Chapter 3
Pulmonary Manifestations of Predominantly Antibody Deficiencies

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3.1 Introduction

Predominantly antibody deficiencies (PADs) are the most frequent forms of primary immunodeficiency diseases (PIDs). These conditions are resulted from a primary defect in B-cells. Though to a lesser extent, they are caused by a defect in T-cells or other immune cell populations known to contribute to B-cell or plasma cell development and function. Overall, PADs are characterized by a malfunctioned antibody response which is reflected in low or undetectable levels of immunoglobulin(s). As a result, recurrent infection is the most common presentation leading to diagnosis of PADs. It would also remain the cause of most complications during the course of disease. Overall, physicians who are the most likely to encounter patients with PADs are those of infectious disease specialists [1].

Patients with chronic and recurrent respiratory infections are prone to develop severe respiratory conditions such as bronchiectasis and obliterative bronchiolitis. Therefore, patients with respiratory infections need particular attention. They should be prescribed an appropriate therapy as soon as possible and have to be adhering to

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more and longer medical therapies. Immunoglobulin substitution therapy along with prophylactic antibiotics remained the cornerstone of treatment for PADs and related complications [2]. Generally, immunoglobulin replacement therapy can effectively reduce both incidence and severity of infections [2]. However, immunoglobulin products contain only purified IgG antibodies and lack other antibody isotypes. It is thus expected that pulmonary infections may persist and even flourish under regular immunoglobulin replacement therapy. Thereby, the patient will be more predisposed to chronic lung diseases and related severe sequels such as respiratory failure [3]. Recent studies have identified a gap for screening protocols to monitor respiratory manifestations in patients with PADs [4].

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3.2 X-Linked Agammaglobulinemia (Bruton's Disease or BTK Deficiency)

Among the most severe types of PADs is X-linked agammaglobulinemia (XLA), the first PID described by Ogden Bruton in 1952. XLA is the most common monogenic immunodeficiency [5] resulting from mutations on the X chromosome in the gene encoding a tyrosine kinase, the so-called Bruton's tyrosine kinase (Btk). These mutations are of loss-of-function type, making an arrest in the early stages of B-cell development [5]. XLA is therefore a humoral immunodeficiency characterized by depletion of B-cells and low levels of all immunoglobulins (IgG, IgA, IgM, IgD, and IgE) [6]. While the number of T-cells and NK cells varies within normal range, it is however realized that lack of B-cells might lower the optimal function of T-cells, as reflected in the diminished T-cell memory to specific antigens. For example, patients with XLA show a defect in T-cell memory to *N. meningitidis* but not influenza [7]. The presentation of this antibody immunodeficiency is expected to occur (a) earlier than other types of PADs, (b) after maternal antibodies waned, and (c) during the first 2 years of life with recurrent and severe sinopulmonary infections [8–11]. However, there are reports, for example, from China, where the mean age at diagnosis was more than 6 years. Even, there have been reports of late-onset XLA (up to the fourth decade of life) [12]. Overall, the mean age at diagnosis falls within the range 3.2–7.7 years, whereas the mean age at onset of symptoms happens within the range 1.8–4.2 years [13–17, 10, 18]. This reflects the delay in diagnosis ranging from 1.4 to 3.6 years.

In conjunction with its expression on different cells such as B-cells, monocytes, macrophages, granulocytes, dendritic cells, and osteoclasts, BTK serves as a potential contributor to various intracellular functions, essentially B-cell development [19] and differentiation [20], natural killer (NK) cell activation [21], and T-cell

memory [22]. While BTK deficiency can leave the body in a state of immunodeficiency (e.g., XLA), its upregulation may lead to autoimmune states, such as rheumatoid arthritis and systemic lupus erythematosus [19], as well as malignant states, notably B-cell malignancies [23], squamous cell carcinoma, and pancreatic cancer [24]. Hundreds of variants have been identified in the gene BTK from patients with XLA [25–29, 18] which may explain phenotypic divergence in XLA [30]. Therefore, data are integrated to investigate genotype-phenotype interactions [31]. Overall, the most common complications of XLA are pulmonary infections and bronchiectasis.

3.2.1 Pulmonary Infections

Generally, infections account for the highest proportion of presenting manifestations of XLA [9, 10, 16, 29]. In particular, a prospective study of 101 individuals with XLA reported the presence of at least one of these three infectious complications: pneumonia, sinusitis, and chronic lung disease with bronchiectasis in 76% of patients with XLA [14]. Moreover, the majority of infections affect the upper and lower respiratory tracts [16, 10, 18, 32] and are of bacterial origin, among which bronchitis, pneumonia, chronic sinusitis, otitis, and conjunctivitis are the most common complications of XLA [33]. Infections occur not only before diagnosis but remain a major cause of complications during the course of disease, immunoglobulin substitution, and death in patients with XLA [32, 10]. The most common infections prior to and after diagnosis include otitis media, pneumonia, and sinusitis [9, 29].

Pneumonia is the most common acute infection associated with XLA [14]. Recurrent pneumonia should be, therefore, regarded as an alarm sign for PIDs including XLA [34, 35]. Before the diagnosis is made, between 60% and 83% of patients with XLA have a history of at least one episode of pneumonia [36], and approximately 30% of patients have a history of hospitalization due to pneumonia [16]. With an adequate immunoglobulin therapy, the rate of pneumonias is reduced by more than 10% [14] and lies within the range of 0.00–0.10 pneumonias per treatment year [13, 37]. However, approximately 50% of patients might experience deterioration in their respiratory status while receiving immunoglobulin therapy [38]. The rate of infectious episodes during immunoglobulin therapy seems to be age-related, since there is a threefold increased risk for infections in adult patients compared with pediatric patients (2.12 vs. 0.74 infections/patient/year) [38]. More important is that pneumonias after initiation of immunoglobulin therapy might be severe as many as half of episodes might require hospitalization for intravenous antibiotic treatment [13]. In multivariate analysis, patients with bronchiectasis had a > 3-fold increased risk of pneumonia during the 5-year immunoglobulin therapy [14]. Its source remained unknown in almost 80% of cases. However, sputum cultures could reveal the following as bacterial pathogens underlying pneumonia in patients with XLA: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Mycoplasma pneumonia* [13, 33]. Analysis of bron-

choalveolar lavage (BAL) in patients with XLA without acute pulmonary function identified bacterial pathogens such as *Haemophilus influenzae* and *Veillonella* [39]. Also, bacteria that were observed through protected specimen brush samples included *Haemophilus influenzae*, *β-hemolytic streptococci*, and *Porphyromonas* [39]. Other bacterial pathogens found in association with pneumonia among patients with XLA are *Pseudomonas* species and *M. tuberculosis* [16]. Looking at chest X-ray, pneumonia in patients with XLA can cause peribronchial thickening and then segmental atelectasis [13]. Antigen-specific immunological responses might predict the risk of respiratory tract infections in patients with XLA. More precisely, individuals who developed IgG and IgM responses specific to bacteriophage phi-X 174 were less likely to be affected by respiratory tract infections (RTI) compared with those who developed only IgM responses [22]. Although very rare, there are reports of pulmonary infections with fungal (aspergillosis and *Pneumocystis jiroveci*) [40] and viral pathogens (respiratory syncytial virus) [41–43] in patients with XLA even despite regular immunoglobulin substitution therapy. Chronic sinusitis seems to predispose individuals with XLA to pulmonary aspergillosis [40].

3.2.2 Bronchiectasis

There are individuals with impaired pulmonary function, as revealed through pulmonary function test, that show a normal chest X-ray [13]. However, an abnormal chest X-ray clearly warrants that pulmonary function is impaired [13]. Patients with XLA show changes in pulmonary function test (PFT) that favor obstructive lung disease. These include a reduction in forced expiratory volume in the first second (FEV1) as well as a reduction in forced expiratory flow (FEF) [13]. Pulmonary function abnormalities appear not to be age-related [13]. The delay in diagnosis has shown an inverse association with the risk of chronic lung disease. Supporting this, lung function decreases with aging in patients with XLA and is worsened by smoking and bronchiectasis. A longitudinal study of patients with XLA ($n = 8$) over an average period of 7.6 years calculated an average annual decline of 65 ± 11 mL/year and 58 ± 20 mL/year for FEV1 and FVC, respectively [15]. Immunoglobulin therapy dose demonstrated a negative association with lung function decline. This reflects the protective effect of immunoglobulin therapy [15].

Evidence of chronic lung disease (CLD) before diagnosis is present in nearly one-third of patients with XLA [16]. Factors known to increase the risk of CLD before diagnosis of XLA include higher age at diagnosis and the presence of a lower respiratory tract infection (LRTI) [16]. This may indicate that delayed diagnosis might leave patients facing higher risk of CLD [18]. CLD is observed in 40% of patients with XLA who had a history of LRTI. Approximately, 30% of patients develop CLD later in the course of disease [16]. CLD risk after diagnosis of XLA is predicted by pneumonia and inappropriate immunoglobulin substitution therapy [16]. Study of 201 US patients with XLA identified CLD as the cause of death in 25% of cases [9]. CLD also has been shown to have a negative impact on the life quality of patients with XLA [44].

