Asian Biomedicine Vol. 6 No. 1 February 2012; 129-133 DOI: 10.5372/1905-7415.0601.138

**Clinical report**

# Color Doppler sonography of pulmonary aspergillosis in infants with chronic granulomatous disease

Panruethai Trinavarat[a], Pantipa Chatchatri[b], Poonchavist Chandtranuwatana[c]
*[a]Department of Radiology, [b]Department of Pediatrics, [c]Department of Pathology*
*Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand*

***Background:*** Pulmonary aspergillosis may be the first presentation of chronic granulomatous disease (CGD) and may occur during infancy. Imaging studies with plain chest radiographs and computed tomography may present a diagnostic challenge, and high index of suspicion is required for the diagnosis.
***Objective:*** Report a six-week-old boy with chronic granulomatous disease and invasive pulmonary aspergillosis, in who color Doppler sonography of the chest showed systemic arterial supply to the pulmonary lesions.
***Methods:*** Sonography of the chest using a high-frequency linear transducer was performed in a six-week-old infant with chronic granulomatous disease who presented with noisy breathing, cough, and low-grade fever, and his chest radiograph revealed multiple sites of pulmonary opacities.
***Results:*** The peripheral pulmonary nodules had low-resistant arterial supply derived from a systemic artery of the chest wall. The pulmonary lesion was later proven to be fungal infection. Similar imaging was detected in another two infants with the same disease.
***Conclusion:*** Systemic arterial supply could develop to feed peripheral pulmonary aspergillosis in an infant as young as six-week old who had underling CGD.

***Keywords:*** Aspergillosis, child, chronic granulomatous disease, lung, ultrasound

Chronic granulomatous disease (CGD) is an inherited disorder. Patients with CGD are prone to have recurrent pneumonia caused by catalase-positive organisms, particular aspergillus [1]. Invasive aspergillosis that does not respond to antimycotic treatment is one major cause of death in CGD [1]. It needs early recognition and aggressive treatment. However, early diagnosis of fungal disease is not an easy task. The clinical symptoms and imaging finding are about the same as in bacterial pneumonia, but lack response to antibiotic treatment [2].

We report color Doppler sonography (CDS) findings in an infant with CGD who had invasive pulmonary aspergillosis. Imaging helped us to suspect pulmonary aspergillosis in two other cases.

## Clinical report

A six-week-old term infant, with uncomplicated perinatal period, presented with noisy breathing for one week, low-grade fever, cough, and dyspnea for four days, and bloody streaked sputum for one day. He was admitted to another hospital for four days, and was referred to King Chulalongkorn Memorial Hospital (KCMH) because of persistent fever despite antibiotic treatment. He was known to have CGD diagnosed by flow cytometry. The test was done soon after birth because his brother carried this disease and died from infection during infancy. His mother was the carrier of the X-linked recessive gene.

At KCMH, the boy was without dyspnea. No adventitious lung sounds were heard by auscultation. Some discrete pustules were found on his scalp and face. The liver was palpable 4 cm below right costal margin. He had low-grade fever and leukocytosis (31,750 cells/mm$^3$) with nearly equal numbers of neutrophils and lymphocytes. His chest radiograph showed large nodular opacities in the right upper lobe and left lower lobe at the retro-cardiac area, and a patchy opacity was seen in the right lower lobe as shown in **Figure 1**.

***Correspondence to:*** Panruethai Trinavarat, MD, Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: pantrinavarat@hotmail.com, pantrinavarat@yahoo.co.th

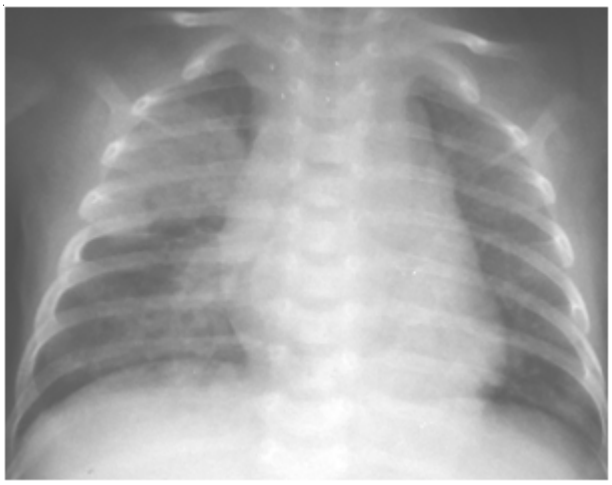

**Figure 1.** Chest X-ray showed large nodular opacities in the right upper lobe, left lower retrocardiac area, and a patchy peribronchial opacity in the right lower lobe.

