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The Radiological Manifestations of Phagocytic Primary Immunodeficiencies in Children

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ABSTRACT

Primary immunodeficiencies are a diverse group of rare genetic disorders, among which phagocytic dysfunction impairs neutrophil function in a wide range of inherited disorders. Due to the heterogeneity of the disorders, a multidisciplinary approach is often required for early diagnosis and initiation of appropriate treatments. The aim of this study was to evaluate the imaging findings in children admitted with phagocytic primary immunodeficiencies.

Thirty-five children who fulfilled the inclusion criteria for phagocytic dysfunction were enrolled in this study. The patients were under close observation and monitoring from January 2011 until data locking in December 2017. The diagnosis of phagocytic immunodeficiency was confirmed by the patient's clinical course, presentation features, and laboratory data.

Among the 35 patients studied, the most frequent condition was chronic granulomatous disease (CGD) (23 patients), followed by different types of neutropenia (8 patients) and Job's syndrome (4 patients). Mediastinal and hilar lymphadenopathies and consolidation were the most frequent presentations. There was a significant relationship between mediastinal/hilar lymphadenopathies and fungal infections. A meaningful relationship was also found between pulmonary nodules without halo signs in patients with concomitant tuberculosis and fungal infections. A significant correlation was found between CGD, pulmonary fibrotic changes, and mediastinal lymphadenopathies.

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Imaging in Phagocytic Primary Immunodeficiencies

The most frequent radiological manifestations in children included mediastinal and hilar consolidations. Physicians' awareness of the radiological and clinical manifestations of these inherited diseases may be helpful in the early diagnosis and timely initiation of specific prophylaxis measures to prevent infections and also to initiate hematopoietic stem cell transplantation as the curative management modality.

Keywords: Chronic granulomatous disease; Lymphadenopathy; Phagocytic bactericidal dysfunction

INTRODUCTION

Primary immune deficiencies are genetic defects that impair the development or function of the immune system, affecting distinct components of the innate and adaptive immune systems and leading to impaired relationships between host and pathogenic agents.[1] Due to the heterogeneity of the disorders and their clinical manifestations and involvement of different organs, a multidisciplinary approach is often required for early diagnosis and the initiation of appropriate treatments.[2,3]

Phagocytic dysfunction, comprising 10% to 15% of primary immunodeficiencies,[4] impairs neutrophil function in a wide range of inherited disorders, with leukocyte adhesion deficiency (LAD), chronic granulomatous disorder (CGD), congenital neutropenia, and Chediac-Higashi syndrome as the most well-known ones.[5] Significant susceptibility to infections may lead to recurrent pneumonia and abscesses in these disorders. Pulmonary complications of phagocytic immunodeficiencies include recurrent pulmonary infections, especially necrotizing pneumonia, lung abscesses, and empyema with bacterial and fungal organisms, including *Staphylococcus aureus*, *Klebsiella*, *Burkholderia cepacia*, *Serratia marcescens*, *Aspergillus*, and *Nocardia*.[4] Failure of phagocyte migration (e.g., in LAD) and impaired intracellular killing of bacteria (e.g., in CGD) may also predispose to bronchiectasis as a long-term pulmonary complication, although with a weak association.[5] Bronchiectasis has been reported in patients with CGD, even in pediatric cases.[6,7] In addition, chest radiographs or computed tomography (CT) may demonstrate chronic or recurrent pneumonia, pleural reaction, osteomyelitis from chest wall invasion, hilar or mediastinal lymphadenopathies, and pulmonary nodules.[8]

The aim of this study is to evaluate the pulmonary radiological manifestations of primary phagocytic immune deficiencies, with a particular interest in CGD in children referring to the immunodeficiency clinic of Mofid Children Hospital, Tehran, Iran.

PATIENTS AND METHODS

Patients

Thirty-five children who fulfilled the inclusion criteria for phagocytic dysfunction were enrolled in this descriptive cross-sectional study. The patients were closely monitored from January 2011 until data locking in December 2017.