Keeping in mind the high incidence of pulmonary infections, bronchiectasis is considered a common complication of XLA. A study of Australian adults estimated a twofold incidence of infection with bronchiectasis compared to infection without bronchiectasis among patients with XLA (67% vs. 33%) [45]. In a multicenter study of 199 patients with XLA, the use of high-resolution chest CT imaging indicated a prevalence of bronchiectasis as high as 56% [33]. The prevalence of bronchiectasis increases with age [14] and that turning 18 years old was the most important factor predictive of bronchiectasis [33]. However, other factors associated with an increased risk of bronchiectasis included a history of pneumonia and treatment with IVIG compared with subcutaneous IG [33]. In addition, patients with chronic sinusitis were four times more likely to have bronchiectasis [14]. It is important that almost half of patients with XLA suffer from chronic sinusitis [14], whereas no effect of IgG levels on the risk of bronchiectasis was found [14]. The age range for development of bronchiectasis was 7–45 years [33]. Regardless of age, bronchiectasis lowers lung function as reflected in reduced FEV1 [33]. Bronchiectasis is, therefore, the real cause of diminished life quality among patients with XLA [38]. CXR findings are often evident in the middle and lower lobes of the lung(s) [11]. HRCT appears to be more sensitive than CXR for evaluation of pulmonary abnormalities in patients with primary hypogammaglobulinemia including XLA [46].

3.2.3 Chronic Pleurisy

There is report of recurrent chronic pleurisy presented with thickened pleura and calcification in CT imaging and intraluminal fibrosis, foamy alveolar macrophages, and chronic inflammation in histopathological examination of the pleural tissue [47]. Broad-range bacterial polymerase chain reaction (PCR) identified *H. equorum*-like bacterium as the underlying pathogen of these abnormalities. Taking high-dose panipenem/betamipron (PAPM/BP) and clarithromycin significantly improved the patients' situation.

3.2.4 Potential Mechanisms of Respiratory Manifestations in XLA

Both lipopolysaccharide (LPS) and anti-IL-8/IL-8 immune complexes act as stimulus to neutrophils [48]. Upon stimulation, FcγRIIa is recruited from intracellular compartments to the cell surface. FcγRIIa recruitment is accompanied with activation of Btk, which in turn induces the expression of adaptor molecule MyD88. In this manner, Btk act to direct cross talk between FcγRIIa and toll-like receptor 4 (TLR4) [49]. It is followed by engagement of MyD88 adapter-like (Mal)/TIRAP interaction which plays a crucial role in TLR-dependent NF-kappaB (NF-κB) pro-inflammatory responses [50]. Matrix metalloproteinases (MMP) mainly MMP9

induced by NF-κB contribute to tissue remodeling in acute lung injury. As expected, Btk inhibitors could abrogate the expression of both Btk and MyD88 in human neutrophils activated with anti-IL-8/IL-8 immune complexes [48]. Additionally, treatments blocking either Btk or MMP9 diminished the expression of MMP9 in neutrophils from mice exposed to secondhand smoke [51]. Altogether, it is plausible to think of Btk-targeted neutrophil-specific therapy in conditions associated with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) [48] and chronic obstructive pulmonary disease (COPD) [51].

Ibrutinib is used in targeted therapy of malignancies and autoimmune diseases to inhibit BTK. It has been shown to prevent influenza-induced acute lung injury through reduction of pro-inflammatory mediators [52]. Btk inhibitor RN983 showed much more anti-inflammatory potency than corticosteroid budesonide in mouse lung in form of inhalation [53]. This makes it effective in the treatment of allergic asthma. RNA interference (RNAi) of Btk has been demonstrated to decrease protein levels of Btk and phosphorylated Btk (p-Btk) and diminish the expression and activation of Btk in alveolar macrophages [54]. In a mouse model of cecal ligation and puncture (CLP)-induced sepsis, pretreatment with Btk RNAi was able to prevent epithelial cell apoptosis, pulmonary edema, vascular permeability, the expression of inflammatory cytokines (TNF-α, IL-1β, and IL-6) and signaling (NF-κB), and neutrophil lung infiltration.

On the contrary, there is evidence that the over-suppression of innate immunity by ibrutinib might cause toxic events. Ibrutinib can lead to epithelial cell apoptosis and inflammation that promote pulmonary infections [55] and fibrosis [56]. Even, there is report of invasive aspergillus infection in association with ibrutinib in patients with chronic lymphocytic leukemia [57]. These toxic effects induced by ibrutinib draw a picture of what happens in patients with XLA, where loss-of-function mutations lead to downregulation of Btk.

Study of XLA mice suggest that IgM contributes to alveolar macrophage phagocytosis and thereby confining the fungal infection to limited areas [58]. In this manner, low IgM levels in patients with XLA make them prone to develop more severe infections with fungal pathogens such as *Cryptococcus neoformans*.

B-cells act as the regulator of neutrophil migration to the site of stimulus. Depletion of B-cells in XLA dictates the rapid migration of neutrophils to the site of stimulus whereby the opportunity of macrophages to attract to the site of stimulus is captured, while macrophage activation is required for engagement of interferon gamma (IFNy)-producing T-cells, which in turn elicit an effective response to bacillus Calmette-Guérin (BCG) vaccination [59]. In this manner, impairment in antituberculosis immunity exists as a result of disrupted IFNy-producing T-cell-macrophage axis in XLA.

TLR signaling pathways as well as TLR effector function are maintained despite loss of Btk function [60]. Neutrophils from patients with XLA upon stimulation with LPS revealed activation of MAPK cascades, production of reactive oxygen species (ROSs), and reduction of neutrophil apoptosis. All these events occurred in a comparable fashion in neutrophils from controls. Particularly, ROSs are required for phagocytosis of pathogens [61].

Impairment in B-cell development causes airway inflammation [62], and therefore allergic symptoms might be present in patients with XLA [63]. Compared with wild-type mice, X-linked immunodeficiency (Xid) mice exhibited an increase in production of cytokines (IL-4, IL-5, IL-10, IL-13, CCL5, and IFNy), lung inflammation, interstitial eosinophilia, and mucus production in response to challenge with cockroach antigen.

3.2.5 Management of Respiratory Manifestations in XLA

Immunoglobulin therapy helps to restore IgG levels to protective levels [13]. Patients on high-dose intravenous immunoglobulin therapy rather than low-dose or intramuscular immunoglobulin therapy are more likely to achieve recommended levels of IgG [64]. Analysis of serial determination of IgG levels in patients with XLA receiving IVIG therapy indicated that a median IgG level of 354 mg/dl predicts that individual immunity against infections is acceptable [65]. The annual incidence of bacterial infections (pneumonia) was estimated to be 0.16 (0.12), 0.05 (0.05), and 0.00 (0.00) when IgG levels are below 500 mg/dL, between 500 and 800 mg/dL, and above 800 mg/dL [37]. Of note, a 5-year prospective study of 101 individuals with XLA identified only one episode of pneumonia in cases with IgG levels >1000 mg/dL [14]. Individuals taking a high dose of IVIG (397 mg/kg) are expected to be infection-free [65].

Lung transplantation (LTx) is the option available for patients with bronchiectasis and end-stage respiratory failure caused by XLA. Even after LTx, regular immunoglobulin substitution is still required for prevention of infections [66]. Although it is promising that the lungs often reach an acceptable or predicted functional level, post-lung transplant infection and respiratory failure remain life-threatening [45]. The authors in [67] reported the long-term outcome of six patients with XLA who underwent LTx. All patients but one died within the first 3 years after LTx. The pulmonary infection (bronchiolitis and pulmonary sepsis) was the cause of death for all but one case who died from progressive multifocal leukoencephalopathy.

3.3 Autosomal Recessive Agammaglobulinemia (μ Heavy Chain Deficiency, λ5 Deficiency, Igα Deficiency, Igβ Deficiency, BLNK Deficiency)

When we have a male child with congenital hypogammaglobulinemia and absent B-cells, the first differential diagnosis to consider is XLA, which is resulted from mutant BTK. When we have a female child with similar clinical and immunological presentation, the first differential diagnosis to consider is autosomal recessive (AR) agammaglobulinemia (ARA). Mutations identified as the cause of autosomal

recessive forms of agammaglobulinemia occur in the genes encoding molecules that contribute to the structure and function of pre-B-cell receptor (BCR) or its downstream pathways such as the μ heavy chain (IGHM), B-cell linker adaptor protein (BLNK), the immunoglobulin λ-like polypeptide1 (IGLL1), leucine-rich repeat-containing 8 (LRRC8A), Igα (CD79A), and Igβ (CD79B) [31].

