

Chronic Granulomatous Disease

Samuel J. Byrne, BS; Richard B. Towbin, MD; Carrie M. Schaefer, MD; Alexander J. Towbin, MD

Abstract

Chronic granulomatous disease (CGD) is an inherited immunodeficiency that typically presents in early childhood due to defects in the nicotinamide adenine dinucleotide phosphate oxidase complex, impairing phagocytic cell function and predisposing patients to recurrent bacterial and fungal infections. Imaging plays a critical role not only in diagnosing CGD but also in guiding treatment interventions, such as image-guided drainage of abscesses and biopsy of infected sites. Common imaging findings include lung consolidation, liver abscesses, lymphadenopathy, osteomyelitis, central nervous system, and gastrointestinal involvement. With early diagnosis, lifelong prophylactic therapy, and advances in treatment, many patients with CGD now survive well into adulthood.

Keywords: pulmonary, cellular Immunity, systemic

Case Summary

A young adult with a known history of chronic granulomatous disease (CGD) presented with cough and fever.

Imaging Findings

Initial chest CT (Figure 1) demonstrated a cavitary pneumonia in the lateral aspect of the left lower lobe. Due to medication noncompliance, follow-up CT of the chest, abdomen, and pelvis performed 8 months later (Figure 2) showed progression of the pulmonary infection and a new lucent lesion within the left iliac bone. Subsequent chest MRI (Figure 3) confirmed the persistent pulmonary infection and additionally revealed osteomyelitis involving the adjacent ribs. Bone biopsy and bronchoalveolar lavage confirmed a diagnosis of trichosporon infection.

Diagnosis

Chronic granulomatous disease.

The differential diagnoses include cystic fibrosis, glucose-6-phosphate dehydrogenase deficiency, glutathione synthase deficiency, Crohn disease, infectious lung disease, hypersensitivity pneumonitis, hot tub lung, berylliosis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, rheumatoid nodules, talc granulomatosis, Langerhans cell histiocytosis, and bronchocentric granulomatosis.^{1,2}

Discussion

CGD is a rare, inherited immunodeficiency disorder that predisposes individuals to recurrent bacterial and fungal infections. It follows either an X-linked or autosomal-recessive inheritance pattern and arises from

a defect in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. This defect impairs the ability of phagocytic cells—including neutrophils, monocytes, and macrophages—to generate oxygen radicals essential for killing catalase-positive pathogens, such as *Staphylococcus*, *Pseudomonas*, and *Aspergillus* species. As a result, neutrophils can phagocytose but are unable to effectively kill these microbes, leading to persistent infections and granuloma formation.³

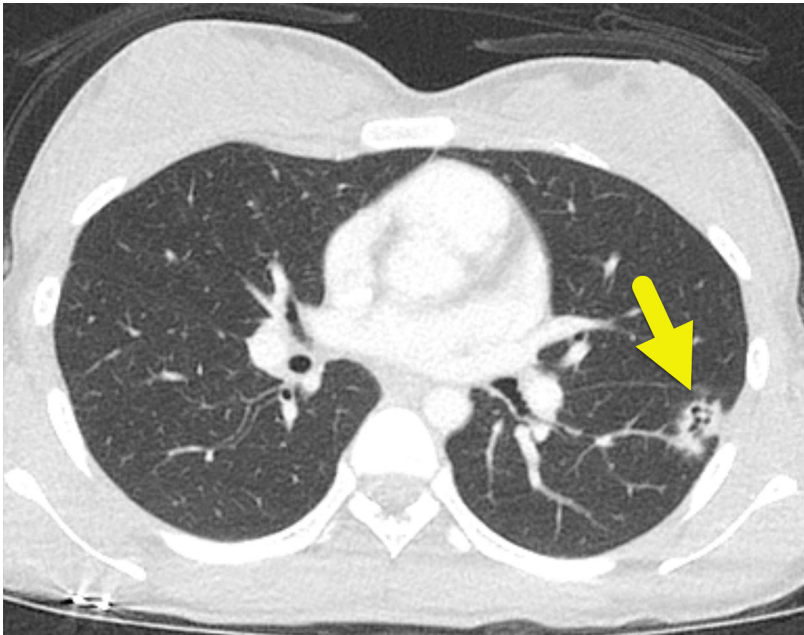
Given its genetic basis and immune dysfunction, CGD is typically diagnosed in early childhood. The disease presents within the first 1-3 years of life, with an incidence of approximately 1 in 200,000 live births in the United States.^{1,3} Each year, about 20 children are born with CGD.⁴ Because 70% of cases result from X-linked inheritance, males account for most cases (80%).¹ X-linked CGD tends to present earlier and with more severe symptoms than autosomal-recessive CGD, though the underlying reason for this difference remains unclear.¹

CGD can affect nearly every organ system, with unique manifestations depending on the site of disease. Pneumonia is the most common infection

Affiliations: University of Arizona College of Medicine–Phoenix, Phoenix, Arizona (Byrne); Department of Radiology, Phoenix Children's Hospital, Phoenix, Arizona (RB Towbin, Schaefer); Department of Radiology, Cincinnati Children's Hospital, University of Cincinnati College of Medicine, Cincinnati, Ohio (AJ Towbin).

