Skeletal and Joint Manifestations of Primary Immunodeficiency Diseases
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Received: May 23, 2016; Accepted: June 16, 2016; Published: June 24, 2016

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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 nonfiction 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 Immunodeficiencies (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 on 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, noninfectious 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...
Table 1: Severe Combined Immunodeficiencies.

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

Table 2: Well Defined Syndrome with Immunodeficiencies.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Bone/Joint Findings</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Wiskott-Aldrich Syndrome</td>
<td>Aseptic Arthritis Arthralgia</td>
<td>[17-20]</td>
</tr>
<tr>
<td>DNA Repair Defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Ataxia-Telangiectasia</td>
<td>Aseptic Arthritis Rickets</td>
<td>[21]</td>
</tr>
<tr>
<td>b. Ataxia-Telangiectasia Like Disease</td>
<td>Microcephaly</td>
<td>[22]</td>
</tr>
<tr>
<td>d. Bloom Syndrome</td>
<td>Bone anomalies: - dolichocephaly - short stature</td>
<td>[27]</td>
</tr>
<tr>
<td>e. Immunodeficiency with centromeric Instability And Facial Anomalies (ICF)</td>
<td>Bone anomalies: - syndactyly - Juvenile Idiopathic Arthritis</td>
<td>[28-30]</td>
</tr>
<tr>
<td>f. MCM4 deficiency</td>
<td>Short Stature</td>
<td>[164]</td>
</tr>
<tr>
<td>Thymic Defects with additional congenital anomalies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. DiGeorge Syndrome</td>
<td>Bone Anomalies Juvenile Idiopathic Arthritis</td>
<td>[31,32]</td>
</tr>
<tr>
<td>Immune-Osseus Dysplasias:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Cartilage Hair Hypoplasia</td>
<td>Aseptic Arthritis Bone anomalies: - Metaphyseal chondrodysplasia - genu varum - metaphyseal flaring - brachydactyly - macrocephaly - lordosis</td>
<td>[33,34]</td>
</tr>
</tbody>
</table>
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 3b 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.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Bone/Joint Findings</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK Deficiency</td>
<td>Aseptic Arthritis, Septic Arthritis, Septic Osteomyelitis</td>
<td>[57-61]</td>
</tr>
<tr>
<td>µ heavy chain deficiency</td>
<td>Aseptic Arthritis</td>
<td>[62,165]</td>
</tr>
<tr>
<td>λ5 deficiency</td>
<td>Aseptic Arthritis</td>
<td>[63]</td>
</tr>
<tr>
<td>Thymoma with immunodeficiency</td>
<td>Aseptic Arthritis, Septic Arthritis</td>
<td>[64,65]</td>
</tr>
<tr>
<td>(Good Syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Variable Immunodeficiency</td>
<td>Septic Arthritis, Rheumatoid Arthritis, Septic Osteomyelitis</td>
<td>[66-70,166]</td>
</tr>
<tr>
<td>ICOS deficiency</td>
<td>Rheumatoid Arthritis</td>
<td>[71,72]</td>
</tr>
<tr>
<td>TWEAK Deficiency</td>
<td>Osteomyelitis</td>
<td>[73]</td>
</tr>
<tr>
<td>Warts, Hypogammaglobulinemia,</td>
<td>Osteomyelitis</td>
<td>[74]</td>
</tr>
<tr>
<td>Myelokathexis Syndrome (WHIM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD40L deficiency</td>
<td>Osteomyelitis, Unspecified</td>
<td>[75]</td>
</tr>
<tr>
<td>AID Deficiency</td>
<td>Aseptic Arthritis</td>
<td>[76,77]</td>
</tr>
<tr>
<td>Isolated IgG Subclass deficiency</td>
<td>Septic Arthritis, Osteomyelitis</td>
<td>[78]</td>
</tr>
<tr>
<td>IgA with IgG subclass deficiency</td>
<td>Rheumatoid Arthritis</td>
<td>[79]</td>
</tr>
<tr>
<td>PRKC &amp;</td>
<td>Bone Anomalies: microcephaly, polysyndactyly</td>
<td>[80]</td>
</tr>
<tr>
<td>Selective IgA Deficiency</td>
<td>Juvenile Idiopathic Arthritis, Rheumatoid Arthritis, Osteomyelitis</td>
<td>[81-84]</td>
</tr>
</tbody>
</table>
### Table 4: Diseases of Immune Dysregulation.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Bone/Joint Findings</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNC13D/MUNC 13-4 Deficiency</td>
<td>Juvenile Idiopathic Arthritis</td>
<td>[85]</td>
</tr>
<tr>
<td>IPEX (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)</td>
<td>Arthritis</td>
<td>[86]</td>
</tr>
<tr>
<td>APCED (Autoimmune polyendocrinopathy candidiasis ectodermal dysplasia)</td>
<td>Short Stature Juvenile Rheumatoid Arthritis Osteopenia/Osteoporosis</td>
<td>[88]</td>
</tr>
<tr>
<td>ITCH Deficiency (Human ITCH E3 ubiquitin ligase deficiency)</td>
<td>Arthritis</td>
<td>[89]</td>
</tr>
</tbody>
</table>

