% had rheumatoid arthritis, 1.6% juvenile idiopathic arthritis, 0.8% septic arthritis (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*), 0.8% septic osteomyelitis [66-70]. Rheumatoid arthritis has been reported in patients with ICOS (inducible costimulator) deficiency [70-72]. TWEAK (TNF-like weak inducer of apoptosis) deficiency has 33% osteomyelitis (unknown if septic or chronic) [73]. In Warts, Hypogammaglobulinemia, Infections and Myelokathexis Syndrome (WHIM), 10% of patients had osteomyelitis [74]. In CD40 ligand deficiency, 1% had osteomyelitis while 11% had aseptic arthritis [75]. Activation-Induced Cytidine Deaminase (AID) deficiency had 7% aseptic arthritis [76,77]. In Isolated IgG subclass deficiency, 27% had septic osteomyelitis with or without septic arthritis with the organisms being staphylococcal species or streptococcal species [78]. In IgA with IgG subclass deficiency, 6% had rheumatoid arthritis [79]. In PRKC δ (protein kinase c delta) deficiency, there exists a case report with a patient that had microcephaly and polysyndactyly [80]. In Selective IgA deficiency, 2% had rheumatoid arthritis, 0.7% had juvenile idiopathic arthritis, with case reports of ankylosing spondylitis, another of aseptic arthritis, and finally one other with osteomyelitis due to *Mycoplasma* species [81-84]. Table 3 includes predominantly antibody deficiency syndromes with their respective bone/ joint findings.

In familial hemophagocytic lymphohistiocytosis type 3 due to mutations in UNC13D deficiency; one patient had juvenile idiopathic arthritis [85]. In Immune Dysregulation, Polyendocrinopathy, Enteropathy Xlinked (IPEX), 33% of patients had aseptic arthritis [86]. In STAT5b deficiency, patients present with dwarfism, eczema, lymphocytic pneumonitis with 10% of patients having juvenile idiopathic arthritis [87]. In Autoimmune Polyendocrinopathy with Candidiasis and Ectodermal Dystrophy (APCED), there exists a case report of a patient that had juvenile idiopathic arthritis [88]. In ITCH deficiency, mutations in an E3 ubiquitin ligase called *ITCH*, patients may have chronic lung disease, autoimmune disease as well as dysmorphic facial features; 90% of patients had macrocephaly while all patients in the case report of 10 had dolichocephaly [89]. In Autoimmune Lymphoproliferative Syndrome (ALPS) due to FAS mutation, 33% of patients developed aseptic arthritis, whereas in ALPS due to FASL mutation rarely osteopenia has been reported [90,91]. IL-10R α and IL-10R β deficiency are associated with aseptic arthritis [92]. In Aicardi-Goutieres Syndrome Type 5 due to *SAMHD1* mutations, patients present with encephalopathy, cerebral atrophy, vasculitis as well as aseptic arthritis, microcephaly, osteopenia, and sporadic reports of aseptic arthritis and scoliosis [93,94]. In case reports of Spondyloenchondrodysplasia with Immune Dysregulation (SPENCD), two patients had vertebral changes and platyspondyly [95]. The bone and joint findings

above have also been listed for each disease in Table 4 or Table 9.

In Glycogen storage disease 1b, 32% had osteopenia, and 12% had short stature [96]. In cyclic neutropenia, there is a report of a patient with unspecified osteomyelitis [97]. Osseous and joint changes are rare in leukocyte adhesion defect 1 (LAD-1) and LAD-2, while osteomyelitis is frequently (33%) observed in LAD-3 [98-100]. In Shwachman-Diamond Syndrome, 64% of patients had osteoporosis, 55% fractures, and 36% with osteopenia [101-103]. X-linked Chronic Granulomatous Disease (CGD) is associated with osteomyelitis with a variety of organisms, including *Cladophialophora arxii*, *Aspergillus nidulans*, *Edwardsiella tarda*, *Serratia marcescens*, *Burkholderia gladioli*, *Chrysosporium zonatum*, *Paecilomyces Variotii*, *Pseudoallescheria boydii*, *Inonotus tropicalis*, *Penicillium piceum* [104-110]. In autosomal recessive CGD-p22 phox and CGD-p67 phox deficiency, patients with osteomyelitis due to *Aspergillus fumigatus* have been reported [111-113]. In autosomal recessive CGD-p47 phox deficiency, juvenile idiopathic arthritis has been reported [114]. In IL12 and IL23 receptor $\beta 1$ chain deficiency, there is a case report of one patient with cryptococcal arthritis as well as osteomyelitis [115]. The defects found in phagocytes with their respective bone findings have been listed in Table 5. In Ectodermal Dysplasia Agammaglobulinemia (EDA) due to mutation in NEMO, 16% of patients had arthritis and osteomyelitis [116,117], while in series of EDA due to IKK β 20% of patients had septic osteomyelitis and arthritis [116]. In IRAK4 deficiency, 29% of patients had septic arthritis while 14% had septic osteomyelitis [118]. In MyD88 deficiency, 6% had septic arthritis and 9% had osteomyelitis [119]. In CARD9 deficiency, one of five patients was found to have osteomyelitis due to Candidal species [119-120]. The bone and joint findings with the diseases have been listed in Table 6.

