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Pulmonary Radiological Manifestations of Humoral and Combined Immunodeficiencies in a Tertiary Pediatric Center

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ABSTRACT

Respiratory diseases are considered as significant causes of morbidity and mortality in primary immunodeficiencies. This study aimed to reveal the radiologic patterns of thoracic involvement in these disorders.

A total of 58 patients, including 38 cases with combined cellular-humoral and 20 cases with humoral immunodeficiencies, were enrolled in this study. The "combined" group consisted of 12 cases with severe combined immunodeficiency (SCID) and 26 cases with combined immunodeficiency. The "humoral" group included seven patients with Hyper IgM syndrome (HIGMs), seven cases with common variable immunodeficiency (CVID), three patients with X-linked agammaglobulinemia, and three patients with other types of humoral primary immunodeficiencies (PIDs). The mean age of patients at the time of evaluation was 3.3±3.8 and 5.3±3.9 years in combined and humoral groups, respectively. The findings of chest X-rays and CT scans were interpreted and compared.

There was a significant difference for alveolar opacification between combined and humoral immunodeficiencies (58% vs. 30%). The bronchopneumonia-like pattern was detected as a significant finding in patients with SCID (42%) and HIGMs (43%). Atrophy of the thymus was detected significantly often in cases of SCID (67%). Two patients with CVID and lipopolysaccharide-responsive and beige-like anchor protein deficiency showed parenchymal changes of granulomatous lymphocytic interstitial lung disease. No significant difference was detected for bronchiectasis, bronchitis/bronchiolitis patterns, pleural effusion, and thoracic lymphadenopathy. lymphadenopathy.

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Distinct subtypes of primary immunodeficiency may provoke differing and comparable radiological patterns of thoracic involvement; which can clue the clinician and radiologist to the diagnosis of the disease.

Keywords: Lung; Pediatrics; Primary immunodeficiency diseases

INTRODUCTION

Primary immunodeficiencies (PIDs) are a heterogeneous, wide-spectrum group of 354 distinct disorders[1] with a variable spectrum of clinical manifestations. PIDs are characterized by the reduced, missing, or improper functioning of one or more immune components that affect the development and function of the immune system.[2,3] Respiratory disease is a significant cause of morbidity and mortality in these disorders.[4] Medical imaging, including chest X-rays and computed tomography (CT) scanning, play a significant role in the multidisciplinary approach to these conditions.[4,5] CT scanning is superior to chest radiography and is considered a key imaging tool in quantifying the extent of thoracic involvement and monitoring the response to treatment.[6] The most common characteristic of radiographic and CT abnormalities are noninfectious airway disorders, infections, chronic lung diseases, chronic inflammatory conditions (granulomatosis, interstitial pneumonia), and neoplasms.[5]

Since early diagnosis is associated with improved prognosis, this study aims to delineate and categorize the radiologic patterns of thoracic involvement in PIDs, which may lead clinicians and radiologists to suspect PID and subtypes of the disorder.

MATERIALS AND METHODS

Study Design and Patients

This is a retrospective descriptive-analytical study carried out on all patients with primary humoral or combined cellular-humoral immune deficiencies (38 with combined immunodeficiency syndrome and 20 with humoral immunodeficiencies) admitted to Mofid Children's Hospital, from 2011 to 2017. The study was approved by the Ethics Committee of Shahid Beheshti Medical University with the registration number of IR.SBMU.MSP.REC.1397.101. Formal consent was obtained from parents or caregivers. All the information was confidential, and all the appropriate measures were taken to ensure patient confidentiality. Definitive diagnoses of primary immunodeficiency were made based on clinical diagnostic criteria and laboratory workup by a clinical immunologist following IUIS report guidelines[1] and European Society for Immunodeficiencies (ESID) criteria. The para-clinical evaluation in this study, including the radiological workup, was part of patients' clinical evaluations with clinical indications. Therefore, no unnecessary investigations were performed for these patients. Patients with incomplete records, without imaging studies, or with a history of bone marrow transplantation were excluded from the study.