As pre-B-cells are known as precursors of B-cells, the pre-B-cell receptor (BCR) is considered as precursor of B-cell receptor. As a result, pre-BCR is an essential to B-cell development. It is composed of the μ heavy chain (μHC) and the surrogate light chain (SLC). The SLC, in turn, includes invariant Vpre-B and λ5 polypeptides. Also, transmembrane protein Igα in association with Igβ serves as the signal transduction component for the pre-BCR complex. Abnormalities in pre-BCR structure and function hinder the transition from pro-B- to pre-B-cell stage [68], predisposing individuals to immunodeficiency, malignancy, and autoimmunity (for review see [69]).

3.3.1 μ Heavy Chain Deficiency

Yel et al. 1996 [70] were the first group to identify mutations in the IGHM gene as a cause of agammaglobulinemia. They reported seven patients from two families with AR B-cell defects. Patients presented between 1 and 15 months of age. Clinical manifestations included fever, weakness, rashes, chronic enteroviral encephalitis, recurrent infections (pneumonia, bronchopneumonia, and otitis), failure to thrive, gastrointestinal disorders, septic shock (due to *Pseudomonas aeruginosa*), arthritis, and perirectal abscesses.

Thereafter, more studies have investigated the IGHM as a potential candidate gene for AR B-cell defects [31, 71–74]. These studies indicate that (a) the IGHM gene is very polymorphic [72], (b) the presence of large deletions rather than point mutations is more likely in patients with agammaglobulinemia [74], and (c) mutant IGHM accounts for about 20–30% of patients who have AR B-cell defects [71] and as well for about 5% of all patients with agammaglobulinemia [74]. Also, it is concluded that patients carrying mutant IGHM experience an earlier onset and more difficult course of agammaglobulinemia compared to patients carrying mutant BTK [71]. Overall, mutant IGHM may cause respiratory manifestations such as recurrent upper respiratory tract infections (viral rhinitis, sinusitis, otitis, pharyngitis, and rhinopharyngitis), recurrent pneumonia, bronchopneumonia, bronchiectasis, and asthma.

3.3.2 λ5 Deficiency

Studies show that despite allelic exclusion of Ig μ heavy chain would remain normal, B-cell development is, however, not completely [75] ablated in mice deficient in λ5 [76]. Minegishi et al. 1998 [77] reported a case with hypogammaglobulinemia, less than 1% of normal number of B-cells, and undetectable levels of CD19. He presented with recurrent otitis at 2 months of age.

3.3.3 *Igα Deficiency*

Minegishi et al. 1999 [78] published the first case of defect in Igα (CD79a) with agammaglobulinemia. The patient presented with recurrent diarrhea, failure to thrive, bronchitis, and neutropenia. The age at onset of disease was before 1 month of age. The authors demonstrated that defect in the Igα gene results in complete blocking of B-cell development as defect in the IGHM. This study proved that the functional role of Igα as a component of signal transduction molecule is not less than the role that the mu heavy chain plays as a structural component of pre-BCR. The second one was reported by Wang et al. 2002 [79]. Clinical and immunologic features consisted recurrent upper and lower respiratory tract infections, otitis media, weakness, almost complete absence of B-cells but not T-cells, hypogammaglobulinemia, dermatomyositis, and diarrhea.

3.3.4 *Igβ Deficiency*

Study in *Drosophila melanogaster* [80] showed that mutant Igβ is a contributing factor to the dissociation of Igα/Igβ, whereby the pre-BCR complex cannot be assembled and B-cell development is blocked. Moreover, deletion of Igβ dictated death in murine developing B-cells including pre-B-cells and immature B-cells [81]. The first patient carrying mutant Igβ (CD79b) was described by Dobbs et al. 2007 [82]. She presented with recurrent bronchitis, persistent cough, pneumonia, and hypogammaglobulinemia. The age at onset of symptoms was about 5 months. Ferrari et al. 2007 [80] were the second group who found mutant Igβ in a patient presented with less than 1% of normal CD19 levels, hypogammaglobulinemia, but normal counts of T and NK cells. His symptoms began to appear at 8 months of age and included recurrent pneumonia, conjunctivitis, otitis media, sinusitis, and bronchitis. At the time of evaluation, he was 20 and demonstrated chronic sinusitis at his CT scan. The third case was recently introduced by Lougaris et al. 2014 [83]. The patient was a female child, whose symptoms started at 14 months of age. She presented with recurrent upper respiratory tract infections, fever, neutropenia, profound hypogammaglobulinemia, and complete absence of B-cells but normal numbers of T and NK cells.

3.3.5 *BLNK Deficiency*

BLNK is essential for B-cell development and function. Mice deficient in BLNK failed to generate B220 + CD43− precursor B-cells and lacked mature B-cells in the periphery [84]. BLNK deficiency also led to reduce IL-10 production in mice [85]. Mutant BLNK in a patient lacking pre-B-cells or mature B-cells was first reported in 1999 [86]. The patient presented with recurrent otitis, pneumonia, and hypogammaglobulinemia. His symptoms commenced at 8 months of age. Other studies that

have found mutant BLNK in association with agammaglobulinemia can be found here [87–89]. They confirm recurrent otitis and sinopulmonary infections as the most common initial presentation of BLNK deficiency [88, 89]. However, other clinical manifestations included diarrhea, enteroviral infection, arthritis, dermatitis, and bronchiectasis [89].

3.4 Other Forms of Agammaglobulinemia with Absent B-Cells (TCF3 Deficiency, LRRC8 Deficiency, Thymoma with Immunodeficiency)

3.4.1 TCF3 Deficiency

Studies of mice have shown that the transcription factor 3 (TCF3) gene plays a crucial role in B-cell development [90–92]. This gene which is also known as E22 gene encodes transcription factors E12 and E47. Mutations in TCF3 have been reported in both autosomal recessive [93] and autosomal dominant [94] agammaglobulinemia. The authors in [93] described a patient with B-cell acute lymphoblastic leukemia (B-ALL) presented with profound hypogammaglobulinemia, recurrent pneumonia, meningitis, pancytopenia, and splenomegaly. His immunological findings included less than 1 percent normal number of CD19+ B-cells in the periphery in the presence of normal counts of CD3+, CD4+, and CD8+ T-cells. Boisson et al. 2013 [94] identified the same de novo mutation in the TCF3 gene (within the exon that encodes E47) in four patients with an unusual phenotype characterized by almost complete absence of BCR in the presence of increased expression of CD19 on B-cells [95]. All patients presented severe hypogammaglobulinemia and less than 3 percent CD19+ cells in the periphery. Age at diagnosis ranged from 9 months to 4 years. Clinical presentations included pneumococcal meningitis, recurrent otitis, vaccine-associated polio, and arthritis. Other clinical findings were dermatitis and hepatomegaly.

3.4.2 LRRC8 Deficiency

Sawada et al. 2003 [96] are the first group that isolated the leucine-rich repeat-containing 8 (LRRC8) and showed that B-cell development is impaired in mouse model for a truncated expression of LRRC8. They also provided a report describing a girl patient with agammaglobulinemia, absence of B-cells, epicanthic folds, mild hypertelorism, high-arched palate, and lowered ears. The patient carried mutant LRRC8. To our knowledge, no other report of mutant LRRC8 in association with agammaglobulinemia has been published.

3.4.3 Thymoma with Immunodeficiency (Good's Syndrome)

Good's syndrome (GS) or thymoma with immunodeficiency refers to the combined conditions of thymoma and immunodeficiency. It is mainly characterized by thymoma, hypogammaglobulinemia, and low number of B-cells in the periphery. However, low number of T-cells and an inverted CD4/CD8 ratio are also common.

Tarr et al. 2001 [97] in the study provided a report of 5 patients with GS presented with infection as well as a review of 46 other patients with GS and infections. Infections have a propensity to affect the respiratory and gastrointestinal tract [98, 99]. The following are infectious complications documented in GS: recurrent sinopulmonary infection, CMV disease, bacteremia, oral or esophageal candidiasis, persistent mucocutaneous candidiasis, chronic diarrhea, urinary tract infections, *P. carinii* pneumonia, tuberculosis, Kaposi sarcoma, disseminated varicella, candidemia, wound infection with *Clostridium perfringens*, Mycoplasma arthritis, etc. However, the main clinical findings at presentation appear to be sinopulmonary infections with encapsulated bacteria. When compared to patients with CVID, patients with GS experience a more difficult course of immunodeficiency complicated with opportunistic infections such as *P. carinii* pneumonia, mycobacterium tuberculosis, and mucocutaneous candidiasis, resembling that which occurs in human immunodeficiency virus (HIV) infection [100]. Therefore, if a patient with thymoma or CVID develops refractory infections, then we should consider GS as a differential diagnosis. Particularly, persistent infection (pneumonia) following thymectomy might warrant that your patient is very likely to have GS [101–105]. Overall, respiratory manifestations in association with GS include recurrent sinopulmonary infections (sinusitis, rhinosinusitis, otitis media, and pneumonia) [106–114] with bacterial (especially with encapsulated bacteria including *Haemophilus influenzae*), fungal (aspergillus and *P. carinii*), and viral (CMV and HSV) pathogens [115–121], tracheobronchitis [118], diffuse panbronchiolitis [122–124], granulomatous lung disease [125], and pulmonary nodules [123]. As for patients with other forms of agammaglobulinemia, patients with GS remain dependent on immunoglobulin replacement therapy. A recent study has estimated the median survival of 14 years for 47 patients with GS [111].