Phagocytic immunodeficiencies were confirmed by reviewing their presentation, laboratory data, and clinical courses. Patients with underlying pulmonary defects, unavailable diagnostic imaging, or incomplete records were excluded from the study.

Study Design

This research is a descriptive cross-sectional study. Therefore, the clinical features of all of the patients were observed, and the basic immunological functions were evaluated. Then, the current reports of the children's images were approved by 2 radiologists, and finally, the interpretations were confirmed by an expert professor of radiology at the Research Board of Mofid Children's Hospital. The interpreted imaging modalities included plain chest radiographs, computed tomography (CT) and magnetic resonance imaging (MRI) scans according to the patients' clinical manifestations at the time of admission. A checklist consisting of demographic and clinical information, including age, sex, and the specific diagnosis, was completed for each patient. Their radiological findings were interpreted and compared according to their specific types of immunodeficiencies.

Immunological Work-up

The routine evaluation of immunological function involved complete blood counts, analysis of lymphocyte

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subsets, the detection of immunoglobulin (Ig) G, IgA, IgM, IgE, and complements C3, C4, and CH50, and the analysis of NADPH oxidase activity in neutrophils.

Lymphocyte subsets

were analyzed using anti-CD3, CD4, CD8, CD16, CD56, and CD19 antibodies. The levels of IgG, IgA, IgM, C3, and C4 were detected by nephelometry. The respiratory burst of neutrophils was determined by measuring hydrogen peroxide production using nitroblue tetrazolium and dihydrorhodamine analysis.

RESULTS

The patients included 18 girls (51.4%) and 17 boys (48.6%). The mean age of the patients was 9.2 years (SD, 4.6 years) at the time of the radiologic evaluation.

Figure 1-A demonstrates the distribution of different disorders characterized by the type of phagocytic immunodeficiency.

Figure 1-B shows the distribution of different infections in the evaluated patients in this study.

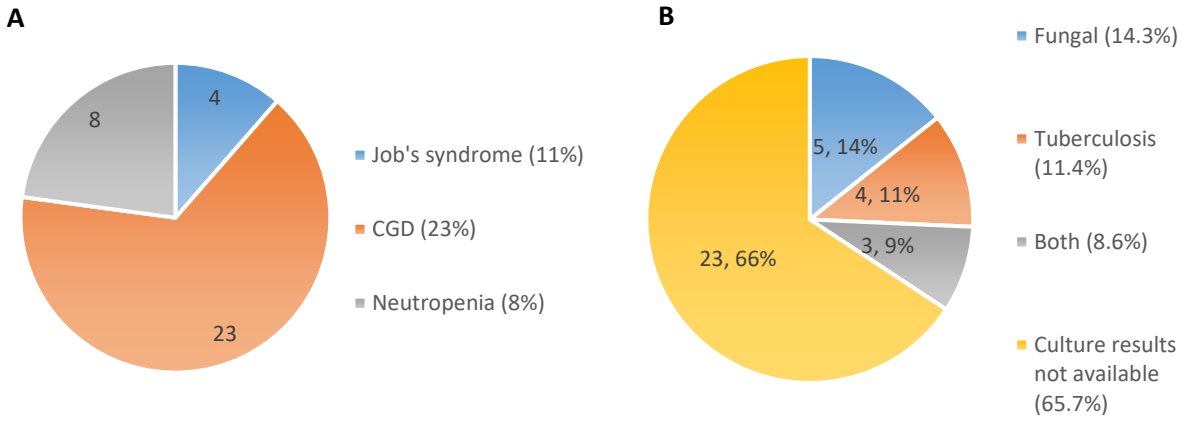

Figure 1. Pie chart. Distribution of different phagocytic immunodeficiencies (A) and different types of infections (B) among the patients. CGD: chronic granulomatous disease.

Tuberculosis and fungal infections were detected only in 12 of the patients. There were no documented isolated microorganisms in the remaining 23 patients. Among phagocytic immunodeficiencies assessed in this study, osteomyelitis of the rib was only found in CGD, as the most common presentation in 26.1% of the cases, followed by osteomyelitis of long bones (8.7%) and short bones (8.7%), spondylodiscitis (8.7%), and muscular abscess (8.7%) as the other musculoskeletal manifestations with lower frequencies.