Radiologic Assessment

All imaging modalities, including plain chest radiography (CXR) and CT scans (with and without contrast) and their relevant reports, were reviewed by a panel of authors. All patients underwent CXR due to clinical indications. CT scan imaging was requested wherever it was necessary for the diagnosis and treatment of the underlying disease. The presence of alveolar airspace opacities, pleural effusions, hilar and mediastinal adenopathy, thymus atrophy, bronchiectasis, and cavitary lesions was recorded. Alveolar airway opacification was further evaluated in two distinct patterns: bronchopneumonia-like (defined as the multiple bilateral, patchy opacification of secondary lung lobules) and consolidation (defined as lobar or sublobar airspace opacification). Bronchitis/bronchiolitis pattern was also defined as bronchial wall thickening, bronchiolar dilation, centrilobular peribronchial micronodules, and mosaic attenuation or air trapping.[7] Then, the prevalence and the distribution pattern of these imaging findings in patients with cellular and humoral PID were compared.

Statistical Analysis

Data analysis was performed using SPSS version 24. Comparisons between quantitative data, such as the prevalence and distribution of patterns, were performed. Nominal qualitative data, including sex, was also analyzed. The collected data are presented as tables and diagrams.

Table 1. Frequency of abnormal imaging findings in humoral and combined immunodeficiencies; PID: primary immune deficiency, n: number of affected patients in each group

	Combined PID n (%)	Humoral PID n (%)	*p*
Alveolar Airspace Opacification	22 (%58)	6 (%30)	**0.04**
Lobar/Sublobar Consolidations	16 (%42)	3 (%15)	0.08
Bronchopneumonia-like Pattern	6 (%16)	3 (%15)	0.623
Pleural Effusion	12 (%32)	2 (%10)	0.06
Bronchitis/Bronchiolitis Pattern	11 (%29)	5 (%25)	0.50
Lymphadenopathy	11 (%29)	6 (%30)	0.58
Bronchiectasis	4 (%10.5)	3 (%15)	0.457
Atrophy of Thymus	8 (%21)	3 (%15)	0.428

RESULTS

Fifty-eight patients were enrolled in this study, of whom 38 had combined immunodeficiency syndrome and 20 had humoral immunodeficiencies. The "combined" group consisted of 12 cases with severe combined immunodeficiency (SCID) and 26 cases with combined immunodeficiency (CID). The "humoral" group included seven patients with hyper IgM syndrome (HIGMs), seven cases with common variable immunodeficiency (CVID), three patients with X-linked agammaglobulinemia (XLA), and three patients with other types of humoral PIDs. The mean ± SD age of patients at the time of evaluation was 3.3 ±3.8 years among the patients with combined immunodeficiencies and 5.3±3.9 years among the patients with humoral immunodeficiencies, which did not represent a significant difference (p = 0.075).

All of the patients in both groups had CXR, and 33 cases underwent CT imaging (22/38 in the combined group and 11/20 in the humoral group). Positive imaging findings were detected in 82% and 70% of CXR in the combined and humoral groups, respectively (p= 0.10). Also, 91% of CT scans in each of the combined and humoral groups had positive findings (p= 0.95).

Table 1 provides a summary of the imaging findings considering both CXR and CT modalities in patients with combined and humoral immunodeficiencies, with their frequencies given as percentages.

There was a significant difference for alveolar opacification in combined PIDs in comparison with humoral immunodeficiencies (p=0.04). There was a considerable difference in terms of the frequency of lobar/sublobar consolidations (Figure 1A) and pleural effusion between humoral and combined immunodeficiencies. However, the difference did not indicate statistical significance (p=0.08 and p=0.06, respectively).

The bronchopneumonia-like pattern was detected in 42% of SCID, 43% of HIGMs, and 4% of CID cases; which indicates this pattern is a significant finding (p=0.01) in patients with SCID and HIGMs, when compared to patients with other types of combined or humoral immunodeficiencies. The bronchopneumonia-like pattern in a SCID patient is shown in Figure 1B.

Thymus atrophy was detected most frequently in SCID patients (8/12; 67%) (Figure 1C) followed by CVID patients (1/7; 14%), HIGMs (1/7; 14%), and CID patients (1/26; 4%). Atrophy of the thymus was detected significantly often in cases of SCID (p=0.001).