3.5 Activated PI3K-δ Syndrome

Activated PI3K-δ syndrome (APDS) is a heterogeneous disorder associated with a spectrum of clinical pictures and immunological findings classified under two types [126]. Autosomal dominant gain-of-function mutations (E1021K and C416R) in the gene PIK3CD (PI3K-δ, phosphoinositide 3-kinase δ) can cause activated PI3K-δ syndrome type 1 (APDS1), while activated PI3K-δ syndrome type 2 (APDS2) is caused by an autosomal dominant gain-of-function mutation in the gene PIK3R1 (phosphoinositide-3-kinase regulatory subunit 1), inducing the skipping of exon 11.

Both types are characterized with similar immunological findings including low levels of IgG2 and lymphocytes and high levels of IgM and B-cells [127]. Overall, patients with APDS are prone to recurrent respiratory infections, airway disease [127], lymphoproliferation, cytopenias, skin diseases, chronic EBV and CMV viremia, and enteropathy [126]. All these major manifestations tend to decrease over time [126]. Of notable importance is that respiratory infections are the most frequent, initial manifestations of APDS [126].

The prospective European Society for Immunodeficiencies (ESID)-APDS registry has recently reported data on 51 patients with APDS1 and 26 patients with APDS2 [126]. Overall, respiratory infections, particularly pneumonia, otitis media, and sinusitis, were observed in nearly all patients and in most patients occurred before 15 years of age. Looking at CT scans, evidences of bronchiectasis were found in 60% of patients with APDS1 and 27% of patients with APDS2. Mean age at diagnosis of bronchiectasis was 11.2 years. Therapeutic options available to patients with APDS include antibiotics, antifungal agents, immunoglobulin replacement therapy, systemic immunosuppressive therapy, and HSCT [126]. Particularly a cohort study of 36 patients with APDS2 revealed that recurrent upper respiratory tract infections were experienced by all patients [128]. Other common respiratory complications in this population included pneumonia and respiratory tract lymphoid hyperplasia, which were found in about 70% and 50% patients.

3.5.1 Potential Mechanisms of Respiratory Manifestations in APDS

PI3K as lipid kinases play role to maintain normal function of airway. Abnormal PI3K signaling can alter airway function, so that inflammatory responses are aggravated [129]. Such a condition is seen in patients with respiratory diseases especially allergic inflammation and asthma. Airway biopsies from 11 patients with atopic asthma provide evidence of increased activation of the PI3K signaling after exposure to allergen [130].

PI3K-δ is a class I PI3K isoform proven to particularly contribute to both innate and adaptive immune responses [129]. Such contribution is resulted from its interaction with Akt, together triggering the PI3K-δ/Akt signaling pathway. Increased activation of this signaling pathway is thought to mediate airway inflammation as seen in obstructive lung diseases [131, 132] and induced by cigarette smoking [133]. Moreover, PI3K-δ is able to reduce glucocorticoid sensitivity of airways ([131, 132]. This explains why some patients are resistant to glucocorticoids. Supporting this, PI3K-δ inhibitor can mitigate allergic inflammation in asthma models [134]. The effect remained true upon exposure to *Aspergillus fumigatus*. At least part of this anti-inflammatory effect of PI3K-δ inhibitor appears to be mediated through reducing endoplasmic reticulum stress [135], hypoxia-inducible factor-1α (HIF-1α), and nucleotide-binding domain, leucine-rich-containing family,

and pyrin domain-containing-3 (NLRP3) expression in lung tissue [136, 134]. All these factors are involved in generating inflammatory responses upon stimulation [136]. Additionally, PI3K-δ contributes to virus escape possibly by increasing the expression of B7-H1 (PD-L1) [137]. Therefore, it is well-expected that APDS, a condition associated with PI3K-δ upregulation, should be accompanied with bacterial and viral infections as well as different respiratory manifestations.

The current literature also supports the potential of PI3K-δ to be exploited as a target for treatment of respiratory infections and airway diseases [138, 139]. For example, anti-inflammatory effect of erythromycin and dexamethasone seems to be mediated via suppression of PI3K-δ signaling [140]. Animal models of asthma demonstrate that PI3K-δ blockade hampers infiltration of inflammatory cells by decreasing vascular permeability [141]. Moreover, PI3K-δ inhibition can help to regain glucocorticoid sensitivity and, therefore, enhance anti-inflammatory effects of glucocorticoids [131, 132, 142]. However, attention should be paid that oversuppression of this pathway might cause toxicities. As for APDS, PI3K-δ function is abnormally high in malignant states particularly B-cell malignancies [143]. As a result, PI3K-δ inhibitor (idelalisib) can be used to treat these malignancies [144]. However, it might reduce cellular respiration and so be toxic to lung tissues [145].

3.6 LRBA Deficiency

Lipopolysaccharide (LPS)-responsive and beige-like anchor (LRBA) protein deficiency is a rare PID characterized by hypogammaglobulinemia and CD19+ B-cell deficiency and also to a lesser extent by CD4+ T-cell deficiency and NK-cell deficiency [146]. Patients with LRBA deficiency often present with recurrent infections (pneumonia, urinary tract infections, and otitis media), lymphoproliferative disorders (lymphadenopathy, splenomegaly, hepatomegaly, and granuloma), autoimmune disorders (type 1 diabetes, ulcerative colitis, immune thrombocytopenic purpura, autoimmune hemolytic anemia, and Graves' disease), atopic disorders (food allergy, insect sting allergies, allergic dermatitis, urticaria, and asthma), enteropathy, and failure to thrive [147, 148, 146]. Therefore, LRBA can be appropriately considered as a subgroup of CVID with autoimmune and inflammatory features.

A retrospective cohort of ten patients with LRBA deficiency in Israel highlighted chronic cough as the most common respiratory manifestation in patients with LRBA deficiency [147]. Less frequent respiratory manifestations were dyspnea, perioral cyanosis, and clubbing. Chest X-rays and CT scans in these cases provided evidences of axillary, hilar, and mediastinal lymphadenopathy, consolidation, lobar and sub-lobar atelectasis, bronchiectasis, and interstitial lung disease [147]. Patients with LRBA deficiency demonstrated no serious abnormalities on PFT. They also were likely to have a normal bronchoscopy. Potential findings in bronchoscopy included tracheomalacia and adenoid hypertrophy. The mean age at onset of symptoms was 4.65 [147].

In a longitudinal study of patients with LRBA (n = 17) in Iran [146], respiratory tract infections were the most common first presentation of immunodeficiency, seen in more than 40% of patients. Additionally, there were two patients (11.8%) presented with allergy and asthma. The median age at onset of symptoms and diagnosis were 2.0 and 7.0 years, respectively. With a median follow-up of 14 years, all patients (100%) developed infectious complications, which in order of frequency were pneumonia, sinusitis, and otitis media.

There is a case report of bronchiolitis obliterans organizing pneumonia (BOOP) in a 10-year-old boy who presented with recurrent respiratory infections, anemia, and thrombocytopenia [149]. He showed hypogammaglobulinemia of IgA and IgG, while IgM levels were normal. He was refractory to regular IVIG and all antimicrobial agents, and his respiratory condition deteriorated during these treatments. Diffuse lung disease with peripheral nodules was found at CT scans. PCR of BAL fluid was positive for *Pseudomonas aeruginosa*, *Pneumocystis jiroveci*, and CMV. Looking at lung tissue, there were evidences of disseminated infiltration of inflammatory cells and bronchiolitis obliterans organizing pneumonia (BOOP). To establish genetic causality, combined homozygosity mapping and exome sequencing was performed and showed a homozygous mutation (NM_001199282: c.743_744insAAGA: p. Asp248Glufs*2) in the gene LRBA. Each parent carried a copy of this mutation, supporting the autosomal recessive form of disease.

In this manner, different mutations in the gene LRBA are associated with the spectrum of phenotypes [150]. Even two siblings might present with incompatible pictures of LRBA deficiency [151].

Polymorphisms of the gene LRBA known to influence the function of LRBA protein have been associated with risk of pneumoconiosis in coal workers [152].

In conclusion, it is promising that respiratory manifestations of LRBA patients are mostly sensitive to therapy with IVIG, systemic immunosuppression, abatacept (CTLA4-Ig), or hematopoietic stem cell transplantation (HSCT) [147]. Drugs for prophylaxis of recurrent infections include antibiotics, antivirals, and antifungal medicines [146]. Mastoidectomy might be indicated in a severe case with frequent otitis media [146]. Therapeutic options for autoimmune complications vary from individual to individual and include IVIG, systemic immunosuppression, thymectomy, and HSCT [146]. However, respiratory failure remains the leading cause of death in these patients [85].

