Diagn Interv Radiol 2017; 23:472–477

PEDIATRIC RADIOLOGY

PICTORIAL ESSAY

Spectrum of imaging findings of chronic granulomatous disease: a single center experience

Minah Lee
Mu Sook Lee
Jeong Sub Lee
Su Yeon Ko
Sun Young Jeong

ABSTRACT

The purpose of this pictorial essay is to present and summarize various imaging findings of chronic granulomatous disease (CGD). CGD represents a heterogeneous group of disorders caused by defective generation of respiratory bursts in human phagocytes. This defect results in abnormal phagocytic functions and defective killing of bacteria by phagocytes. CGD may involve many organs and present with recurrent infections and inflammations. Radiologists should consider the possibility of CGD when a patient presents with atypical and recurrent infection. They must also consider other concurrent infections a patient may have.

Chronic granulomatous disease (CGD) is a rare genetically predisposed immunodeficiency disorder, characterized by recurrent bacterial and fungal infections (1). CGD is caused by a genetic defect in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex, which fails to display a characteristic increase of oxidative metabolism, called the "respiratory burst," during phagocytosis (1). The aspect of oxygen radicals formed by the respiratory burst is the key component in microbial killing. However, this process does not properly occur in CGD patients, resulting in an inability to generate oxygen radicals to kill catalase-positive pathogens such as *staphylococci, mycobacteria, Burkholderia cepacia, Nocardia, Serratia, Klebsiella, Pseudomonas,* and *Aspergillus* spp. (Fig. 1). Accordingly, recurrent chronic inflammation leads to inflammatory granulomas (1).

CGD is an X-linked recessive or autosomal recessive genetic disease. Owing to the attribute of having X-linked recessive inheritance in 65% to 67% of CGD cases, incidence is higher in males than females. The mortality rate of X-linked recessive patients is also higher than that of autosomal recessive patients (1).

Confirmation of defective neutrophil respiratory burst is necessary for the laboratory CGD evaluation. The most frequently used diagnostic methods for CGD are dihydrorhodamine 123 flow cytometry assay and nitrobluetetrazolium dye test (2). Although a genetic test is currently the most accurate diagnostic method available, this test is not routinely utilized except for genetic counseling or tests for gene therapy(3).

Since the first reports of CGD in the 1950s, these patients largely expired before they reached adulthood. However, recent prophylactic antibiotics utilization and vigorous treatment against infection remarkably decreased the mortality rate secondary to severe infection in infants and children (4).

Manifestation of CGD

CGD may manifest as pneumonia, lymphadenopathy, liver abscess, soft tissue infection, osteomyelitis, suppurative arthritis, brain abscess, gastrointestinal infection, and organomegaly in decreasing order. It may also involve the urine bladder.

Pulmonary manifestation

Pneumonia is the most common infectious disease among CGD patients and is detected in about 80% of CGD patients (2). It is most commonly caused by *Aspergillus* spp. (41%), followed by *staphylococci* (11%), *Burkholderia cepacia* (7%), and *Nocardia* spp. (6%)

From the Department of Radiology (M.S.L. ✉ *musuki.lee@gmail.com*), Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Republic of Korea.

Received 30 June 2017; revision requested 19 July 2017; last revision received 17 August 2017; accepted 22 August 2017.

DOI 10.5152/dir.2017.17264.

You may cite this article as: 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; 23:472–477.

(5). The radiologic studies for acute pneumonia show findings of consolidation, ground-glass attenuation and nodules (Fig. 2) (6). Severe pneumonia may progress to lung abscess, while inflammation in the adjacent chest wall may propagate to the ribs and vertebral bodies to cause osteomyelitis (Fig. 3) (2, 5).

Chronic pulmonary infection may be accompanied by pulmonary fibrosis, honeycomb lung, pulmonary artery hypertension, or pleural thickening (Fig. 4) (6).

Lymph node manifestation

Lymphadenopathy is fairly common in patients with CGD (Figs. 5, 6). Suppurative lymphadenitis is found in 60% of CGD patients, having the second highest rate next to lung infection, while *Staphylococcus aureus* is the most common pathogen for this infection. With respect to lesions, cervical lymphadenitis is the most common affliction (1). On CT scan, suppurative lymphadenitis presents with enlarged and contrast-enhanced lymph nodes with a necrotic central low-density area (Fig. 7). Ultrasonography shows internal debris in volute shapes, and some cases reveal a thick septation as well as increased color flow signals within the septation. Nonsuppurative lymphadenitis indicates chronic inflammation with the formation of granulation tissues within the lymph nodes, which appear to be similar to the imaging findings of lymphadenopathy (5). As a sequel of long-term lymph node inflammation, CGD cases with nonsuppurative lymphadenitis may be accompanied by calcification of the lymph nodes (Fig. 8).