Chest US on the following day revealed solid, hypoechoic, mildly heterogeneous lesions with sharp lobulated margins in the periphery of the right and left lung (**Figure 2**).

Systemic arterial supply with low-resistant waveform Doppler pattern from chest wall passing the pleura to these nodules were detected by CDS (**Figure 3**).

The chest US (with Sequoia 512, 15L8 linear transducer) was performed after abdominal US. It showed no abnormality in the abdomen. The computed tomography of the chest on day 6 after admission confirmed pulmonary nodules seen on the chest X-ray and additional smaller pulmonary nodules and some mildly enlarged mediastinal nodes up to 1.5 cm. However, it did not show suggestive findings of aspergillosis, such as the "halo" sign or the "crescent" sign. Cultures from blood and urine yielded no growth. Sputum could not be obtained as his cough was nonproductive. Cytology from fine needle aspiration of the lung mass showed necrotizing granulomatous inflammation. Gram stain and cultures from lung tissue were negative. Pneumonia due to aspergillus or staphyllococcs was considered.

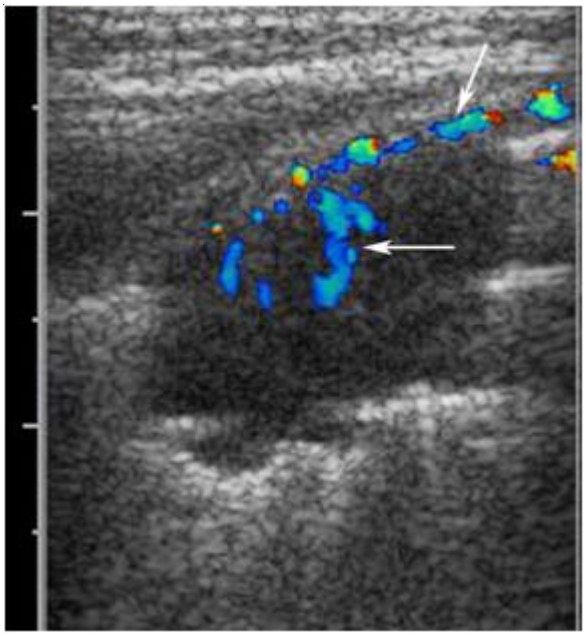

**Figure 2.** Color mode US showing a peripheral pulmonary nodule with sharp lobulated margin. The nodule was fed by a pleural vessel (indicated by arrows).

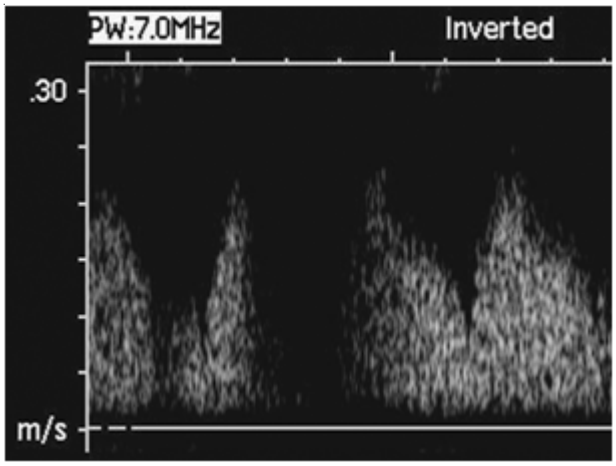


**Figure 3.** Doppler mode US showing low-resistant waveforms of the pulmonary nodule by a systemic arterial supply.

Intravenous amphotericin B was started on day 8 of admission. Chest symptoms and chest radiographic finding slowly subsided. After five weeks of treatment, renal tubular acidosis from amphotericin B developed and therapy was changed to oral itraconazone. There were still residual pulmonary lesions and a lung biopsy was performed. Histology revealed granulomatous inflammation, fragmented fungal hyphae (**Figure 4**) with rare septation within the multinucleated giant cells. No fungal invasion into pulmonary vessels was seen. There was a presence of a systemic arterial branch at the pleural side of the biopsied lung. Amphotericin B was re-started when renal function improved.