3.7 CD19 Complex Deficiencies

The CD19 complex is a transmembrane complex comprising CD19, CD21, CD81, and CD225. It can function as a co-receptor for B-cells that promotes B-cell receptor (BCR) signaling. Therefore, it is well-appreciated that defects in the formation of CD19 complex can cause autoimmunity and impairment of humoral immunity [153].

3.7.1 CD19 Deficiency

CD19 includes two extracellular immunoglobulin superfamily (IgSF) constant domains: a transmembrane region and a cytoplasmic region. Its cytoplasmic tail is comprised of nine tyrosine kinase residues that contribute to intracellular signaling. To our knowledge, there have been reported ten cases of CD19 deficiency [154–160]. The genetic defects responsible for CD19 deficiency include mutations resulting in premature termination codons and also missense mutations leading to an amino acid change. Overall, CD19 deficiency is featured by respiratory manifestations such as recurrent respiratory tract infections (pneumonia, bronchiolitis, and otitis media), wheezing, chronic obstructive pulmonary disease, atopy, and asthma [154]. Hypogammaglobulinemia (IgG and IgM) is also commonly found in patients with CD19 deficiency. Infectious pathogens found in these patients are respiratory syncytial virus, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. CXR and CT scans reveal lobar atelectasis, peribronchial thickening, and bronchiectasis. Despite absence of CD19+ B-cells, flow cytometry can be used to confirm presence of CD20+ B-cells. Patients are also likely to have reduced numbers of transitional B-cells, memory B-cells, CD3+ T cells, and CD16+/CD56+ NK cells. Interestingly, studies indicate a delay between Ca2+ influx and stimulation with anti-IgM in B-cells from patients with CD19 deficiency. It should be noted that Ca2+ influx plays a crucial role in BCR signaling.

3.7.2 CD81 Deficiency

CD81 is a 26KDa surface protein also known as TAPA-1 (target of the antiproliferative antibody 1) and Tetraspanin-28 (Tspan-28). CD81 acts as regulator of proliferation of different cells such as glial cells, astrocytes, oocytes, and retinal pigment epithelial cells [161–164]. It is also required for the expression of CD19 on B-cells and thereby contributes to the activation of B-cells and production of antibodies against T-cell-dependent antigens. Its deficiency interferes with the formation of CD19 complex, resulting in the spectrum of respiratory manifestations related to CD19 deficiency.

The authors in the study [165] presented a patient suffering from recurrent respiratory tract infections during the first 2 years of life. She then developed glomerulonephritis, recurrent thrombocytopenia, and hypogammaglobulinemia of IgG. There was no significant change in the numbers of B, T, and NK cells. However, flow cytometry revealed a reduction in the relative number of transitional B-cells and memory B-cells. Additionally, the patient's B-cells showed loss of both CD19 and CD81. Genetic analysis revealed an intact CD19 gene but homozygous splice site mutation (c.561+1G>A) in the CD81 gene. While the patient's family members (her parents and her brother) harboring a single copy of this mutation were immunologically healthy, the patient did not show the expected increase in IgA and IgG levels upon vaccination with tetanus toxoid and pneumococcal antigens. CD81 is thus essential to produce an appropriate antibody response to protein and polysaccharide antigens.

A study of mice links CD9/CD81 double knockout to the spontaneous development of pulmonary emphysema [166]. It is accompanied with an increase in the activity of matrix metalloproteinases MMP-2 and MMP-9 in alveolar macrophages. The role of MMPs is well-appreciated in the degradation of the alveolar matrix as well as in the aggravation of pulmonary inflammatory processes, which both events have been implicated in COPD [167]. It is thus suggested that obstructive lung disease might arise from CD81 deficiency, owing to abnormal activity of MMPs.

Also, allergen-induced airway activity in CD81-deficient mice is decreased compared to wild-type mice [168]. CD81-deficient mice also demonstrated a reduced production of Th2 inflammatory cytokines IL-4, IL-5, and IL-13. It is therefore possible to assume that CD81 plays role in allergen-induced airway hyperactivity by inducing the expression of cytokines.

3.7.3 CD21 Deficiency

CD21 or complement receptor type 2 (CR2) precursor is a 145 KDa protein implicated in EBV entry [169]. It is expressed by mature B-cells and follicular dendritic cells, whereby activation of B-cell responses is enhanced by binding of immune complexes that comprise cleavage products of C3d and antigens [170]. This is beneficial in combating against toxic or infectious agents and on the other hand can cause an imbalance favoring autoimmunity.

The study [171] provides a report of first case of CD21 deficiency. Early childhood respiratory tract infections forced the patient to undergo tonsillectomy at 6 years old. Then, the patient experienced a long remission for about 20 years. At 28 years old, his symptoms including recurrent respiratory tract infections, myalgia, diarrhea, and weight loss began to flare up. The pathogen found in his respiratory secretions was *Haemophilus influenzae*. The patient also showed hypogammaglobulinemia of IgG1 and IgG4 and was thus considered for immunoglobulin replacement therapy. The patient's B-cells completely lacked CD21. Genetic analysis revealed two heterozygous mutations: one resulting in the skipping of exon 6 and the other being a premature stop codon mutation occurring in exon 13.

The patient reported in [172] was a 13-year-old boy who presented with myalgia, rigidity, and hypogammaglobulinemia of IgG1, 2, and 4. Flow cytometry revealed absence of CD21. Sequencing of CD21 gene identified two heterozygous mutations: one nonsense mutation occurring in exon 2 and the other being a frameshift mutation in exon 15. Interestingly, the patient remained free of serious infections until writing the paper.

In the study [173], the authors have described two siblings who carried CD21 deficiency. Symptoms began to manifest at 5 and 7 years of age. Clinical manifestations mainly included recurrent otitis media, rhinopharyngitis, bronchitis, and lobar pneumonia.

3.8 Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is the most common symptomatic PID estimated to occur in 1/10,000–1/200,000 depending on the study population. It is mainly characterized by a defective B-cell differentiation resulting in hypogammaglobulinemia of IgA, IgG, and IgM with two or more standard deviations below the normal mean. Also, about half of patients manifest characteristics of malfunctioning T-cells and cytokine/chemokine system including a reduction in CD40 ligand expression and IL-2 production [174]. Therefore, CVID covers a spectrum of disease phenotypes, and the diagnosis should only be made after ruling out other potential causes of hypogammaglobulinemia including other PIDs and immunodeficiency diseases due to infectious agents, malignancies, protein-losing agents, and drugs [175]. CVID involves a complex interaction of different disease processes. However, there are a few monogenetic forms of CVID that are caused by defect in a single gene such as ICOS [176, 177], TACI [178, 179], and CD19 [155]. Clinical presentations mainly include recurrent bacterial infections especially affecting upper and lower respiratory tracts, inflammatory diseases, autoimmune disorders, lymphoproliferative disorders, chronic lung diseases, gastrointestinal disorders, malabsorption, hepatitis, and malignancies (especially lymphomas). Clinical symptoms usually peak in the second or third decade of life. Early-onset disease is, however, common, especially in male patients [180]. Recently a multicenter study of 2212 patients with CVID has reported that the median diagnostic delay is around 4–5 years in most populations [181]. Overall, as much as all patients with CVID experience infectious respiratory diseases [182–184] and more than half of patients develop noninfectious respiratory complications as well [185].

3.8.1 Respiratory Tract Infections

The French national study of adults with CVID ($n = 252$) confirmed recurrent respiratory tract infections, e.g., bronchitis, sinusitis, and pneumonia, as the most common initial presentation [181]. In order they were found in about 69%, 63%, and 58% of patients. Lower respiratory tract infections are also found in 84% of patients [182]. In particular, pneumonia is experienced by about 32–77% of patients [180, 182, 184, 186]. Early-onset CVID in male (before 10 years of age) patients is considered a discrete disease entity characterized by a higher risk of infectious complications including pneumonia, but not noninfectious complications [180]. Encapsulated bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* are the main pathogens associated with respiratory tract infections in patients with CVID. In particular, *Bordetella pertussis* may contribute to the development of respiratory disease in children with CVID. About 13% of patients reveal a severe defect in switched memory B-cells (IgD-CD27+ cell percentage $\leq$2% of B-cells), which is related to an increased need for antibiotic

therapy. Follow-up studies indicate that the incidence of acute pneumonia and otitis will decrease by time [186]. Other infectious respiratory manifestations that are possible but less frequent than the aforementioned ones include mycoplasma pneumonia, cryptococcal lung abscess, and *Mycobacterium avium* complex pulmonary disease [184].