Main points

- Chronic granulomatous disease (CGD) is a very rare immunodeficiency disorder with a functional compromise of the phagocytes, because of which CGD patients cannot protect themselves from an infection. A bacterial or fungal infection may infiltrate the body systemically, leading to atypical repeated infections.
- CGD patients most often develop a pulmonary infection, but they may also contract infections that invade multiple organs such as the lymphatic system, liver, the gastrointestinal tract, the musculoskeletal system, or the central nervous system. In particular, CGD patients tend to contract infection in unusual areas, in which children with normal immunity are not prone to infection. A severe infection developed in an organ may propagate to adjacent tissues, causing complications such as tissue necrosis or fistula formation.
- Clinicians should consider the possible diagnosis of CGD in patients with unexplainable recurrent infections, unresponsiveness to treatment, or continuous infectious symptoms.

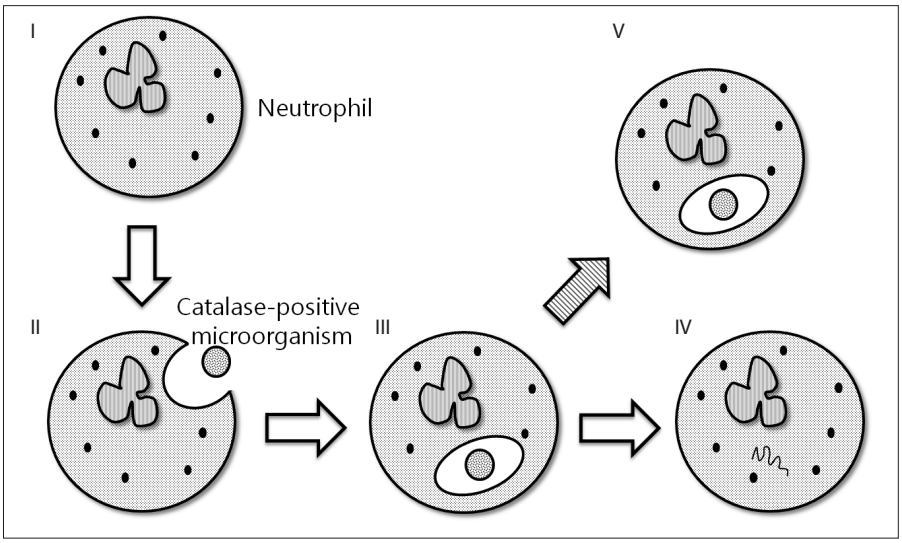


Figure 1. Pathogenesis of chronic granulomatous disease (CGD). Neutrophil **(I)** is a type of phagocyte with a single or multilobed nucleus, and granules. Normally, microbial phagocytosis **(II)** is carried out by neutrophils. Then, respiratory burst occurs by activation of the NADPH oxidase **(III)**. Finally, microorganisms are effectively removed by the reactive oxygen species formed within the phagosomes **(IV)**. However, owing to the genetic defect of NADPH oxidase enzyme complex in CGD patients, the reactive oxygen species are not generated. Thus, microorganisms remain alive within the phagosomes, causing chronic infection **(V)**.

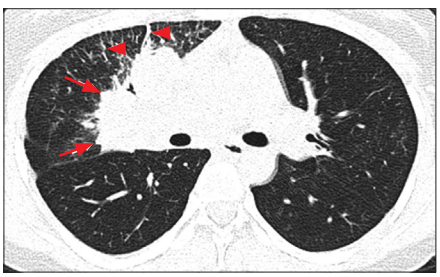


Figure 2. Pneumonia in a 17-year-old girl with CGD who presented with fever and chronic cough. Axial chest computed tomography (CT) shows subsegmental consolidations *(arrows)* and septal thickening *(arrowheads)* in the right upper lung. The diagnosis of pneumonia caused by a *Mycoplasma* sp. was confirmed.

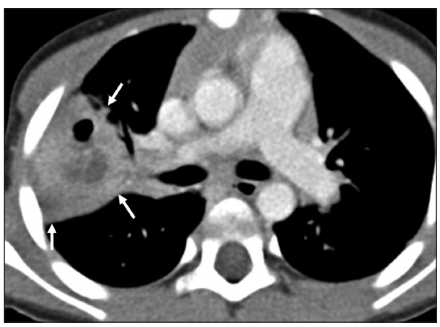


Figure 3. Lung abscess in an 11-year-old boy with CGD who presented with fever. Axial contrast-enhanced chest CT reveals an air-fluid level within the consolidation *(arrows)* of the right upper lung.

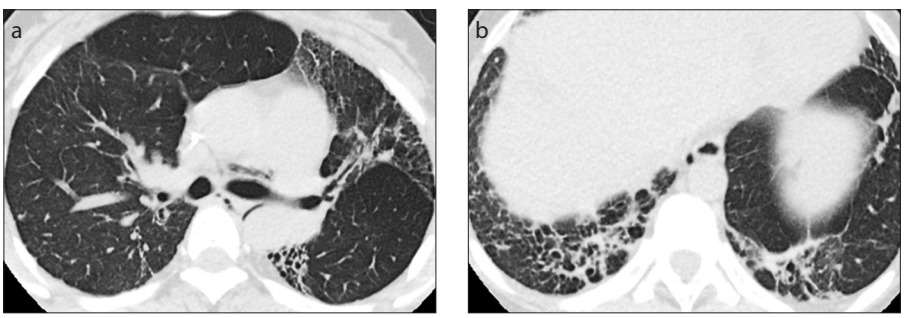


Figure 4. a, b. Chronic pulmonary manifestation in a 26-year-old female with CGD who presented with chronic cough. Axial chest CT **(a)** shows traction bronchiectasis associated with reticulation in the left lower lobe at the level of the carina. It also shows honeycomb appearance in both lower lobes at the level of the lung base **(b)**.