**Autoimmune Lymphoproliferative Syndrome**
- a. ALPS-FAS                          Osteopenia            [90]        
- b. ALPS-FASL (TNFR)                   Arthritis/Arthralgia   [91]        

**Immune Dysregulation with Colitis**
- a. IL-10 Rα deficiency                Arthritis/Arthralgias  [92]        
- b. IL-10 Rβ 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]  

### Table 5: Congenital Defects of Phagocytes number, Function or Both.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Bone/Joint Findings</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Defects of Neutrophil Differentiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Glycogen storage disease 1b</td>
<td>Short Stature Osteopenia</td>
<td>[96]</td>
</tr>
<tr>
<td>b. Cyclic Neutropenia</td>
<td>Osteomyelitis</td>
<td>[97]</td>
</tr>
</tbody>
</table>

**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]  

**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 CGD p-67 phox deficiency | Septic Osteomyelitis | [112,113]  

Mendelian susceptibility to mycobacterial disease (MSMD)
- a. IL12 and IL23 Receptor β1 chain deficiency | Septic Arthritis Osteomyelitis | [115]  
- b. GATA2 deficiency | Arthritis | [169]
### Table 6: Defects in Innate Immunity

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Bone/Joint Findings</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhidrotic Ectodermal Dysplasia with immunodeficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. EDA-ID, X Linked</td>
<td>Septic Arthritis&lt;br&gt;Septic Osteomyelitis</td>
<td>[116,117]</td>
</tr>
<tr>
<td>b. EDA-ID, Autosomal Dominant</td>
<td>Septic Arthritis&lt;br&gt;Septic Osteomyelitis</td>
<td>[116]</td>
</tr>
<tr>
<td>TIR signaling pathway defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. IRAK4 deficiency</td>
<td>Septic Arthritis&lt;br&gt;Septic Osteomyelitis</td>
<td>[118]</td>
</tr>
<tr>
<td>b. Myd88 deficiency</td>
<td>Septic Arthritis&lt;br&gt;Septic Osteomyelitis</td>
<td>[119]</td>
</tr>
<tr>
<td>Predisposition to fungal diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. CARD 9 Deficiency</td>
<td>Osteomyelitis</td>
<td>[119,120]</td>
</tr>
</tbody>
</table>

### Table 7: Autoinflammatory Diseases

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

### Table 8: Complement Deficiencies

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Bone/Joint Findings</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1q deficiency</td>
<td>Lupus Arthritis</td>
<td>[139,140]</td>
</tr>
<tr>
<td>C1s deficiency</td>
<td>Lupus Arthritis</td>
<td>[141]</td>
</tr>
<tr>
<td>C4 deficiency</td>
<td>Lupus Arthritis</td>
<td>[141]</td>
</tr>
</tbody>
</table>
TABLE 9: Phenocopies of PID Associated with Somatic Mutations.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Bone/Joint Findings</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune lymphoproliferative syndrome (ALPS-FAS)</td>
<td>Aseptic Arthritis</td>
<td>[155,156]</td>
</tr>
</tbody>
</table>

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-I) deficiency known for autoimmunity, ectodermic dysplasia, and myopathy also had a casereport 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 (FLS) 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 HLA may contribute to invasive K. pneumoniae infection. A single case of aseptic arthritis has been reported with hyper IgM deficiency and L5 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 (CVI), 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 (unidentified 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% septic 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 PRKδ (protein kinase δ 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 X-linked (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-10Ra and IL-10Rβ 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 (SPENDC), 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 deficiency 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, Pseudolomycetes variotii, Pseudallescheria 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 β1 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 IKKβ 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 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 abnormalities 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 \textit{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 (\textit{Haemophilus influenzae}, \textit{Streptococcal pneumoniae}), septic osteomyelitis (\textit{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 \textit{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.

Acknowledgement

This study was supported by funds from the Division of Basic and Clinical Immunology. We would also like to thank Arash Gharib for assisting in editing the paper.

Declarations

Dr. Gupta is on the advisory board for Baxter and Kedron, is on the speakers bureau for Baxter, participated in clinical trials with Baxter and Octapharma, received a publication grant from CSL Behring and received a research grant from Baxter, and he is an Advisor to the speakers bureau for Baxter, participated in clinical trials with Baxter and Octapharma, received a publication grant from CSL Behring and received a research grant from Baxter, and he is an Advisor to Baxter and Octapharma.

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