3.8.2 Chronic Lung Disease

Of note, some patients remain refractory to immunoglobulin therapy and continue to suffer from upper respiratory tract infections [181]. These patients are prone to progress to chronic sinusitis and CLD including bronchiectasis. As expected, longitudinal studies show that the prevalence of chronic sinusitis and CLD will increase by time [186]. Studies estimate the prevalence of CLD to be between 22% and 67.5% in patients with CVID [182–184, 186]. In particular, bronchiectasis is found in 37–58% of patients with CVID [181, 182]. Patients who have a positive sputum culture are more likely to demonstrate evidence of bronchiectasis in HRCT [187]. In addition to the pathogens mostly involved in respiratory tract infections including *Streptococcus pneumoniae* and *Haemophilus influenzae*, bronchiectasis has been associated with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Corynebacterium* spp. [182]. A severe defect in total B-cells (CD19+ cell percentage ≤1%) was present in about 40% of patients and was associated with a higher risk of bronchiectasis. In addition, patients with CD4+ cell count below 700 cells/μL, patients with a history of pneumonia, and patients with older age were more prone to bronchiectasis [188].

3.8.3 Lymphocytic Interstitial Lung Disease and Follicular Bronchitis/Bronchiolitis

As reviewed in [189], both profiles of lymphocytic interstitial pneumonia (LIP) and follicular bronchitis/bronchiolitis have been detected in lung tissues from patients with CVID. LIP presents "with a diffuse, interstitial infiltrate of lymphocytes, immunoblasts, plasma cells, fibroblasts, and scattered macrophages that sometimes aggregate into granulomas" [189]. Follicular bronchitis/bronchiolitis is characterized by "reactive lymphoid follicles mainly around airways with minimal interstitial disease" [189]. While LIP has been associated with both hypogammaglobulinemia and hypergammaglobulinemia, follicular bronchitis/bronchiolitis does not appear to have been accompanied by any immunoglobulin abnormalities [189]. Clinical symptoms include cough, dyspnea, fever, and pleuritic chest pain.

The first case of LIP in CVID was described by Levinson et al. [190] and that the first case of nodular lymphoid interstitial pneumonia in CVID was documented by Kohler et al. [191]. Duke et al. also found two other cases with pulmonary infiltration in CXR, which were then histologically diagnosed with LIP [192].

3.8.4 Granulomatous Lung Disease

Generally, granulomatous lesions are found in 5.4–10% of patients with CVID [189]. Noninfectious diffuse lung complications which are collectively referred to granulomatous-lymphocytic interstitial lung disease (GLILD) predict worse survival in patients with CVID [185]. Patients with defects in T-cell function, low CD3+ cell count, and low CD8+ cell count are more likely to develop GLILD. The presence of GLILD has been linked to dyspnea, splenomegaly, restrictive pattern of pulmonary function (a low DL_{CO}), consolidation, ground-glass opacity, interstitial infiltrates, and reticular pulmonary opacification. GLILD in CVID has been associated with a higher prevalence of HHV8 infection, leading to an increased risk of lymphoproliferative disorders [193]. It is promising that monoclonal antibodies and immunosuppressive agents can effectively assist with resolution of granulomas and restoration of lung structure [194]. FDG PET-CT imaging can be used to monitor therapeutic response [194].

3.8.5 Pulmonary Function

The majority of patients in spirometry are normal. About 25% of patients show abnormal features favoring an airflow obstruction and to a lesser extent a restrictive pattern [187]. When compared to patients without bronchiectasis, the spirometry test revealed reduced values of FEV_1, $FEF_{25–75\%}$, and FVC in patients with bronchiectasis [182].

On the contrary, more than 60% of patients have abnormal MMEF. Therefore, there is a large subgroup of patients who are abnormal in MMEF and normal in spirometry [187].

3.8.6 Imaging Findings

HRCT in patients with CVID may provide evidence of granulomatous lung disease, hilar and mediastinal lymphadenopathy, pulmonary nodules, ground-glass opacity, bronchiectasis, and reduced peribronchiectatic shadowing [187, 188]. In particular, patients with bronchiectasis may demonstrate parenchymal scarring, pleural thickening, and atelectasis [182]. Bronchiectasis in patients with CVID has been shown to occur with the involvement of left lower lobe; lingual, right lower lobe; right middle lobe; right upper lobe; multiple lobes; and both lungs [182]. Patients with LIP demonstrate pulmonary infiltration especially basilar, coarse interstitial-alveolar infiltrations in CXR [189]. Patients with ground-glass appearance are more likely to have a high monocyte count, reduced number of CD19 + IgM-IgD-CD27+ isotype-switched memory B-cells, a history of lung disease, and pulmonary nodule(s) and be younger than those with bronchiectasis without interstitial lung disease [188]. Patients who exhibit evidence of bronchiectasis on their CT scan are

more likely to have lower CD4+ T-cell counts [188]. Patients with five or more pulmonary nodules have lower CD8+ T-cell counts [188].

3.8.7 Morbidity and Mortality

Immunoglobulin dose required for prevention of bacterial infections is between 0.2 and 1.2 g/kg/months [195]. A higher dose of replacement immunoglobulin is, however, required to benefit cases with CLD including bronchiectasis [196]. Regular immunoglobulin therapy has shown to be effective in reducing the incidence of acute infections. A study of 50 patients with CVID with pneumonia demonstrated that the prevalence of pneumonia was reduced from 84% to 22% following immunoglobulin therapy [197]. Additionally, immunoglobulin therapy can effectively improve pulmonary function test results and HRCT scores in patients with CVID with CLD [196]. Such improvement does not appear to reach significance in cases with CVID without CLD [196]. Given that the mortality of CVID increases with age, it is not clear whether it can be effective in long term as well as short term. Lung transplant is the option available to patients with respiratory failure. Altogether, acute or chronic respiratory tract infections and associated respiratory failure are a leading cause of morbidity and mortality in patients with CVID [187, 186], especially in cases below 40 years of age [183].

3.9 CD20 Deficiency

It is a humoral immunodeficiency resulting from a homozygous mutation (MS4A1) in a splice junction of the CD20 gene, leading to the production of nonfunctional mRNA species [198]. Despite normal development of antigen-independent B-cells, CD20-deficient mice fail to generate normal antibody response to T-cell-independent antigens. Also, T-cell-dependent humoral immunity is impaired in CD20 deficiency [199]. This is thought to be a secondary effect of the impairment in B-cell function [199].

3.9.1 Potential Mechanisms of Respiratory Manifestations in CD20 Deficiency

CD20 acts as a regulator of B-cell development. It is thus well-understood that chronic administration of anti-CD20 antibodies can lead to B-cell depletion [200]. The effects that CD20 deficiency might have on lung tissues can be tackled in those who received anti-CD20 treatments. As reviewed by [201], anti-CD20 treatments predispose patients to severe and refractory respiratory infections with bacteria, fungi, and viruses, while, anti-CD20 antibodies are being increasingly

used to treat autoimmune diseases and non-Hodgkin lymphoma [202]. This has been parallel by increasing the number of cases of pneumocystis pneumonia [203]. This increased susceptibility might be due to suppressive effect of anti-CD20 antibodies on type 2 helper T (Th2) responses, e.g., production of cytokines interleukin (IL)-4, IL-5, and IL-13 [202]. Moreover, there is a report of antisynthetase syndrome after treatment with rituximab, a CD20 monoclonal antibody [204]. The patient was presented with recurrent respiratory infections, arthropathy, and interstitial pneumonitis. Immunoglobulin replacement therapy was shown to improve immunodeficiency and pneumonitis. It is also interesting that treatment with 25-OH vitamin D3 has been shown to enhance CD20 levels [205].

3.10 Other Monogenic Defects Associated with Hypogammaglobulinemia (ICOS Deficiency, TACI Deficiency, BAFF Receptor Deficiency, TWEAK Deficiency, and NFKB2 Deficiency)

As above explained, CVID is not usually a single-gene disorder but rather is a complex disorder resulting from the combined effect of several genes. Overall, monogenic defects account for just 2–10% of cases with CVID [206].

3.10.1 ICOS Deficiency

The inducible T-cell co-stimulator (ICOS) is shown to stimulate differentiation of T follicular helper (TFH) cells and development of Treg, Th17, and Th2 cells that can promote autoimmunity and local inflammation [207]. In this manner, myeloid cells (CD11+ cells) expressing this co-stimulator can contribute to the generation of inflammatory processes in lung tissues [207]. What more supports this is increased expression of ICOS in autoimmune conditions (acute graft-versus-host disease) and allergic airway diseases [208]. Also, its ligand ICOS-L display by dendritic cells is capable to improve Treg or Th17 responses [209], whose pathogenic roles in autoimmunity and organ rejection have been well-described [210]. ICOS deficiency in mice could diminish lung tissue fibrosis [211] and delay rejection of the transplanted bronchus by reduction of relative numbers of Th17, Th2, and Treg cells [54]. By contrast, lung fibrosis was exacerbated in isolated ICOS-L deficiency and in double ICOS/ICOS-L deficiency [211].