Disclosures: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Figure 1. Initial chest CT showing a cavitary pneumonia (arrow) in the lateral aspect of the left lower lobe.



in CGD, occurring in approximately 80% of patients.⁵ Radiologic findings may include septal thickening, consolidation, nodules, ground-glass attenuation, and a honeycomb appearance.⁵⁻⁷

Lymphadenitis is another frequent manifestation, most commonly affecting the cervical lymph nodes. Suppurative lymphadenitis occurs in approximately 60% of patients with CGD and appears on contrast-enhanced CT as enlarged, enhancing lymph nodes with a central low-density necrotic core.⁵

Liver abscesses are a hallmark complication, affecting 25-50% of patients with CGD.⁵ Among these, 60% develop multiple concurrent abscesses. The imaging appearance of liver abscesses varies by size:

- Small phlegmon (< 1 cm): homogeneous enhancement.
- Medium-sized abscesses (1-3 cm): low central attenuation with peripheral ring enhancement.
- Large abscesses (>3 cm): loculated with multiple small cavities.⁵

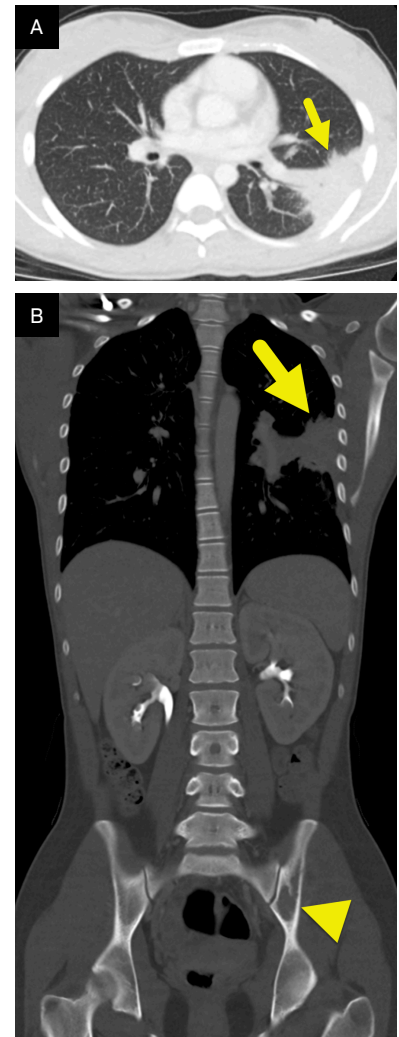
Musculoskeletal involvement is also common, with osteomyelitis occurring in approximately 25% of cases. The extremities, skull, and chest wall are the most frequently affected sites.⁵ On imaging, osteomyelitis typically presents as a lucent lesion.^{5,8}

Other less common manifestations involve the central nervous system (CNS) and gastrointestinal tract.⁵ Notably, gastrointestinal involvement may cause thickening of the gastric antrum or mimic Crohn disease when the intestinal tract is involved.

The diagnosis of CGD is established using the nitroblue tetrazolium test, which detects the inability of phagocytes to generate a normal respiratory burst. Flow cytometry is also commonly used to assess superoxide production, providing a functional evaluation of NADPH oxidase activity.³

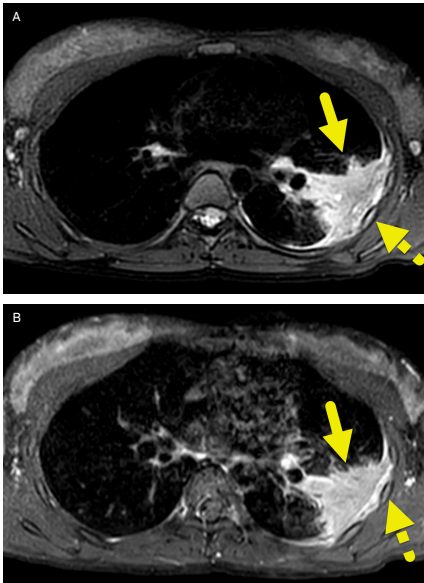
Imaging plays an increasingly important role in both the diagnosis and management of CGD. It allows for accurate identification of infections, assessment of

Figure 2. Follow-up CT of the chest, abdomen, and pelvis performed 8 mo later, displayed using (A) lung and (B) bone windows, showing persistent and worsening left lower lobe pneumonia (arrow) and new osteomyelitis involving the left iliac bone (arrowhead).



granuloma progression, and evaluation of lung disease severity. Beyond detecting complications, imaging is also crucial for guiding diagnostic and therapeutic interventions. For example, image-guided aspiration of abscesses or biopsy of osteomyelitis sites can aid in isolating causative organisms.⁹ In large or symptomatic abscesses, image-guided drainage is often the primary therapeutic option.

Figure 3. (A) Axial T2-weighted and (B) axial T1-weighted postcontrast MRI of the chest demonstrating the left lower lobe pneumonia (arrow) and osteomyelitis of the adjacent ribs (dashed arrow). The affected ribs are T2 hyperintense and show mild enhancement.



