



# Atypical Presentation of Chronic Granulomatous Disease in a Neonate with a Pulmonary Granuloma Mimicking a Tumor: A Case Report

신생아에서 종양으로 오인되는 폐 육아종의 비전형적인 소견을 보인 만성 육아종성 질환: 증례 보고

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Chronic granulomatous disease (CGD) is an uncommon primary immune deficiency caused by phagocytes defective in oxygen metabolite production. It results in recurrent bacterial or fungal infections. Herein, we present a case of CGD with a large pulmonary granuloma in a neonate and review the imaging findings. The patient was a 24-day-old neonate admitted to the hospital with fever. A round opacified lesion was identified on the chest radiograph. Subsequent CT and MRI revealed a round mass with heterogeneous enhancement in the right lower lobe. There were foci of diffusion restriction in the mass. Surgical biopsy of the mass revealed chronic granuloma. Finally, the neonate was diagnosed with CGD caused by mutation of the gp91<sup>phox</sup> gene. Herein, we present the clinical and imaging findings of this unusual case of CGD.

**Index terms** Newborn; Pulmonary Aspergillosis; Infection; Genetic Disease; Congenital

## INTRODUCTION

Chronic granulomatous disease (CGD) is a rare genetic disease manifesting as im-

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immune deficiency caused by the defect in biosynthesis of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (1). This genetic defect results in the inability of phagocytes to destroy certain bacteria and fungi. Most reported cases of CGD are usually seen as multiple pulmonary nodules or consolidations. To the best of our knowledge, there is only one reported neonatal CGD case with pulmonary granulomas (2). In this context, we review the clinical course, imaging findings, and diagnosis of a large pulmonary granuloma in a neonate with CGD.

## CASE REPORT

A 24-day-old male admitted to the emergency room with fever and feeding difficulty. The neonate was delivered in a local hospital by normal spontaneous vaginal delivery at 37 weeks gestation. The pregnancy was uneventful and there was no history of documented infection. The prenatal ultrasounds (USs) were normal. Screenings for *Chlamydia trachomatis*, Group B *Streptococcus* were negative. The infant's birth weight was 2960 g.

His physical findings on admission were as follows; weight of 3880 g, body temperature of 37.4°C, systolic blood pressure of 80 mm Hg, 155 pulse-beats/min, respiratory rate of 50 breaths/min at maximum, and the oxygen saturation 100%. The patient had sputum and no apparent rash or jaundice was observed. His fontanelle was flat and there was no enlarged cervical or inguinal lymph nodes. Biochemical studies revealed leukocytosis at 18900/ $\mu$ L (normal range: 4000–11000/ $\mu$ L), with 57.8% of neutrophils (normal range: 33–74%) and C-reactive protein of 6.66 mg/dL (normal range: 0.0–0.5 mg/dL). Aspartate aminotransferase was at 43 U/L (normal: less than 40 U/L) and alanine aminotransferase was at 38 U/L (normal: less than 41 U/L). Electrolyte levels and the results of renal function tests were normal.

On the chest radiograph, which was taken on the first day of admission, there was a round opacified lesion in the right lower lung zone (Fig. 1A). Antibiotic was administered for two days, but the opacification did not change. Consequently, chest CT with contrast enhancement was done.

On chest CT, there was a 4.0 cm  $\times$  3.4 cm  $\times$  4.7 cm heterogeneously enhancing lesion in the right lower lobe (Fig. 1B). There were focal low attenuating portions in the mass. There was no evidence of chest wall invasion. There was no definite internal bronchus or pulmonary arterial structure visible and there was no systemic artery extension to the mass. There was another 0.5 cm subpleural nodule in the right middle lobe with similar enhancement. There was small amount of right pleural effusion. There was diffuse peribronchial bundle thickening in the both lungs.

On MRI, which was done after five days, the mass showed iso-signal intensity on T1-weighted images and high signal intensity on T2-weighted images (Fig. 1C). On enhancement, there were focal non-enhancing foci in the mass which showed higher signal intensity on T2-weighted images. The focal non-enhancing foci showed diffusion restriction on diffusion-weighted images. There was no evidence of chest wall involvement. The subpleural nodule in the right middle lobe showed similar characteristic with the main mass. There were several enlarged lymph nodes in both axillae, but there was no evidence of hilar or mediastinal lymphadenopathy.