No significant difference was detected between bronchitis/bronchiolitis (Figure 1D and 1E) and thoracic lymphadenopathy in patients with either humoral or combined cellular-humoral immunodeficiencies. Bronchiolitis was found in 25 to 29% of cases in the two groups without significant difference between them (p=0.50).

The frequency of bronchiectasis (Figure 1F) was compared in patients with humoral and combined immunodeficiencies (Table 1). There was no significant difference between these two groups of patients regarding the development of bronchiectasis (p=0.457). Figure 2 demonstrates the frequency of bronchiectasis among distinct primary immunodeficiencies in the studied patients.

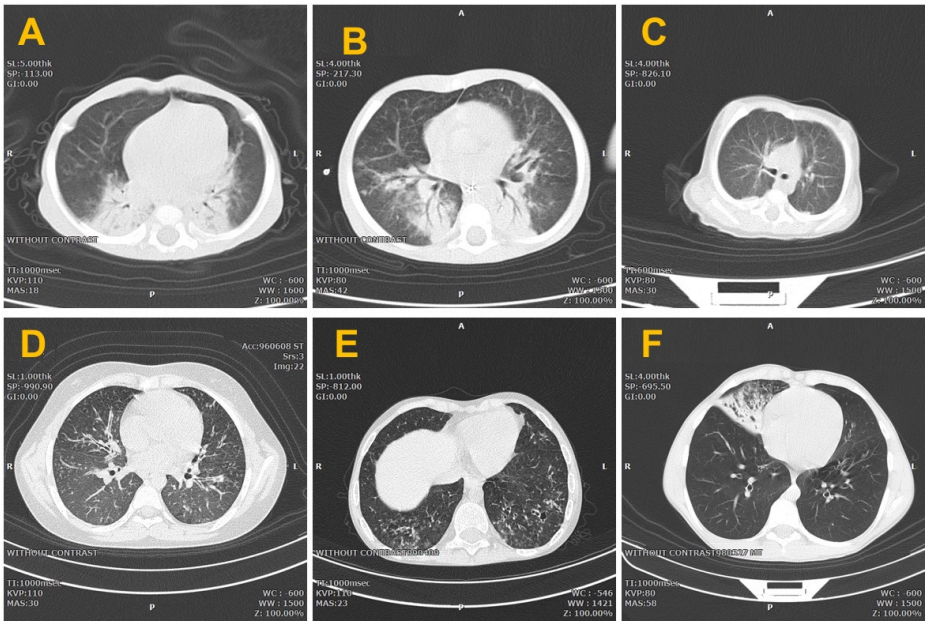

Figure 1. Variable patterns of pulmonary involvement in primary immunodeficiencies. (A) a 12-months male infant with SCID, with bilateral airspace consolidations and air-bronchogram in right and left lower lobes of lungs. (B) 11-months male infant with SCID and bronchopneumonia-like pattern: bilateral segmental airspace consolidations in lower lung fields, and multiple patches of peribronchial airspace opacification. (C) a 24-months female toddler with SCID; with atrophy of the thymus gland. (D) a 12 y/o female with CID and bronchitis/bronchiolitis pattern: bronchial wall thickening, tiny ill-defined peribronchial nodules, and subtle mosaic attenuation. (E) a 15 y/o male with CVID and bronchitis/bronchiolitis pattern: subtle bronchial wall thickening and bronchiolar dilatations, and ill-defined peri-bronchial nodular opacities. (F) a 15 y/o male adolescent with CID; with airspace consolidations and bronchiectasis in the right middle lobe of the lung. SCID: severe combined immunodeficiency, CID: combined immunodeficiency, CVID: common variable immunodeficiency