Significant advancements in CGD treatment have led to improved survival rates since its discovery.¹ Early diagnosis is crucial to limit complications and prevent organ damage. Hematopoietic stem cell transplantation is the only curative treatment, but it is not always feasible due to donor availability and transplant-associated risks.³ As a result, most patients rely on lifelong prophylactic therapy and targeted treatment of infections as they arise.³

Prophylactic antimicrobial therapy remains the cornerstone of CGD management. Trimethoprim-sulfamethoxazole (TMP/SMX) and itraconazole are the primary agents used to prevent bacterial and fungal infections.³ In one study, TMP/SMX prophylaxis extended the infection-free interval from one infection every 10 months to one infection every 40 months in patients with CGD.⁶

Interferon-gamma (IFN- γ) therapy serves as an additional immunomodulatory treatment for some patients with CGD. While not universally adopted, IFN- γ

is used in select US centers but is less common worldwide due to concerns regarding cost, necessity, and physician familiarity. The precise mechanism of IFN- γ remains unclear, but it is believed to enhance neutrophil bactericidal activity, promote nitric oxide production, and increase class II major histocompatibility complex antigen expression, thereby improving antigen processing and adaptive immune responses.¹⁰ Other potential mechanisms include proteasomal degradation and enhanced cell adhesion.¹¹ A 2022 meta-analysis found that IFN- γ therapy reduced the risk of serious infection by 44% (risk ratio: 0.56).¹² However, the analysis also emphasized that limited clinical data exists, and further trials are needed to assess efficacy and long-term safety.¹²

Conclusion

CGD is an inherited immunodeficiency that typically presents in early childhood due to defects in the NADPH oxidase complex, impairing phagocytic cell function and predisposing patients to recurrent bacterial and fungal infections. Imaging plays a critical role not only in diagnosing CGD but also in guiding treatment interventions, such as image-guided drainage of abscesses and biopsy of infected sites. Common imaging findings include lung consolidation, liver abscesses, lymphadenopathy, osteomyelitis, CNS, and gastrointestinal involvement. With early diagnosis, lifelong prophylactic therapy, and advances in treatment, many patients with CGD now survive well into adulthood.

References

- 1) Lent-Schochet D, Jialal I. Chronic granulomatous disease. In: *StatPearls* [Internet]. StatPearls Publishing. 2024. <https://www.ncbi.nlm.nih.gov/books/NBK493171/>

- 2) Ohshimo S, Guzman J, Costabel U, Bone-lla F. Differential diagnosis of granulomatous lung disease: clues and pitfalls: number 4 in the series “pathology for the clinician” edited by peter dorfmueller and alberto cavazza. *Eur Respir Rev.* 2017;26(145):170012. doi:10.1183/16000617.0012-2017
- 3) Yu H-H, Yang Y-H, Chiang B-L. Chronic granulomatous disease: a comprehensive review. *Clinic Rev Allerg Immunol.* 2021;61(2):101-113. doi: 10.1007/s12016-020-08800-x
- 4) Rider NL, Jameson MB, Creech CB. Chronic granulomatous disease: epidemiology, pathophysiology, and genetic basis of disease. *J Pediatric Infect Dis Soc.* 2018;7(suppl_1):S2-S5. doi: 10.1093/jpids/piy008
- 5) Lee M, Lee MS, Lee JS, Ko SY, Jeong SY. Spectrum of imaging findings of chronic granulomatous disease: a single center experience. *Diagn Interv Radiol.* 2017;23(6):472-477. doi:10.5152/dir.2017.17264
- 6) Jana M, Sinha P, Garg P, et al. Imaging findings in Chronic Granulomatous Disease (CGD). *Indian J Pediatr.* 2024;91(3):242-247. doi:10.1007/s12098-022-04350-6
- 7) Towbin AJ, Chaves I. Chronic granulomatous disease. *Pediatr Radiol.* 2010;40(5):657-668. doi:10.1007/s00247-009-1503-3
- 8) Bennett N, Maglione PJ, Wright BL, Zerbe C. Infectious complications in patients with chronic granulomatous disease. *J Pediatric Infect Dis Soc.* 2018;7(suppl_1):S12-S17. doi:10.1093/jpids/piy013
- 9) Khanna G, Kao SC, Kirby P, Sato Y. Imaging of chronic granulomatous disease in children. *Radiographics.* 2005;25(5):1183-1195. doi:10.1148/rg.255055011
- 10) The International Chronic Granulomatous Disease Cooperative Study Group*. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. *N Engl J Med.* 1991;324(8):509-516. doi:10.1056/NEJM199102213240801
- 11) Leidinger JW, Holland SM. Chronic granulomatous disease. In: *Stiehm's Immune Deficiencies.* 2020:829-847. doi:10.1016/B978-0-12-816768-7.00037-5
- 12) Ambruso DR, Briones NJ, Baroffio AF, et al. In vivo interferon-gamma induced changes in gene expression dramatically alter neutrophil phenotype. *PLoS One.* 2022;17(2):e0263370. doi:10.1371/journal.pone.0263370