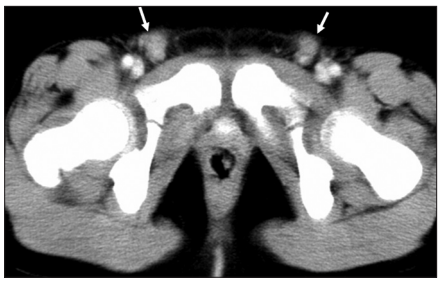


Figure 5. Bilateral inguinal lymphadenopathy in an 8-year-old child with CGD who presented with a palpable inguinal mass. Axial abdominal and pelvic CT shows multiple enlarged lymph nodes *(arrows)* in bilateral inguinal areas.

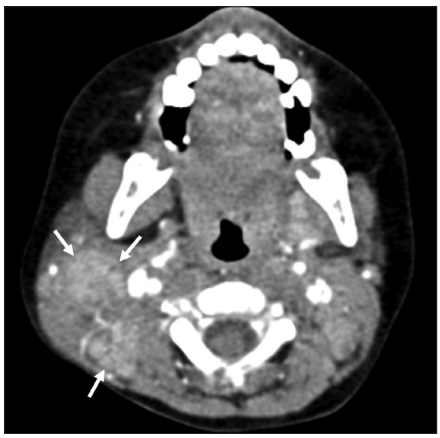


Figure 6. Cervical lymphadenopathy in a 9-year-old girl with CGD who presented with right neck swelling. Her contrast-enhanced neck CT shows multiple enlarged and enhanced lymph nodes *(arrows)* in the right cervical chain.

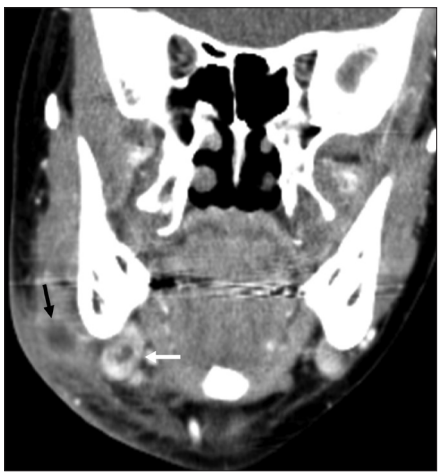


Figure 7. Suppurative cervical lymphadenitis in a 13-year-old girl with CGD who presented with palpable, painful mass in the right submandibular area. Contrast-enhanced coronal neck CT shows enlarged and enhanced lymph nodes with a central low-density area *(white arrow)* in the right cervical chain. It also reveals cellulitis accompanied by an adjacent soft tissue abscess *(black arrow)*. The result of a bacterial culture done for this abscess revelaed an isolate of *S. aureus*.

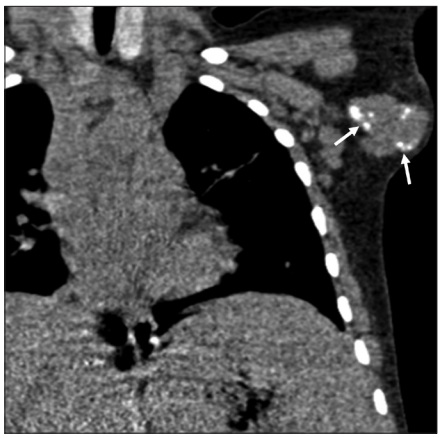


Figure 8. Calcified lymph node in a 4-year-old boy with CGD who presented with recurrent axillar swelling. A coronal unenhanced CT image exhibits enlarged lymph nodes *(arrows)*, accompanied by multiple small calcifications, in the left axillar area.

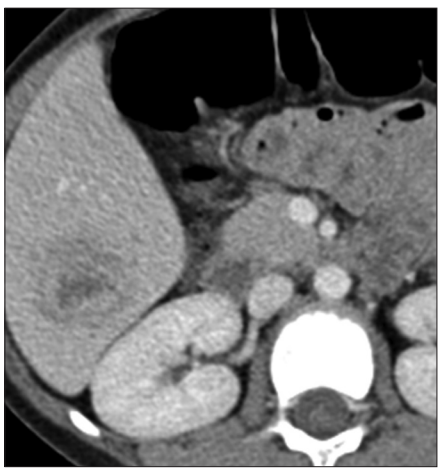


Figure 9. A liver abscess in an 8-year-old girl with CGD who presented with fever and abdominal pain. Axial contrast-enhanced CT exhibits classic liver abscesses with central low attenuation and peripheral rim enhancement in the right liver. Culture study of abscess aspirate revealed an isolate of *S. aureus*.