The infant spent most of his life in hospital because of repeated infections. He also had meningitis, acute necrotizing granulomatous lymphadenitis of neck nodes, a scrotal ulcer, a peri-anal abscess, and infection at double-lumen catheters. He died at age of 18 months from recurrent pneumonia and septic shock.

## Discussion

CGD is a rare inherited disorder from X-linked recessive gene with mutation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [3]. Reactive oxygen species, the product of NADPH oxidase, are lacking resulting in a disorder of phagocytosis oxidative bursts [3]. That is why patients with CGD are prone to recurrent infections from catalase-positive organisms such as staphylococcus, salmonella, candida, aspergillus, and pseudomonas species [4]. Pneumonia is the most common infection and aspergillus is the most prevalent cause [1]. Pneumonia, patients with CGD have exaggerated

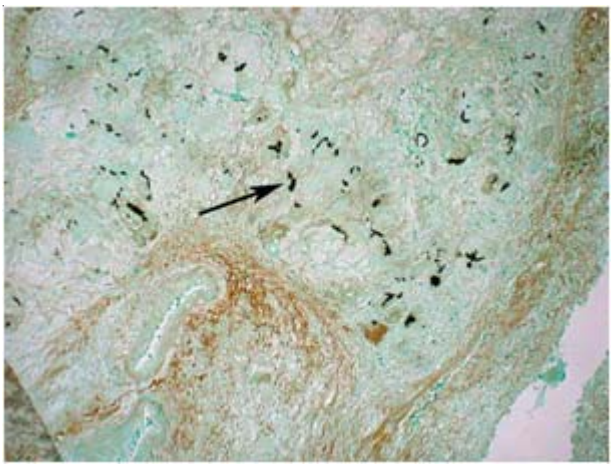

**Figure 4.** Microscopic image of the lung by Grocott's methenamine silver staining. Degenerated fungal hyphae (indicated by arrow) were demonstrated in the granuloma (Original magnification:100x).

inflammatory responses in the lung with granuloma formation and development of chronic inflammation [5]. This response is found not only in fungal but also in bacterial infections [5].

Chest radiography in aspergillus pneumonia is usually nonspecific and cannot be differentiated from bacterial pneumonia. Chusid et al. [6] suggested that when chronic, multiple, mostly nodular lesions were found in pediatric lungs, aspergillus infection, and CGD should be considered in the differential diagnosis [6]. Many studies of CT findings in invasive pulmonary aspergillosis in adults reported nodular lesions as the most common but nonspecific finding, and the "halo" sign as an early finding [7]. However, the halo sign is not common in children with this disease [8].

To our knowledge, there has been no report of CDS findings in pulmonary aspergillosis. We found several pleural pulmonary lesions accessible to US. On B-mode US, the findings differed from usual alveolar infiltrates, as they were nodular-like with sharp lobulated margins. Pleural effusion was not seen. Striking findings on CDS and spectral Doppler was arterial supply from dilated intercostal arteries, traversing the pleura feeding the pulmonary lesions with a high blood flow pattern.

We found two similar cases one year and three years later. In a three-month-old boy and a two-month-old girl, we had nearly identical chest X-rays and CDS findings. The possibility of pulmonary aspergillosis and CGD was raised in both cases from imaging studies, and the diagnoses were later confirmed by lung biopsy and flow cytometry assay. The pulmonary lesions seen from US in both cases were nodules and consolidates. Some of these lesions had a systemic arterial supply. In the case of the two-month-old girl, chest CT (Somatom Sensation 16, Siemens Medical Solutions, Forchheim, Germany) was performed in the aorta-enhancing phase. It revealed dilatation of left intercostal arteries, the ipsilateral internal mammary artery, and the contralateral bronchial artery, corresponding to the locations of the pulmonary lesions. CT parameters used were 80 kVp, 40 mAs, and 1.15 pitch. The dose length product (DLP) was 16 mGy cm.