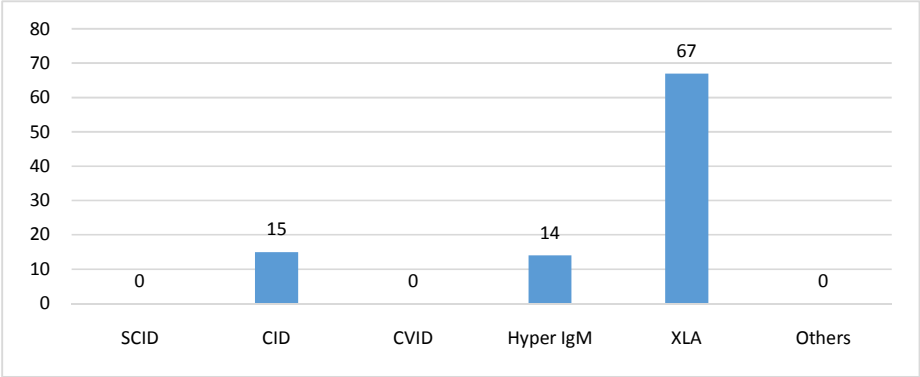

Figure 2. Prevalence of bronchiectasis among distinct primary immunodeficiencies, values are presented as percentages; SCID: severe combined immunodeficiency, CID: combined immunodeficiency, CVID: common variable immunodeficiency, XLA: X-linked agammaglobulinemia.

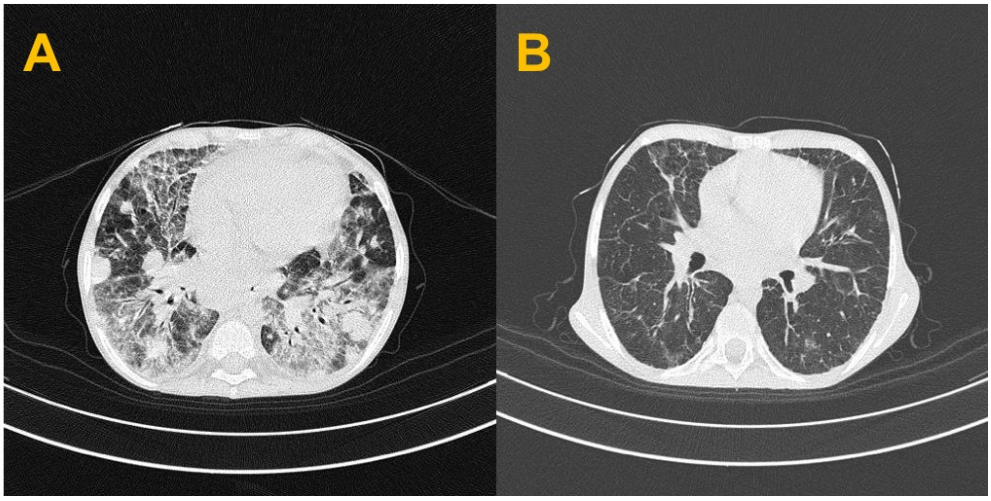

Figure 3. Granulomatous lymphocytic interstitial lung disease (GLILD) in a patient with common variable immunodeficiency (CVID) and lipopolysaccharides responsive beige-like anchor protein (LRBA) deficiency before treatment (A) and after successful treatment (B).

Three patients with CID (11.5%) revealed pulmonary cavitary changes due to necrotizing pneumonia or pulmonary abscesses in the lower zones of the lung fields (i.e., the left and right lower lobes and right middle lobe).

Two patients with CVID and associated lipopolysaccharide responsive beige-like anchor protein (LRBA) deficiency showed parenchymal modifications, including nodular opacities and increased interlobular and axial septal thickness with secondary lobule opacification. Pathological evaluations suggested the incidence of granulomatous lymphocytic interstitial lung disease (GLILD). Figure 3 illustrates GLILD in one patient with CVID and LRBA deficiency before (3A) and after (3B) treatment.

DISCUSSION

Primary immunodeficiency disorders comprise a spectrum of diseases that are sometimes associated with a delay in diagnosis. The main initial manifestation of the majority of patients with PIDs is respiratory symptoms.[8-11] The purpose of this study was to determine the diagnostic and discriminative values of distinct radiologic patterns of thoracic involvement in various subtypes of PIDs.