Loss-of-function mutations in the ICOS gene as seen in patients with ICOS deficiency lead to reduce the numbers of TFH cells [212]. It has been demonstrated that intranasal application of Protollin, a TLR4 ligand adjuvant, can play a protective role against allergic lower airway disease upon stimulation with pollen allergen. This TLR4-dependent protection was accompanied by engagement of

CD4+ T-cells expressing ICOS [213]. Additionally, adoptive transfer of CD4+ T-cells expressing ICOS could reverse allergen-induced airway hyper-responsiveness [213]. Whereas, inhibition of TLR4 signaling (TLR4-TRIF pathway) exacerbating allergen-induced airway hyper-responsiveness resulted in a reduction of CD4+ T-cells expressing ICOS [214]. Therefore, ICOS deficiency is expected to increase the risk of allergic airway diseases. As for B-cells expressing CD40, all CVID patients show diminished number of CD4+ T-cells expressing ICOS [215].

As above mentioned, ICOS is also implicated in development of Th2 immunity. Th2 cytokines (IL-5) are essential to the recruitment of eosinophils into the airway [216]. Therefore, it is expected that ICOS-deficient mice exhibit impairment in the generation of antigen-induced airway eosinophilia and inflammation [217]. It should be noted that CD28 also plays a crucial role in this context.

3.10.2 TACI Deficiency

Antiviral antibodies are essential to the generation of antiviral immunity. Animals deficient in transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) were not able to achieve protective titers of antibodies against influenza virus [218]. Even, mice that carried only a single copy of mutation in the TACI gene showed reduction of TACI expression on B-cells and were more susceptible to pneumococcal infections [219]. In this manner, TACI deficiency would predispose the lungs to viral and bacterial infections. TACI deficiency has been observed among patients with PADs who had hypogammaglobulinemia of IgG [220] and IgA [221]. It can cause phenotypes in the spectrum of clinical presentations correlated to CVID or even beyond them, for example, lymphoproliferation and IgG subclass deficiencies [222]. Later in life, it might lead to autoimmune disorders [221, 223].

3.10.3 NFKB2 Deficiency

Germline heterozygous mutations in NFKB2 are known to cause an early-onset type of CVID characterized by B-cell deficiency, T-cell deficiency, hypogammaglobulinemia, central adrenal insufficiency, alopecia totalis or areata, and trachyonychia [224–230]. They can contribute to changes in NK-cell count or function as well. Autoimmunity is present in the majority of patients with NFKB2 deficiency. Other presentations of this immunodeficiency include recurrent respiratory tract infections [228, 231].

Animal studies provide evidence that NFKB2 deficiency can cause serious lung inflammation by inducing the expression IFN-γ and thereby Th1 cytokines. Due to extensive infiltration of lymphocytes, this long inflammation is considered an autoimmune condition that can be potentially fatal [232, 233].

3.10.4 BAFF Receptor Deficiency

B-cell-activating factor of the TNF family (BAFF) emerged as an innate mediator that is involved in antiviral immunity. Upon exposure to viral dsRNA, Ig class switching is induced by TLR3-expressing B-cells of the upper respiratory tract. NFKB activation and TLR3 signaling are central to Ig class switching, which are in turn required for production of IgA and IgG antibodies in response to viral antigens [234]. Patients in intensive care unit (ICU) show increased susceptibility to hospital-acquired pneumonia. This is suggested to be caused by pulmonary IgA deficiency secondary to antibiotic therapy. Patients in this condition often reveal low expression of BAFF [235]. BAFF neutralization in mice has been associated with reduction in the number of antibody-secreting cells (ASC) that contribute to antiviral immunity [218]. Interestingly, immunoglobulin D has been shown to improve immunity in basophils of the upper respiratory tract. Its role is mediated by increasing the expression of pro-inflammatory in addition to B-cell stimulating factors, for example, BAFF [236].

On the other hand, BAFF acts to facilitate the cross talk between IL-1β and Th17 cell development, whereby Th1 and Th17 responses which mainly contribute to inflammatory and autoimmune processes are augmented [237]. Overexpression of BAFF is implicated in lung fibrosis [238], and therefore its inhibition is proposed as a targeted therapy for conditions associated with long fibrosis such as scleroderma [239].

3.10.5 TWEAK Deficiency

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) binding to fibroblast growth factor-inducible 14 (Fn14) leads to activation of intracellular signaling cascades that are likely to contribute to progression of a variety of tumors favorably non-small cell lung cancer (NSCLC) [240].

To the knowledge of the authors, there are not any respiratory manifestations documented as complications of other monogenic defects associated with hypogammaglobulinemia such as MOGS deficiency, TRNT1 deficiency, and TTC37 deficiency.

3.11 Immunoglobulin Class Switch Recombination Deficiencies Affecting B-Cells (AICDA Deficiency, UNG Deficiency, MMR Deficiency, and INO80 Deficiency)

3.11.1 AICDA Deficiency

The activation-induced cytidine deaminase (AICDA) gene encodes the enzyme activation-induced cytidine deaminase (AID) required to CSR in addition to Ig gene somatic hypermutation (SHM) [241]. More importantly, AID plays a crucial role in DNA methylation and reprogramming of somatic cells into induced pluripotent

stem cells (iPSC) [242]. Besides the role of activated B-cell CD40 signaling, bacterial and viral antigens can lead to the expression of AID by engaging IL-4-secreting CD4+ T cells or TLR signaling [241].

Patients with AICDA deficiency often present with lymphoid hyperplasia [243]. Also, they frequently develop sinopulmonary infections (sinusitis and pneumonia), and finally their CT scan may reveal evidences of bronchiectasis [244]. Immunological findings include hypogammaglobulinemia of IgA, IgG, and IgE in addition to hypergammaglobulinemia of IgM [244].

The early clearance is an important component in engendering protective immunity against pneumococci [245]. Mice deficient in AID failed to effectively clear pneumococcal bacteria from pulmonary tissues at early time points [246]. The issue was resolved by adoptive transfer of AID+ B1a cells.

3.11.2 UNG Deficiency

The uracil-DNA glycosylase (UNG) gene encodes a base excision repair (BER) enzyme that functions to exclude misincorporated uracil. Cancerous cells deficient in UNG will develop hypersensitivity to pemetrexed (a chemotherapy drug). On the contrary, lung cancer cells carrying high expression of UNG reveal resistance to pemetrexed [247]. Moreover, it has been shown that viral UNG aids replication and dissemination of murine gammaherpesvirus 68 [248]. It seems that viral UNG expression is induced as a compensatory mechanism to increase UNG activity in host lung cells, which typically express low values of UNG [248]. As for AICDA deficiency, UNG deficiency is characterized with hypergammaglobulinemia of IgM along with hypogammaglobulinemia of other immunoglobulins. Also, lymphoid hyperplasia is commonly seen in patients with this immunodeficiency.

3.11.3 MMR Deficiency

DNA mismatch repair (MMR) is a mechanism of DNA repair conserved during evolution from bacteria to humans. It provides a compensatory pathway for correcting mismatched bases during DNA replication. Therefore, patients with MMR deficiency are prone to genomic instability and ultimately malignant transformation. MMR defects have been discovered in cancers of different primary sites such as the colon, rectum [249, 250], stomach [251], prostate, esophagus, endometrium, oral cavity [252], skin, head and neck, and brain [253]. Due to their role in class switch DNA recombination (CSR) and somatic hypermutation (SHM), MMR components are required for the regulation of antibody response as well [254]. Mice deficient in MMR components exhibit spontaneous development of premalignant and malignant lung lesions [255]. It is consistent with some observations of MMR defects in human lung cancers [256–258]. Moreover, defective mismatch repair system can contribute to chronic lung infection with *Pseudomonas aeruginosa* [259].

3.11.4 INO80 Deficiency

The INO80 ATPase takes part in formation of the ATP-dependent chromatin remodeling complex, which is involved in nuclear transactions, e.g., DNA replication, DNA repair, and transcription [260]. Energy-dependent metabolic pathways are accompanied by increased expression of the INO80 complex. While, defective INO80 complex correlates to decreased glycolysis, increased oxidative stress, and increased oxygen consumption. In this manner, the INO80 complex acts as a regulator of respiratory capacity [261]. On the other hand, INO80 is also generated as a nuclear protein to assist with genome replication of herpes simplex virus [262] and with oncogenic transcription and tumorigenesis of non-small cell lung cancer (NSCLC) [263]. However, study of NSCLC cells has recently revealed that the increased activity of chemotherapeutic agents (cisplatin) is underpinned by increased expression of more than 100 genes among which is INO80 [264].

Two patients with nonsynonymous, compound heterozygous single-nucleotide variants in INO80 have been described in [143]. The first one presented with recurrent bacterial infections at 5 years of age and the second with severe and recurrent respiratory infections at 18 years of age. The second also progressed to chronic obstructive pulmonary disease (of course with a history of 35 years of smoking).