Fungal and *Mycobacterium tuberculosis* infections were detected in 40% and 50% of the patients with rib osteomyelitis, respectively. Of those, 66.7% showed both infections concurrently. Table 1 demonstrates pulmonary imaging findings according to the isolated infectious microorganisms.

Fungal infections were significantly associated with mediastinal and hilar lymphadenopathy (p<0.023). Pulmonary nodules without the halo sign also showed a significant correlation with concurrent tuberculosis and fungal infections (p<0.014). In addition, CGD had a significant statistical association with both pulmonary fibrotic changes and mediastinal lymphadenopathies (p<0.042 and p<0.001, respectively).

A p value of 0.015 was detected in CGD patients who showed pulmonary nodules (without a halo sign) in their lung CT scans.

In patients with Job's syndrome, there was a meaningful association with lung abscess (p=0.019).

Table 1. Pulmonary imaging findings according to isolated microorganisms.

Imaging Findings	Percentage of patients showing radiologic manifestations with specific types of infections			
	Fungal	Tuberculosis	Fungal and tuberculosis	No organism isolated
Consolidation	60%	50%	33.3%	13%
Pleural manifestation	20%	0%	100%	8.7%
Satellite/galaxy sign	40%	25%	33.3%	4.3%
Fibrotic changes	20%	25%	66.7%	21.7%
Fibrosing mediastinitis	20%	25%	33.3%	0%
Necrotizing pneumonia	20%	50%	33.3%	4.3%
Peribronchovascular bundle thickening	20%	0%	0%	4.3%
Mediastinal/hilar lymphadenopathies	100%	75%	100%	39.1%
Pulmonary abscess	0%	0%	0%	4.3%
Enlargement of central pulmonary artery	20%	0%	33.3%	8.7%

DISCUSSION

Primary defects of neutrophil function with particular susceptibility to *S aureus*, *Nocardia*, *Aspergillus*, and *Candida* species and also specific defects in phagocytic function leading to increased intracellular infections such as *Mycobacteria*, *Histoplasma*, *Listeria*, and *Salmonella* species[9] are associated with aberrant inflammatory responses that may cause chronic sequelae even in children. In view of the fact that the lung is one of the most common sites of involvement with various manifestations in phagocytic immunodeficiencies,[10] this study aimed to evaluate the radiographic and CT scan findings of the chest in these children with a particular focus on CGD.

The findings of the current study were in line with another study recently performed by Kashani et al.[11] on radiographic manifestations in patients with CGD, where hilar lymphadenopathy was the most common presentation. Cavitating lesions, lung abscesses, pulmonary nodules, and pleuritic nodules were other lung complications in Kashani's study, indicating that any combination of pulmonary nodules, abscesses, cavitation, or hilar lymphadenopathy in an individual is suggestive of underlying immunodeficiency.[11] The imaging findings of our study, detailed in Table 1, were compatible with the aforementioned findings. Likewise, mediastinal and hilar lymphadenopathies were also common in another study by Yao et al.,[10] although pulmonary nodules were the most common in that study.

Fungal infections are variably implicated in causing infections in patients with phagocytic primary immune deficiencies.[12] Invasive aspergillosis has been the leading cause of mortality in CGD,[13,14] mostly affecting the lungs.[15] Our findings were also indicative of fungal infections in 14.3% of the patients with a pathogen being isolated. *M tuberculosis* was the next intracellular microorganism isolated in this study, accounting for 11.4% of cases. Susceptibility to mycobacterial infections is variable in different primary immunodeficiencies due to the involvement of distinct pathophysiological mechanisms as well as the patients' living area.[14] Since tuberculosis is highly endemic in Iran, routine Bacillus Calmette-Guerin (BCG) immunization is administered during the neonatal period. This may explain the high rate of this intracellular infection in our patients with phagocytic immunodeficiency. However, in the majority of the cases in the present study, no microorganism could be isolated, which could be attributed to technical defects. These findings were consistent with intracellular bacterial killing defects in primary phagocytic

immunodeficiencies leading to fungal infections in the majority of cases (p<0.002).