In familial Mediterranean fever syndrome, aseptic arthritis (2/2 patients), rheumatoid arthritis (2/2), 0.8% juvenile idiopathic arthritis, and ankylosing spondylitis (1/1) have been reported [121-125]. In Hyper IgD Syndrome, 50% have aseptic arthritis while 4% have contractures [126]. Muckle-Wells patients may have arthritis [127,128]. In familial cold autoinflammatory syndrome, 96% of patients have arthralgias [129]. A Neonatal Onset Multisystem Inflammatory Disease (NOMID) patient presented with arthritis while the majority of patients have hyperostosis (92%), patellar overgrowth (92%) and contractures (85%) [130]. TNF-Receptor Associated Periodic Syndrome (TRAPS) is associated with aseptic arthritis and arthralgias [131]. In Pyogenic Sterile Arthritis Pyoderma Gangrenosum Acne (PAPA) syndrome, all patients had aseptic arthritis while 20% had chronic osteomyelitis [132]. In Blau syndrome, 50% had aseptic arthritis while the other 50% of patients in the study had boutonniere's deformity [133]. In chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia, all patients had aseptic osteomyelitis while 12% had concomitant septic osteomyelitis [134]. In Deficiency of the Interleukin 1 Receptor Antagonist (DIRA), the skeletal anomalies include widened ribs, periosteal reaction, vertebral fusion, and proximal interphalangeal joint swelling [135,136]. In addition to the main pathophysiologic finding of fibro-osseous bone formation, craniosynostosis has been

reported in Cherubism syndrome, where a mutation in *SH3BP2* causes bone degeneration in the jaws [137]. Microcephaly and contractures have been described in Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy (CANDLE) syndrome [138]. The bone findings with autoinflammatory diseases have been summarized in table 7.

Complement deficiencies have many skeletal manifestations. C1q deficiency has been associated with lupus arthritis in 50% of cases [139,140]. There is a case report of a C1s deficiency also having lupus arthritis [141]. In C4 deficiency, 4% had lupus arthritis [141]. In C2 deficiency, septic arthritis (*Haemophilus influenzae*, *Streptococcal pneumoniae*), septic osteomyelitis (*Streptococcal pneumoniae*), osteoporosis, fractures, and lupus arthritis have been reported [142-145]. Osteomyelitis has been observed in C3 deficiency [140,142]. There are case reports of gonococcal arthritis in a patient with C5 deficiency [146,147], and septic as well as aseptic arthritis in C6 deficiency [148,149]. C7 deficiency is associated with ankylosing spondylitis and rheumatoid arthritis [150,151]. C9 deficiency has reports of ankylosing spondylitis [152]. In C1 inhibitor deficiency, 0.6% had lupus arthritis, 0.6% had rheumatoid arthritis and 0.6% had polyarthritis [153]. In Properdin deficiency, septic arthritis and osteomyelitis due to *Neisseria meningitidis* have been reported [154]. Factor I deficiency may present with juvenile idiopathic arthritis or septic arthritis [155-156]. Lastly, the bone findings in complement deficiencies have been summarized in table 8.

In summary, osteomyelitis and septic and aseptic (rheumatoid arthritis and lupus arthritis, respectively) are the most common osseous and joint manifestations in PID; however frequency of certain other osseous abnormalities may be observed with specific PID syndrome.

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Declarations

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