Systemic-to-pulmonary collaterals had been described in conditions causing reduced pulmonary arterial perfusion, prematurity, neoplastic disease, and chronic infection/inflammation [9, 10]. As aspergillus has a tendency to invade blood vessels causing vascular thrombosis and tissue infarction or ischemia [11], the affected lung may develop collateralization from adjacent intercostal arteries and internal mammary artery. However, there was no imaging or pathological proof of pulmonary vascular thrombosis in our cases. Inflammation and angiogenesis may be the explanation. Airway/pulmonary infection and inflammation are associated with angiogenesis demonstrable in animal models within 10-15 days post microbial inoculation [12]. The angiogenesis may occur in the pulmonary [12] and systemic circulation [13]. Transpleural systemic-pulmonary artery anastomoses have been reported to develop in chronic pulmonary infection [14]. Our cases were rather young infants, six weeks, three months, and two months old, with duration between onset of symptom to chest US of 14 days, two months, and one month. In the first case, it was difficult to determine whether he had chronic infection. We could not be sure whether he had insidious onset of fungal infection for a few weeks before overt symptoms appeared. Infection/inflammation in neonate/infants may have a shorter course in development of angiogenesis. There is no information on whether pneumonia in the neonatal period may develop systemic collateral connections in an acute or subacute course of the disease. CDS is not the usual investigation in neonatal pneumonia or lung masses. It would be interesting to obtain more such data in the future.

## Conclusion

Our three patients with CGD presented with pulmonary aspergillosis early in their first few months of life. Multiple pulmonary nodules were found in their chest radiographs, and systemic arterial feeders to the pleural-based lesions could be detected by chest CDS. Whether or not these findings are specific for pulmonary aspergillosis needs further study.

The authors have no conflict of interest to declare.

## References

1. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease: report on a national registry of 368 patients. Medicine. 2000; 79:155-69.
2. Harris JB, Michelow IC, Westra SJ, Kradin RL. Case records of the Massachusetts General Hospital. Case 21-2008: an 11-month old boy with fever and pulmonary infiltrates. N Engl J Med. 2008; 359:178-87.
3. Pollock JD, Williams DA, Gifford MA, Li LL, Du X,

Fishernan J, et al. Mouse model of X-linked chronic granulomatous disease, an inherited defect in phagocyte superoxide production. Nat Genet.1995; 9: 202-9.
4. Liese J, Kloos S, Jendrossek V, Petropoulou T, Wintergerst U, Notheis G, et al. Long-term follow-up and outcome of 39 patients with chronic granulomatous disease. J Pediatr. 2000; 137:687-93.
5. Moskaluk CA, Pogrebniak HW, Pass HI, Gallin JI, Travis WD. Surgical pathology of the lung in chronic granulomatous disease. Am J Clin Pathol. 1994; 102: 684-91.
6. Chusid MJ, Sty JR, Wells RG. Pulmonary aspergillosis appearing as chronic nodular disease in chronic granulomatous disease. Pediatr Radiol. 1988; 18:232-4.
7. Brodoefel H, Vogel M, Hebart H, Einsele H, Vonthein R, Claussen CD, et al. Long-term follow-up in 40 non-HIV immunocompromised patients with invasive pulmonary aspergillosis: kinetics of CT morphology and correlation with clinical findings and outcome. Am J Radiol. 2006; 187:404-13.
8. Thomas KE, Owens CM, Eeys PA, Novelli V, Costoli V. The radiological spectrum of invasive aspergillosis in children: a 10-year review. Pediatr Radiol. 2003; 33: 453-60.
9. Bruzzi JF, Remy-Jardin M, Delhaye D, Teisseire A, Khalil C, Remy J. Multi-detector row CT of hemoptysis. Radiographics. 2006; 26:3-22.
10. Yu CH, Chen MR. Clinical investigation of systemic-pulmonary collateral arteries. Pediatr Cardiol. 2008; 29: 334-8.
11. Patterson TF. Aspergillus species. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 6th ed. Philadelphia:Churchill Livingstone, 2005; p. 2958-62.
12. Hopkins N, Cadogan E, Giles S, McLoughlin P. Chronic airway infection leads to angiogenesis in the pulmonary circulation. J Appl Physiol. 2001; 91: 919-28.
13. Majno G. Chronic inflammation: links with angiogenesis and wound healing. Am J Pathol. 1998; 153:1035-9.
14. Webb WR, Jacobs RP. Transpleural abdominal systemic artery-pulmonary artery anastomosis in patients with chronic pulmonary infection. Am J Roentgenol. 1977; 129:233-6.