On following US study, the mass showed heterogeneously high echogenicity (Fig. 1D). On

**Fig. 1.** A 24-day-old male patient with fever.

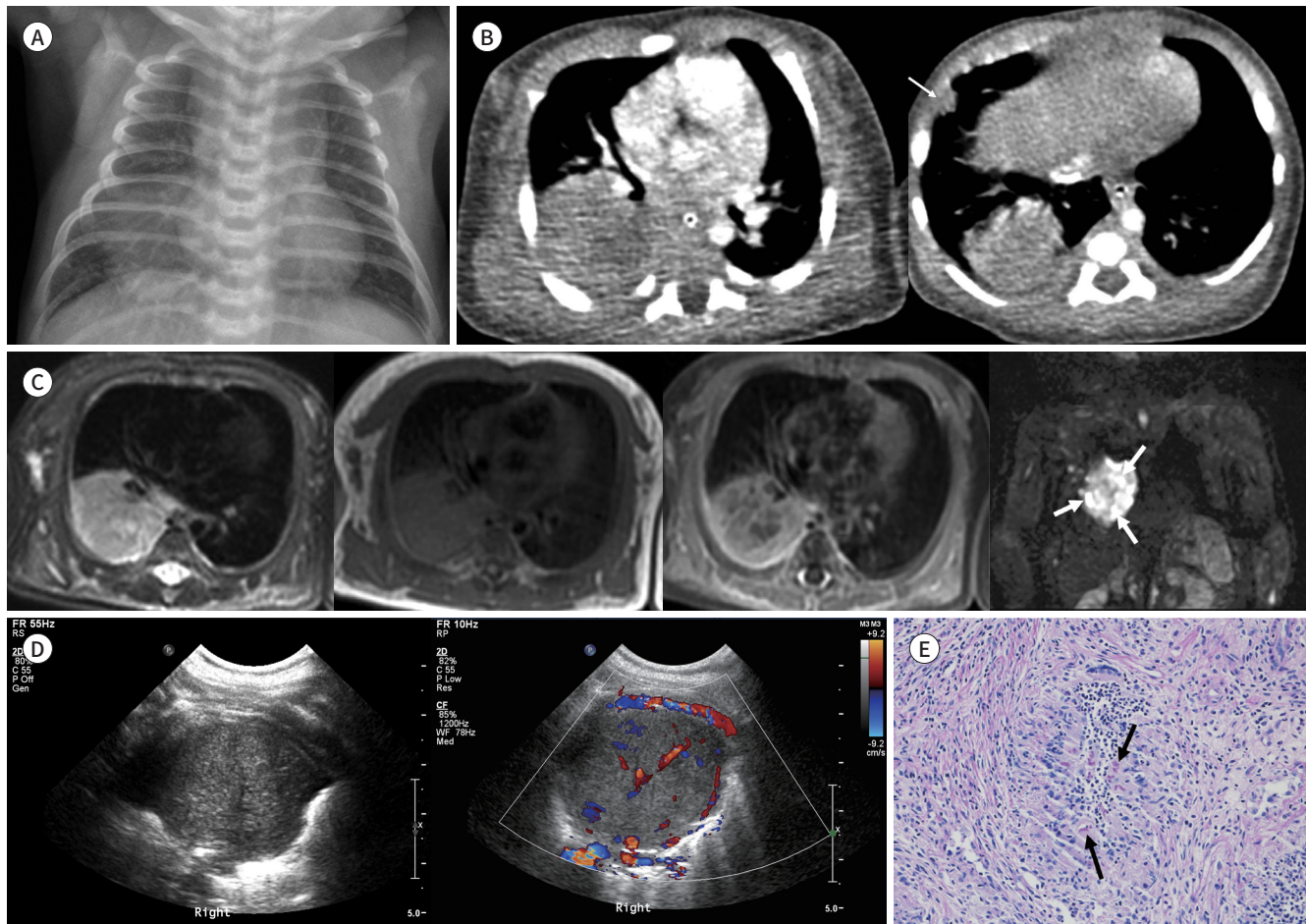
**A.** The chest radiograph shows a round opacified lesion in the right lower lung zone.

**B.** The axial contrast-enhanced CT shows a 4.7-cm mass, with heterogenous enhancement and internal low-attenuation portions in the right lower lobe, and a 0.5-cm subpleural nodule in the right middle lobe (arrow).

**C.** The mass shows high signal intensity with multiple small high-signal-intensity foci on axial T2-weighted MRI (1st image). On axial T1-weighted MRI, the mass shows iso-signal intensity (2nd image). On axial contrast-enhanced T1-weighted MRI (3rd image), there are areas of nonenhancement, which show diffusion restriction on the coronal diffusion-weighted image (4th image) (arrows). There is a subpleural nodule in the right middle lobe showing similar characteristics as the main mass and several enlarged lymph nodes in both the axilla (not shown).