In the present study, nearly twice as many patients had combined PIDs in comparison to patients with humoral PID, which contrasts with the general dominance of humoral immunodeficiencies. However, this can be explained by the earlier onset of the cellular immunodeficiencies and, therefore, younger age at referral for these patients to this tertiary center when compared to patients with humoral immunodeficiencies who were generally referred at a later age at the onset of their initial manifestations.

Bondioni et al. reported thoracic changes in 60% of the patients in their study with bronchiectasis as the most frequent and important finding.[12] In the present study, the thoracic manifestations detected were not discriminative for either group. Martinez et al.[13] and Membrila-Mondragon et al.[14] also described bronchiectasis as the most common finding in their studies, followed by interstitial damage and pulmonary fibrosis.

Considering that a range of PIDs (mostly humoral immunodeficiencies) could predispose a patient to recurrent respiratory tract infections and lead to the development of bronchiectasis,[15] we could not find a significant difference (p=0.457) between patients with humoral PIDs and patients with combined PIDs. This could be explained by the young age of the patients and the insufficient time for the development of this complication in the pediatric age group due to the short follow-up duration after the diagnosis of primary immunodeficiency in this study. On the other hand, our center is a children's hospital.

In this study, some radiological findings were detected more often in a specific group of primary immunodeficiencies; thymus atrophy was frequent in

patients with SCID, the bronchopneumonia-like pattern was frequent in patients with SCID and hyper IgM syndrome, pulmonary cavitary lesions were frequent in patients with CID, and bronchiectasis was frequent in patients with X-linked agammaglobulinemia, hyper IgM syndrome, and combined immunodeficiency.

Also, two different specific patterns of alveolar opacification were presented: lobar/sublobar consolidations and a bronchopneumonia-like pattern. Most bacterial pneumonia cases are exemplified by streptococcus in a consolidation-predominant pattern.[16] In this study, patients with humoral immunodeficiencies, in whom the pathogenic organisms are mainly capsulated, appeared in consolidation and bronchopneumonia-like patterns at an equal frequency (15%). Interestingly, in contrast to previous studies, our patients with combined PIDs showed a higher occurrence of the consolidation-predominant pattern (42%) than the bronchopneumonia-like pattern (16%), which is generally expected in opportunistic infections, including viral and fungal infections.[17]

GLILD is a distinctive manifestation of CVID characterized by a combination of granulomatous and lymphoproliferative interstitial features.[18] Hurst et al. suggested that although the diagnosis of GLILD requires the discovery of new abnormalities in chest imaging, no radiological findings are considered sufficiently diagnostic to avoid the need for biopsy.[19] Common chest findings in GLILD include multifocal air space consolidation, smooth thickening of the interlobular septa, widespread centrilobular micronodules, mediastinal and hilar lymphadenopathies, bronchiectasis, patchy bilateral ground-glass opacities, and air trapping.[17] In the present study, GLILD was suspected in CT scans of two patients with LRBA deficiency from two different pedigrees with typical findings including nodular lesions, increased septal thickness, and mediastinal lymphadenopathies, which was later confirmed with histopathological evaluation. These findings were consistent with the studies of Hurst et al.[19] and Ohshimo et al,[20] with a suggested incidence of GLILD in 8 to 22% of patients with CVID. The lower incidence of GLILD in this study was attributed to the relatively small number of patients with CVID, as GLILD may develop in approximately 20% of such patients.[21]

The main limitation of this study was its small sample size. Also, all studied patients had CXR, but only 33/58 (56%) underwent CT imaging. Indeed, CT imaging was required under clinical indications, and due to the increased risk of malignancy in some immunodeficient patients, no unnecessary imaging was done. However, some pulmonary pathology might be missed due to the lower sensitivity of the CXR modality in patients who were not evaluated by CT imaging. The low prevalence of immunodeficiencies necessitates multi-centered studies so that the sample size can be large enough to yield an accurate analysis and description of the condition.

Imaging is an important tool in the initial multidisciplinary approach when assessing patients with primary immunodeficiencies. Radiologists should be aware of common radiological manifestations of primary immunodeficiencies and their pulmonary patterns of involvement.

CONFLICT OF INTEREST

The authors disclose no personal and financial support or commercial associations that might create a conflict of interest in connection with the submitted manuscript.

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