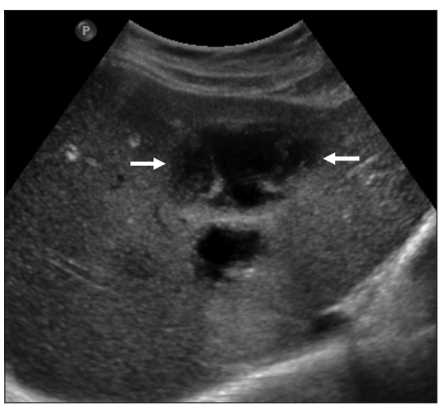


Figure 10. A liver abscess in a 14-year-old girl with CGD who presented with fever. Transabdominal ultrasonography shows lobulated thick-walled cystic lesions *(arrows)* with internal septations in the right lobe of the liver.

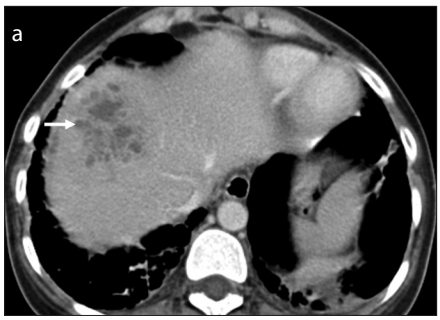
Hepatosplenic manifestation

More than 90% of CGD patients are afflicted with hepatosplenomegaly (2). Liver and splenic abscesses are found in 25% to 50% of CGD patients. Since a liver abscess is generally very rare among children, clinicians should be suspicious of CGD upon confirmation of one (5). Radiologic studies of sporadic liver abscess commonly show a single lesion and recurrence is rare after treatment. However, the proportion of CGD with a liver abscess comprises 27% of CGD patients, while *S. aureus* is the cause for approximately 50% or more CGD patients with liver abscess (1). Since CGD symptoms are not severe, CGD patients often present with fever only, and have no accompanied abdominal pain. In about 60% of CGD patients with liver abscess, multiple abscesses of various size develop concurrently; after treatment, recurrent liver abscesses are seen in about 40% of the cases. Liver abscess in CGD shows findings of various imaging morphologies (7). On CT scan, a small-sized liver abscess (<1 cm) displays homogeneous contrast enhancement. A medium-sized liver abscess (1–3 cm) shows typical abscess characteristics of central low attenuation and peripheral rim enhancement (Fig. 9). A large-sized abscess (>3 cm) might be seen as a multiloculated abscess. On ultrasonography, a hypoechoic or isoechoic lesion compared to adjacent liver parenchyma, containing semi-solid debris may indicate a liver abscess (Fig. 10). A large-sized liver abscess can be treated with fluoroscopy-guided percutaneous catheter drainage (Fig. 11) (5).

Splenic abscess is less frequent than liver abscess among CGD patients; nonetheless, one-third of CGD patients with liver abscess are concurrently inflicted with splenic abscess (5).

Musculoskeletal manifestation

Soft tissue abscess is the third most common infection among CGD patients, caused most commonly by *staphylococci* (1). An abscess may occur even in the subcutaneous layer, which is usually accompanied by inflammation in the adjacent skin. On ultrasonography, soft tissue abscesses are shown as diffuse homogeneous hypoechoic or anechoic lesions, while the tissues adjacent to the periphery of abscess are also affected with inflammation (Fig. 12) (8). On magnetic resonance imaging (MRI), soft tissue abscess shows relatively homogeneous signal intensity similar to that of fluids, and



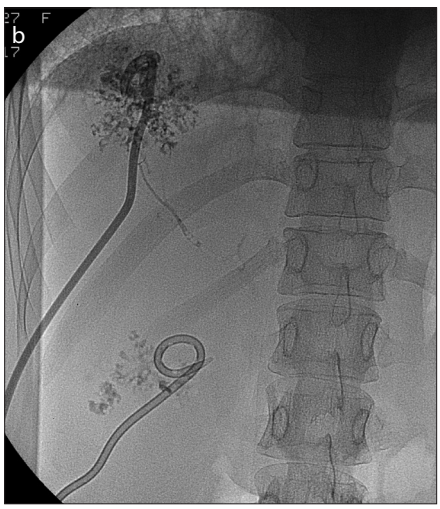


Figure 11. a, b. Multiple liver abscesses in a 23-year-old patient with CGD who presented with fever. Axial contrast-enhanced CT **(a)** shows a multiloculated abscess with peripheral and septal enhancement in the right lobe of the liver. A fluoroscopic abscessogram **(b)** obtained after percutaneous catheter drainage shows amorphous collection of contrast material in the liver abscess.