**D.** On ultrasound, the lung mass shows heterogeneously increased echogenicity. On Doppler ultrasound, there is internal vascularity.

**E.** The surgical specimen ( $\times 200$ ) stained with the periodic–acid–Schiff diastase stain shows the hyphae of *Aspergillus* species (arrows).



Doppler US, there was internal vascularity of the mass. The mass moved freely apart from the pleura during respiration. On abdominal US, there was no significant finding such as hepatosplenomegaly or lymphadenopathy.

The first impression with the chest radiograph was round consolidation. However, as the mass did not improve after antibiotic therapy and the following image studies showed enhancement of the mass, pulmonary tumor such as type III pleuropulmonary blastoma was suggested.

The neonate underwent wedge resection of the subpleural nodule in the right middle lobe and core-needle biopsy of the mass in the right lower lobe. Histologic examination revealed chronic granuloma with multifocal abscesses. On D-pas (+) staining, *Aspergillus* was revealed

(Fig. 1E). In genetic counseling, the patient's mother was suspected of having Behcet's disease and was taking medication since early twenties. After the histologic diagnosis and the genetic counseling, the dihydrorhodamine 123 assay revealed the diminished superoxide ability of this patient's neutrophils. The diagnosis of CGD was finally confirmed by CYBB gene (gp91-phox) mutation analysis.

## DISCUSSION

CGD is a rare genetic immune deficiency disorder that is characterized by recurrent infection due to phagocytosis failure (3). Proper phagocytosis is mediated by the oxidative metabolism of NADPH oxidase enzyme complex. CGD is caused by mutations in any one of the genes encoding subunits of phagocyte NADPH oxidase. More than half of all CGD cases are X-linked CGD caused by mutations in CYBB gene encoding gp91-phox subunit. This genetic defect results in the failure to destroy certain bacteria and fungi. The diagnosis of CGD is usually established early in life, and the majority of patients are diagnosed with the disease before they are 5 years old. Although the disease can present in adulthood, most such cases are autosomal recessive forms in which residual production of superoxide can be seen (4).

Pneumonia is the most common pulmonary manifestation of CGD and may progress to lung abscess. *Aspergillus*, which was revealed on our case, is the most common pathogen. Typical imaging finding of pulmonary infection of CGD is focal consolidation or miliary nodules. Many pulmonary infections in CGD patients is complicated by granulomatous inflammation as in our case. Complicated infection with abscess formation is shown in 20% of patients. Our case presented atypical manifestations, since the patient was diagnosed in a very young age and manifested as large pulmonary granuloma with internal micro-abscesses. Pulmonary infection spreading to the chest wall and associated osteomyelitis is common in CGD, but our case did not extend or disseminate to the adjacent bone. In more advanced cases, CGD may show fibrosis, honeycombing, pulmonary artery hypertension, or pleural thickening on CT.

CGD can involve other multiple organ systems. Suppurative lymphadenitis is found in 60% of CGD patients, having the second highest rate next to lung infection. Our case did not show any other extrapulmonary manifestation, but there were multiple enlarged axillary lymph nodes. For lymphadenitis, *Staphylococcus aureus* is the most common pathogen. Although there was no significant finding on abdominal US in our case, more than 90% of CGD patients are afflicted with hepatosplenomegaly. In addition, liver and splenic abscesses are found in up to 50% of CGD patients. Gastrointestinal infection in CGD patients may be caused by granulomatous inflammations in the entire gastrointestinal system from mouth to anus. The central nervous system infection is rather rare in CGD patients but may include brain abscess and infections of the ear, nose, and throat.

Although the majority of CGD patients are diagnosed in childhood, the neonatal presentation and diagnosis of CGD is uncommon. Previously reported neonatal CGD case was a full-term female neonate presenting with fever at 16 days of age (2). On chest radiograph and CT, there were multiple and bilateral nodules, which are more typical imaging finding of CGD compared to our case. The presence of *Aspergillus* hyphae was also confirmed after biopsy. Another neonatal CGD case was a 31-day-old male presenting with extrapulmonary symp-



toms (5). The major complications were candidemia and hepatosplenomegaly.