3.12 Transient Hypogammaglobulinemia of Infancy

The physiologic hypogammaglobulinemia is what is typically happening in the first 3–6 months of life. Along with IgG subclass deficiency, partial antibody deficiency with impaired polysaccharide responsiveness, and selective IgA deficiency, transient hypogammaglobulinemia of infancy (THI) is one of the common immune-deficiency conditions of children [265], where the certain period of the physiologic hypogammaglobulinemia is extended. The way to diagnose THI is not straightforward; but its diagnosis requires a retrospective look of the patient characteristics: early hypogammaglobulinemia of at least one immunoglobulin isotype, later achieving normal levels for all immunoglobulin isotypes, and no diagnosis more likely than THI is suspected [266]. Overall, recurrent respiratory tract (pneumonia) infections, ENT (otitis media) infections, bronchitis, and asthma are the most common presentations of THI [267–269]. However, other infectious complications that may affect patients with THI include sinusitis, enteritis, lymphadenitis, meningitis, mastoiditis, impetigo [267], urinary tract infections, and sepsis [266]. Moreover, atopic reactions in THI are common and mainly include bronchial hyperreactivity, food allergy, and atopic dermatitis [266]. Study of a single center in Jordan estimated that the average age of onset and diagnosis for THI ($n = 10$) are 1 and 1.6 years [267]. So the diagnostic delay was less than 1 year [267]. In other studies from Turkey and the United States, the mean age of onset was less than 1 year of age [266, 270]. Often it is spontaneously resolved by 3–5 years of age [270], and more than 90% of patients achieve normal immunoglobulin levels by 10 years of age. However, some patients continue to have hypogammaglobulinemia, the so-called

undefined/unclassified hypogammaglobulinemia. Of note is that both conditions, i.e., THI and undefined/unclassified hypogammaglobulinemia, share common clinical characteristics [268]. However, patients with persistent antibody deficiency are less able to produce IgA responses against pneumococcal polysaccharide (PnPS) vaccine compared to patients with transient antibody deficiency [271].

3.12.1 Respiratory Tract Infections

Infections affecting the upper and lower respiratory tract are commonly seen among patients with THI. Overall patients with THI have a benign clinical outcome [272]. They usually do not develop life-threatening infections [269] requiring long-term immunoglobulin replacement therapy [267]. Immediate treatment is, however, indicated in severe respiratory tract infections. Also, additional treatments may be warranted according to the type and severity of infection. For example, extracorporeal membrane oxygenation (ECMO), ribavirin, and steroid (albeit along with immunoglobulin replacement therapy) benefited a THI case with severe human parainfluenza viruses (HPIVs) [273]. Moreover there are reports of *Pneumocystis carinii* pneumonia in patients with THI [274–276]. It is a life-threatening infection [277], and despite high rates of drug adverse reactions, drug therapy should be started once the diagnosis of *Pneumocystis carinii* pneumonia is suspected.

3.12.2 Asthma

Studies estimate that about 27–55% of patients with THI suffer from asthma [268, 269]. The history of recurrent upper respiratory tract infections showed a negative association to asthma. Whereas, patients with THI who had history of recurrent lower respiratory tract infections were more likely to suffer from asthma [268].

3.12.3 Potential Mechanisms of Respiratory Manifestations in Transient Hypogammaglobulinemia of Infancy

Patients with THI are categorized into three according to their initial immunoglobulin levels: isolated IgG deficiency, isolated IgA deficiency, isolated IgM deficiency, IgG and IgA deficiency, IgG and IgM deficiency, and IgG, IgA, and IgM deficiency. The majority of patients show IgG and IgA deficiency [266], whereas isolated deficiency of IgA or IgM are relatively rare in patients with THI [269]. It has been well-appreciated that hypogammaglobulinemia either in primary immunodeficiency

disorders or secondary to other conditions (malignancies and immunosuppressive drugs) increases the risk of infections.

It has been shown that antibody response to specific respiratory viral antigens (influenzas A and B, adenovirus, mycoplasma, respiratory syncytial virus, and parainfluenzas 1, 2, and 3) is more likely to be impaired in patients with THI than in age-matched controls without THI [270]. This is reflected in increased risk of viral infections in these patients.

3.13 Selective IgA Deficiency

Selective IgA deficiency (SIgAD) is the most common PID where B-cell switching to IgA-producing cells is impaired [278]. For children aged 1–18 years with recurrent infections and warning signs of immunodeficiency, it is the most commonly diagnosed disease [279]. Compared to other PIDs, patients with SIgAD appear to less prone to lower respiratory tract infection, sepsis, skin infections, mucocutaneous candidiasis, dental alterations, cardiovascular malformations, angioedema, hospitalizations, and death [280]. The world's epidemiology data indicate that the incidence of SIgAD varies by a family history of SIgAD and ethnicity ranging from 1:18,500 in Japan to 1:143 in the Arabian Peninsula [278, 281]. Intrinsic factors causing IgA deficiency include both monogenic mutations (TNFRSF13B/TACI) [282, 283, 220] and chromosomal abnormalities mainly involving chromosome 18 [278, 1]. SIgAD is indicated by low levels of serum IgA (below 7 mg/dl) in presence of normal levels of IgG and IgM after the age of 4 years in whom other causes of hypogammaglobulinemia have not been identified. Clinical presentations may range from asymptomatic to clinically overt complications including recurrent sinopulmonary infections [284], autoimmune diseases [285], allergies, atopic disorders [286], gastrointestinal disorders, and malignancies [278]. Fortunately, about 65–90% of patients with SIgAD are asymptomatic [1, 287]. Only the minority of patients suffer from severe disease. They are those who may progress to CVID at later time points [278]. Follow-up study reveals that unlike patients with partial IgA deficiency and patients with partial IgA + IgG subclass deficiency, patients with selective IgA deficiency never can achieve normal levels of IgA during study [288]. This indicates the importance of periodic monitoring in these patients.

After IgG, IgA is the second most abundant immunoglobulin in the blood circulation [281]. It is secreted into the circulation and mucosal secretions. Two subclasses of IgA are present in humans: IgA1 and IgA2. Circulating IgA which is mainly comprised of IgA1 (80–90%) may help to regulate immune response via activation of the phagocyte system and inhibition of neutrophil chemotaxis. Mucosal secretions mainly include IgA2, which is more resistant to bacterial proteases present in the respiratory and gastrointestinal tract than IgA1. Secretory IgA contributes

to the coating of mucosa-associated bacteria and therefore plays an important role to prevent penetration of bacteria into the mucosa. In addition, patients with SIgAD demonstrated altered cytokine/chemokine system in terms of increased levels of CXCL10/IP-10, IL-10, and G-CSF and decreased levels of IL-9 and IL-12 (p70) [289]. In this manner, SIgAD is regarded as a risk factor of recurrent respiratory infections and bronchial hyper-responsiveness [290].

About 40–90% of patients with symptomatic SIgAD report recurrent sinopulmonary infections as the most important manifestations leading to diagnosis of SIgAD. In particular, adults with SIgAD are more prone to upper respiratory tract infections (e.g., infectious conjunctivitis, common viral cold, pharyngitis, and laryngitis) and lower respiratory tract infections (e.g., bronchitis and pneumonia) [287]. Overall, the main pathogens involved are encapsulated bacteria including *Haemophilus influenzae* and *Streptococcus pneumoniae*. Bronchiectasis and obliterative bronchiolitis represent the most severe respiratory conditions experienced by patients with SIgAD. Studies demonstrate that deficiency of any of IgG subclasses is also present in about 20% of patients with SIgAD [291], rendering them more susceptible to sinopulmonary infections and respiratory insufficiency [292]. Moreover, patients with a low percentage of switched memory B-cells have a higher incidence of pneumonia and bronchiectasis compared to patients with a high percentage of switched memory B-cells [293]. On the contrary, an increased number of IgM-producing B-cells as a compensatory mechanism are commonly found in SIgAD. Because of the functional overlap between IgA and IgM, high levels of secretory IgM may protect patients against infections and help to maintain them asymptomatic [281]. When compared to controls without SIgAD, adults with SIgAD are more likely to be diagnosed with allergic rhinoconjunctivitis, but not asthma [287].

Rarely, SIgAD has been observed concurrent with other respiratory conditions including severe asthma, chronic granulomatous disease [294–296], chronic pulmonary aspergillosis [297], tracheobronchopathia osteochondroplastica [298], pulmonary nodules, disseminated cat-scratch disease [299], pleuropulmonary blastoma [300, 301], eosinophilic pneumonia [302], cryptococcal pneumonia [303], and idiopathic pulmonary hemosiderosis [304]. Also, SIgAD can mimic Churg-Strauss syndrome and hypereosinophilic syndrome [302].

As reviewed in [278], the management of patients with SIgAD includes education and periodic monitoring (every 4–6 months), treatment of allergic and autoimmune disorders, prophylactic antibiotics (especially for patients with chronic and recurrent sinopulmonary infections), pneumococcal vaccine (especially for patients with IgG subclass deficiency), and intravenous or subcutaneous immunoglobulin replacement therapy (especially for patients with recurrent infections). Immunoglobulin products low in IgA that can be administered to those patients include lyophilized Gammagard, Gammaplex, Vigam, Iveegam, Polygam, and Nanogam with IgA <10 mg/ml. Also lobectomy can be considered in cases of bronchiectasis [305]. Monoclonal antibodies such as rituximab (anti-CD20) might be effective in treating autoimmune disorders associated with SIgAD such as autoimmune thrombocytopenia [296].

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