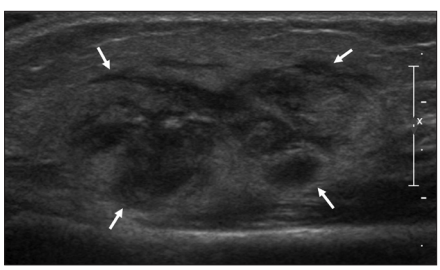


Figure 12. Subcutaneous abscess in a 16-month-old patient with CGD who presented with right upper arm swelling. Ultrasonography shows an ill-defined heterogeneous hypoechoic lesion *(arrows)* in the subcutaneous layer of the right upper arm, accompanied by perilesional edema and swelling.

reveals diverse signal changes depending on abscess contents such as proteinaceous debris, necrosis, or gas (9).

Osteomyelitis occurs in 25% of all CGD patients (1). Infection caused by *Serratia* spp. is the most common, and *Aspergillus* spp. infection is the second most common affliction in CGD (1). Osteomyelitis develops generally in the metaphysis of long bones,

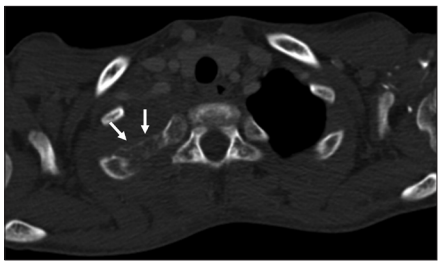


Figure 13. Osteomyelitis of the ribs in a 16-year-old boy with CGD who presented with the right shoulder pain when he was being treated for pneumonia. Axial chest CT reveals a focal osteolytic lesion *(arrows)* in the second rib.

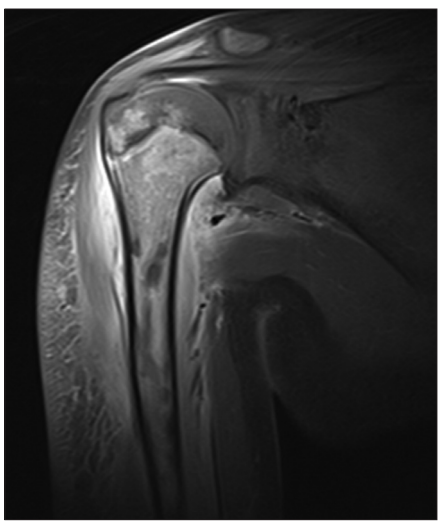


Figure 14. Acute osteomyelitis in a 7-year-old girl with CGD who presented with right shoulder pain. Contrast-enhanced T1-weighted magnetic resonance imaging (MRI) shows diffuse enhancement in humeral metadiaphysis and epiphysis, periosteal reaction, and surrounding soft tissue changes.

while osteomyelitis in CGD patients usually invades the small bones of the ribs, the vertebrae, or the lower extremities. This is due to the fact that severe pneumonia or soft tissue infection propagates to the adjacent bones in CGD patients (Fig. 13) (5). Furthermore, osteomyelitis invading the small bones of the hands and feet directly develops and propagates from inflammation in the skin (2). Osteomyelitis in the upper and lower extremities may be caused by hematogenous propagation of inflammation (Fig. 14) (2). The early phase of osteomyelitis may reveal osteolytic lesions on x-ray imaging (Fig. 15), but the later phase of the disease displays osteosclerotic lesions (2).

The characteristic image findings of myositis in CGD patients have not been reported yet. Nevertheless, on MRI, myositis in immunocompromised patients may show

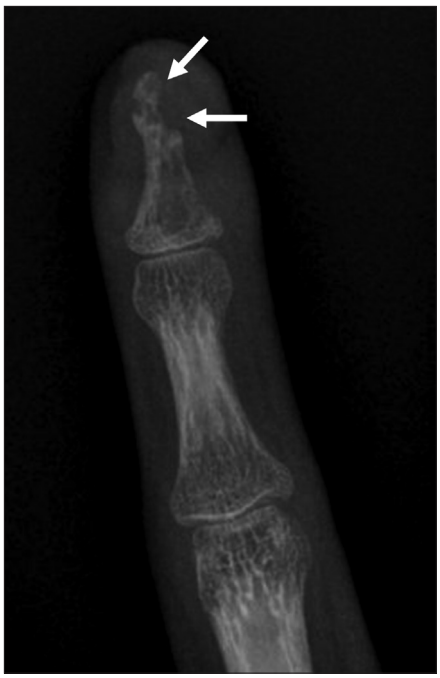


Figure 15. Acute osteomyelitis in an 18-year-old female with CGD who presented with recurrent soft tissue swelling in the right third finger. The radiograph of her right third finger discloses a destructive osteolytic lesion *(arrows)* on the tip of the distal phalanx in her third finger.

focal high signal intensity lesions within the muscles, accompanied by severe perilesional edema. It may also exhibit abscess formation (Fig. 16) (10).

CNS and ENT manifestation

The central nervous system (CNS) infection is rather rare in CGD patients, showing a prevalence rate of 5% or less (1). Brain abscess may occur as a secondary infection caused by pathogens like *Aspergillus* spp. or *S. aureus* through hematogenous transmission (1). Contrast-enhanced MRI of CNS infection, which largely occurs in the gray matter-white matter junction, may show typical rim-enhancing lesions with peripheral vasogenic edema (Fig. 17) (5).