The differential diagnosis for a pulmonary mass in neonates include congenital pulmonary airway malformation (CPAM), pulmonary sequestration, and pleuropulmonary blastoma (6). The typical imaging findings of CPAM are air-filled cystic lesions with or without communication with each other. However, type 3 CPAM tends to be seen as homogeneous soft tissue density mass due to microscopic cysts that can be identified only at histologic evaluation (7). In the presence of infection, there may be adjacent alveolar consolidation. CPAM may show normal communication with the bronchial tree, which was not evident in our case. Pulmonary sequestration is defined as a segment of lung parenchyma that receives its blood supply from the systemic circulation and that does not communicate with the tracheobronchial tree (7). Type III pleuropulmonary blastoma may also present as a heterogeneous mass lesion. This feature is different from type I or II pleuropulmonary blastoma, which show internal cystic portions. Pleuropulmonary blastoma are usually right-sided without chest wall invasion as in our case. However, since it is usually pleural-based lesion, the free movement of the mass from the pleura revealed on US in our case was not consistent with pleuropulmonary blastoma's characteristic. In addition, focal restricted diffusion areas were more specific for abscesses rather than primary pulmonary tumor with internal necrosis.

There are other diseases that can develop into pulmonary granulomas in children. For example, tuberculosis infection can develop pulmonary granulomas in children. Caseating granulomas are one of the hallmarks of tuberculosis and the granulomas can involve airways and mediastinal lymph nodes (8). Pulmonary hyalinizing granuloma, a kind of fibrosclerosing inflammatory disease, can also develop in the pulmonary system, but it is rare in children (9).

Generally, acute infections in CGD patients are treated with prophylactic antibiotics and antifungal agents (10). Interferon-gamma is additionally administered to stimulate superoxide release and is a prophylactic agent for CGD. Surgery plays an important role in the management of CGD. Early extensive surgery appears to be important in fungal osteomyelitis due to *Aspergillus* that are refractory to medical therapy. Allogeneic hematopoietic stem cell transplantation from a human leukocyte antigen identical donor is currently the only proven curative treatment for CGD and can be offered to the selected patients. Furthermore, gene therapy provides promise as a future potentially definitive treatment of the disease.

Our case was a male with an X-linked recessive CGD with CYBB gene (gp91-phox) mutation. Up to 70% of CGD cases are X-linked recessive inheritance and the incidence is higher in males. Genes encoding p22phox, p47phox, p67phox, and p40phox are all autosomal recessive and account for the remainder. The mortality rate of X-linked recessive patients is also higher than that of autosomal recessive patients (3).

The radiologists and clinicians must be cautious about the rare manifestation of CGD in neonate with intrapulmonary granuloma mimicking a pulmonary tumor.

#### Author Contributions

Conceptualization, K.H.G.; investigation, Y.Y.J., K.H.G.; methodology, Y.Y.J., K.H.G.; project administration, K.H.G.; resources, S.J.S., J.H.J., K.Y.H., J.J., L.J.H.; supervision, K.H.G.; visualization, Y.Y.J., K.H.G., S.J.S.; writing—original draft, Y.Y.J., K.H.G.; and writing—review & editing, S.J.S., L.J.H., J.H.J., K.Y.H., J.J., K.H.G.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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## 신생아에서 종양으로 오인되는 폐 육아종의 비전형적인 소견을 보인 만성 육아종성 질환: 증례 보고

유영진<sup>1</sup> · 선주성<sup>1</sup> · 이장훈<sup>2</sup> · 정현주<sup>2</sup> · 고영화<sup>3</sup> · 정준호<sup>4</sup> · 김현지<sup>1,5\*</sup>

만성 육아종성 질환은 유전성 면역결핍질환으로 포식세포가 정상기능을 하지 못함으로써 만성적이고 반복적인 감염이 생긴다. 염증성 육아종의 형성은 다양한 장기에서 관찰되며 폐를 침범할 경우 영상학적 특징으로는 대부분 다발성 결절 또는 경결로 나타난다. 저자들은 신생아에서 종양으로 오인되는 폐 육아종의 비전형적인 소견을 보인 만성 육아종성 질환을 경험하였기에 이를 보고하고자 한다. 본 증례는 발열을 주소로 내원한 생후 24일된 남아로 전산화단층촬영 영상에서 우하폐에 위치한 비균질 조영 증강되는 종괴가 있었다. 종괴 내부 조영 증강되지 않는 부분은 자기공명영상의 확산강조영상에서 고신호 강도를 보였다. 환자는 수술적 절제를 시행하였고 X-염색체 연관 gp91<sup>phox</sup> 유전자 돌연변이의 만성 육아종성 질환으로 확인되었다. 이에 우리는 본 증례 발표를 통해 이러한 비전형적인 만성 육아종성 질환의 임상적, 영상학적인 특징에 대해 서술하고자 한다.

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