Osteomyelitis has been described in defects of neutrophil differentiation, motility, respiratory burst, and Mendelian susceptibility to mycobacterial disease.[16] Bone infections may involve the spine in primary immunodeficiencies, particularly due to fungal infections spreading from the lungs. There are reports of osteomyelitis in the literature with cyclic neutropenia,[17] LADs,[18-20] and X-linked CGD.[21-24] Osteomyelitis has been a common finding in CGD occurring in 25% of the patients, with the ribs,[25] vertebrae, and lower extremities as the most commonly involved sites.[26] In this study, rib infection was the most frequent (26.1%) bone involvement, while osteomyelitis in long and short bones each comprised 8.7% of the cases, all of which were diagnosed and treated in the patients. We interpret this complication as the locoregional extension of infection from the chest wall. Osteolytic lesions were detected in the early phase, and osteosclerotic lesions were found in the later phase of this infectious process. All the patients in the present study were infected with either fungal microorganisms, *M tuberculosis*, or both concurrently, which was mainly due to the adjacent contagious extension of infection from the lungs to the ribs documented by the imaging modalities and cultures obtained from the prior infection in the chest and also the microorganisms isolated from the osteomyelitis site.

Godoy et al, [27] described the thoracic radiological findings in 4 adults with CGD as consolidation (60%), diffuse reticulonodular opacities (40%), pleural effusion (20%), and pulmonary artery enlargement (20%). CT findings in their study included areas of consolidation (60%), primary nodules (60%), tree-in-bud opacities (40%), areas of scarring and traction bronchiectasis (100%), emphysematous changes (75%), areas of mosaic attenuation (50%), mediastinal or hilar lymphadenopathy (60%), pulmonary artery enlargement (50%), and pleural effusion (20%).[27] The most frequent finding in our study was hilar lymphadenopathy (100% of fungal infections and 75% of tuberculosis infections), followed by consolidation (60% of fungal infections and 50% of tuberculosis infections). Sattelite and galaxy signs were the next common findings in 40% and 25% of our patients with fungal and tuberculosis infections, respectively. Pleural manifestations, fibrotic changes, fibrosing mediastinitis, necrotizing pneumonia, pulmonary abscess, peribronchovascular bundle thickening, and pulmonary artery enlargement were also commonly detected in the children with CGD in our study, but with lower frequencies. Mediastinal and hilar lymphadenopathies were interpreted as a sign of chronic infection, inflammation, and granulation tissue formation in the children in our study. Chronic pulmonary infections are accompanied by fibrotic changes, pulmonary artery hypertension, and pleural thickening.[26] Despite the patients' frequent pulmonary infections, bronchiectasis was not a common finding in our study. This could be attributed to insufficient time for these changes to occur in children in this age range.

We believe that the small number of patients with phagocytic immunodeficiencies and the limited types of immunodeficiencies in each group were two of the limitations of the current study. Secondly, as this study was performed retrospectively, data were sometimes unavailable or incomplete. However, due to the low prevalence of primary immunodeficiencies, we believe the data were convincing to conclude the key role of radiologic assessments in the timely diagnosis of these rare diseases.

Primary phagocytic immunodeficiencies, with particular attention to CGD in this study, are characterized by repeated infections in children. The most frequent radiological manifestations in children included mediastinal and hilar consolidations. Physicians' awareness of the radiological as well as clinical manifestations of these inherited diseases may be helpful in the early diagnosis and timely initiation of specific prophylaxis measures to prevent infections and also to initiate hematopoietic stem cell transplantation as the curative management modality.

STATEMENT OF ETHICS

This study was approved by the Pediatric Research Ethics Board of Mofid Children's Hospital. Because all participants were children, written informed consent was obtained from their parents.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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