Infections of the ear, nose, and throat (ENT) occur in 12% of CGD patients. Among them, the most common infection is otitis, which accounts for 33% of ENT infections, while parotitis takes up 5% (11). Radiologic findings of external and middle ear diseases in CGD patients are similar to those of patients with normal immunity. In particular, necrotizing otitis externa, an infection that occurs in the cartilage and bones of the external auditory canal, develops mainly in immunocompromised patients (12). On the CT scan, the skin of the external auditory canal and the auricle

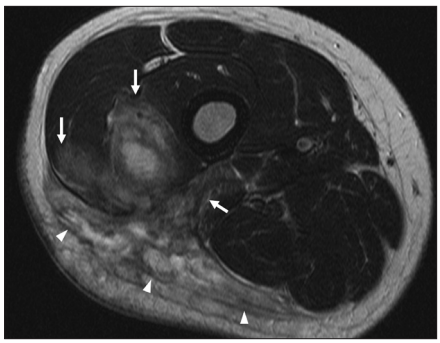


Figure 16. Infectious myositis and cellulitis in the right lateral thigh in a 6-year-old boy with CGD who presented with painful swelling in the right thigh. Axial T2-weighted MRI shows multifocal high signal intensity lesions *(arrows)* within the muscle. In particular, a necrotic fluid collection is demonstrated within the vastus lateralis muscle. The adjacent subcutaneous tissues are inflicted with cellulitis *(arrowhead)*.

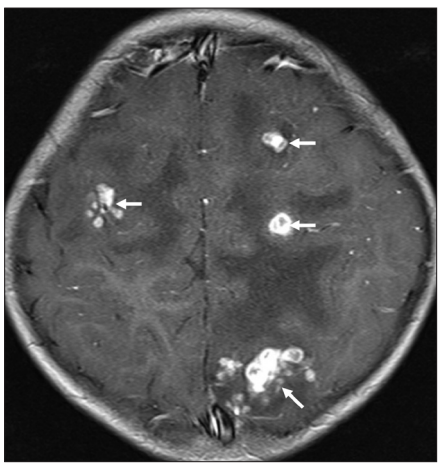


Figure 17. Multiple brain abscesses in a 6-year-old boy with CGD who presented with headache. Contrast-enhanced T1-weighted MRI shows multiple rim-enhancing lesions *(arrows)* with vasogenic edema in the brain, mainly in the gray matter-white matter junction.

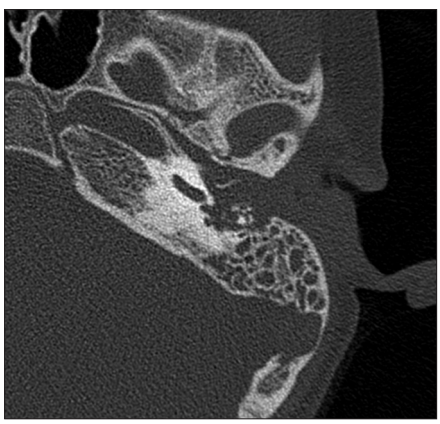


Figure 18. Necrotizing otitis externa in a 9-year-old boy with CGD who presented with continuous otorrhea. Temporal bone CT shows soft tissue density that fills the external auditory canal, erosion of the ossicles, and destruction of the mastoid bone.

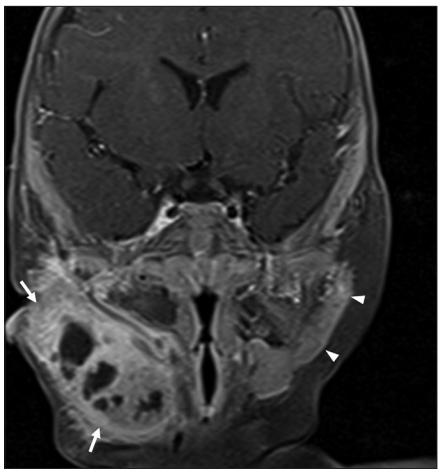


Figure 19. Parotitis with an abscess in a 5-year-old girl with CGD who presented with a mass on the right neck. Contrast-enhanced T1-weighted MRI shows an enlarged right parotid gland *(arrows)* with abscess formation. The right parotid gland *(arrows)* is markedly enlarged in comparison with the left parotid gland *(arrowheads)*.

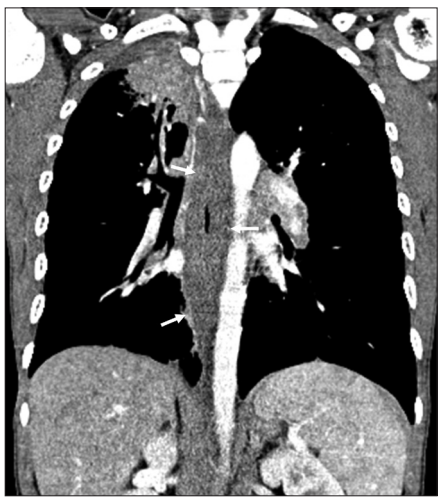


Figure 20. Esophagitis in a 12-year-old patient with CGD who presented with fever and dysphagia. Coronal contrast-enhanced chest CT shows diffuse edematous wall thickening *(arrows)* of the esopgahus. There is subsegmental consolidation in the upper lobe of the right lung.

are thick with contrast enhancement. Cases accompanied by bony destruction of the tympanic bone and mastoid bone, especially, suggest a grave prospect of life-threatening necrotizing external otitis (Fig. 18) (12).

The characteristic image findings of parotitis in CGD cases have not been reported yet. The typical image findings of parotitis show an enlarged parotid gland and diffuse enhancement with contrast. Parotitis is also accompanied by inflammatory change in subcutaneous soft tissues (Fig. 19) (5).

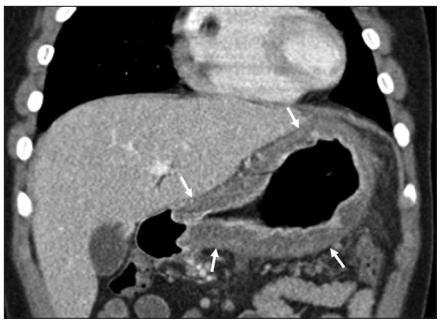


Figure 21. Granulomatous gastritis of CGD in a 12-year-old patient who presented with epigastric pain. A coronal contrast enhanced CT image shows diffuse gastric wall thickening *(arrows)* including the antral wall without the gastric outlet symptom.

Gastrointestinal manifestation

Gastrointestinal infection in CGD patients may be caused by granulomatous inflammations in the entire gastrointestinal system from mouth to anus (13). The pathogens that cause granulomatous inflammation include mostly gram-positive *S. aureus* and gram-negative organisms such as *Escherichia coli*, and *Salmonella* and *Klebsiella* spp. (2). Granulomatous inflammation of the upper gastrointestinal tract was shown as diffuse edematous wall thickening of the esophagus and the stomach (Fig. 20). In particular, the antral wall of the stomach may thicken due to granulomatous inflammation. Owing to the nonspecific attribute of wall thickening in such images, this disorder may be mistaken for peptic ulcer disease, Crohn disease, or eosinophilic gastritis (Fig. 21) (2). In the lower gastrointestinal tract, inflammatory granulomatous colitis is the most common manifestation in CGD patients. However, CGD patients with inflammatory granulomatous colitis have nonspecific symptoms and radiologic findings similar to the clinical and radiologic manifestations of inflammatory bowel diseases such as ulcerative colitis or Crohn disease (Fig. 22). Thus, differentiating the symptomatic onset of CGD-related lower gastrointestinal tract disorder from inflammatory bowel diseases may be challenging (14). Furthermore, CGD patients may also develop peritoneal abscess, lymphadenopathy, lymphadenitis, or peritonitis (5).

Genitourinary manifestation

Infection of the urinary system is relatively rare in CGD patients, but recurrent urinary tract infections, cystitis, renal and perinephric abscesses may occur (2). Granulomatous cystitis is shown with dif-

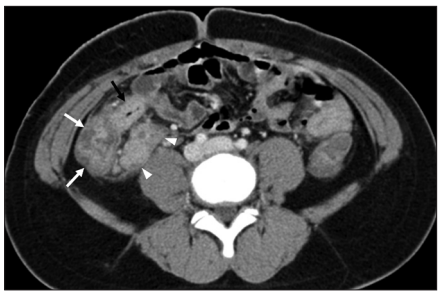


Figure 22. Lower gastrointestinal tract involvement in a 15-year-old boy who presented with abdominal pain. Axial contrast enhanced CT shows abnormal segmental wall thickening of the cecum *(white arrows)* and the terminal ileum *(black arrow)*, and conglomerated multiple lymph nodes *(arrowheads)* adjacent to the ileocecal valve.

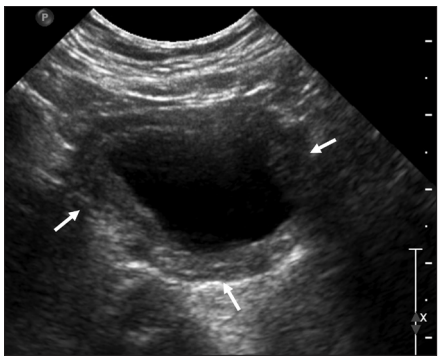


Figure 23. Cystitis in an 11-month-old patient with CGD who presented with abdominal pain. Transabdominal ultrasonography shows diffuse wall thickening *(arrows)* in the urinary bladder.

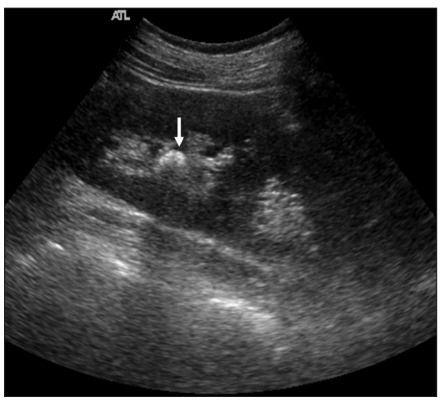


Figure 24. Renal calcification in a 16-year-old girl with CGD who presented with a history of recurrent renal infection. Renal ultrasonography shows calcification *(arrow)* with a posterior shadowing in the mid part of the left kidney.

fuse wall thickening of the urinary bladder in imaging studies (Fig. 23). This disorder may also be accompanied by an inflammatory pseudotumor. Wall thickening in the ureterovesical junction leads to a ureteral outflow obstruction, which may cause secondary hydronephrosis (5). A long-term infection of pyelonephritis or renal abscess may lead to renal calcification (Fig. 24) as a complication (5). About 3% of CGD patients develop an end-stage renal disease. This is largely due to a long-term nephrotoxicity secondary to antibiotic treatments (15).

Although inflammation of the genital system is rather rare, orchitis and epididymitis can occur in CGD patients (5).

Treatment

Generally, acute infections in CGD patients are treated with prophylactic antibiotics and antifungal agents. Recently developed antibiotics and antifungal agents have contributed to extended survival rates for most patients well into their adulthood. Interferon-γ is additionally administered in an effort to boost the phagocytic oxidative metabolism in some forms of CGD that respond to this treatment. Lately, allogeneic hematopoietic stem cell transplantation has also been restrictively implemented (3).

Conclusion

CGD is a very rare immunodeficiency disease characterized by repeated infections that invade multiple organs. CGD patients are prone to catalase-positive bacterial or fungal infections. CGD patients are likely to contract atypical infections or inflammations such as liver abscess, pneumonia-accompanied thoracic infection, or persistent lymphadenitis, which is an unlikely prospect for children with normal immunologic functions. Accordingly, clinicians should consider the possibility of CGD in pediatric patients with an infection unresponsive to treatments, repeated infections, unusual location of infection, or a severe infection that propagates to adjacent tissues.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Winkelstein JA, Marino MC, Johnston RB, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 2000; 79:155–169. [CrossRef]
2. Khanna G, Kao SC, Kirby P, Sato Y. Imaging of chronic granulomatous disease in children. Radiographics 2005; 25:1183–1195. [CrossRef]
3. Seger RA. Modern management of chronic granulomatous disease. Br J Haematol 2008; 140:255–266. [CrossRef]
4. Berendes H, Bridges RA, Good RA. A fatal granulomatosus of childhood: the clinical study of a new syndrome. Minn Med 1957; 40:309–312.
5. Towbin AJ, Chaves I. Chronic granulomatous disease. Pediatr Radiol 2010; 40:657–668. [CrossRef]
6. Godoy MC, Vos PM, Cooperberg PL, Lydell CP, Phillips P, Muller NL. Chest radiographic and CT manifestations of chronic granulomatous disease in adults. AJR Am J Roentgenol 2008; 191:1570–1575. [CrossRef]
7. Garcia-Eulate R, Hussain N, Heller T, et al. CT and MRI of hepatic abscess in patients with chronic granulomatous disease. AJR Am J Roentgenol 2006; 187:482–490. [CrossRef]
8. Bureau NJ, Chhem RK, Cardinal E. Musculoskeletal infections: US manifestations. Radiographics 1999; 19:1585–1592. [CrossRef]
9. Beaman FD, Kransdorf MJ, Andrews TR, Murphey MD, Arcara LK, Keeling JH. Superficial soft-tissue masses: analysis, diagnosis, and differential considerations. Radiographics 2007; 27:509–523. [CrossRef]
10. Schulze M, Kotter I, Ernemann U, et al. MRI findings in inflammatory muscle diseases and their noninflammatory mimics. AJR Am J Roentgenol 2009; 192:1708–1716. [CrossRef]
11. Liese J, Kloos S, Jendrossek V, et al. Long-term follow-up and outcome of 39 patients with chronic granulomatous disease. J Pediatr 2000; 137:687–693. [CrossRef]
12. Trojanowska A, Drop A, Trojanowski P, Rosinska-Bogusiewicz K, Klatka J, Bobek-Billewicz B. External and middle ear diseases: radiological diagnosis based on clinical signs and symptoms. Insights Imaging 2012; 3:33–48. [CrossRef]
13. Barton LL, Moussa SL, Villar RG, Hulett RL. Gastrointestinal complications of chronic granulomatous disease: case report and literature review. Clin Pediatr (Phila) 1998; 37:231–236. [CrossRef]
14. Huang A, Abbasakoor F, Vaizey CJ. Gastrointestinal manifestations of chronic granulomatous disease. Colorectal Dis 2006; 8:637–644. [CrossRef]
15. Bolanowski A, Mannon RB, Holland SM, et al. Successful renal transplantation in patients with chronic granulomatous disease. Am J Transplant 2006; 6:636–639. [CrossRef]