# COMMON CHEST AND ABDOMINAL COMPUTED TOMOGRAPHY FINDINGS AMONG PATIENTS WITH DISSEMINATED BCG DISEASE

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**Abstract.** The Bacillus Calmette-Guerin (BCG) vaccine, given to prevent *Mycobacterium tuberculosis*, may cause disseminated BCG, an infection and inflammatory reaction in immunocompromised individuals. In this study, we aimed to determine the chest and abdominal computed tomography (CT) findings among patients with disseminated BCG disease in order to identify some potential consequences of this vaccine and their frequencies. This study was conducted among all patients aged <16 years admitted to Masih Daneshvari Hospital, Tehran, Iran, during 2016-2019 who received the BCG vaccine and had disseminated BCG disease. Disseminated BCG disease was defined as having miliary pulmonary nodules or lymphadenitis or an abscess or fistula at the BCG vaccination site and >2 of the following: a temperature >38.5°C for >2 weeks, a familial history of immunodeficiency, weight loss, recurrent or persistent diarrhea, recurrent or persistent oral candidiasis, body aches, a hemoglobin <10 mg/dl or hepato- or splenomegaly. Exclusion criterion for study subjects were having a history of a lung disease unrelated to disseminated BCG disease or a diagnosis of tuberculosis or other atypical mycobacterial infections. Chest and abdominal CT scans were performed within 48 hours of admission on each study subject. A total of 22 subjects were included in the study; 14 males. The mean (+standard deviation) age of study subjects was 68 (+51) (range: 3-192) months. The chest and abdominal CT scan results among study subjects revealed: 55% (*n*=12) had a mediastinal mass, 36% (*n*=8) had a lung parenchymal mass, 36% (*n*=8) had a fusion of lung and mediastinal tissue, 36% (*n*=8) had invasion of the mediastinum, 32% (*n*=7) had lung parenchyma collapse, 27% (*n*=6) had invasion of the chest wall, 18% (*n*=4) had invasion of the ribs, 9% (*n*=2) had lobulated soft tissue lesions and 9% (*n*=2) had a cutaneous tract. In summary, we identified the most common chest and abdominal CT findings among subjects with disseminated BCG disease. We conclude that due to the not uncommon problem of immunocompromised patients in the study population and relatively common problem of disseminated BCG disease, these CT results should be considered as possible manifestations of disseminated BCG disease. Further studies are needed to determine if any of these chest and abdominal CT findings can be used for the early diagnosis of disseminated BCG disease.

**Keywords:** computerized tomography, infection, public health, primary immunodeficiency

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## INTRODUCTION

Vaccines are an important public health preventive tool because they cost less than the disease and its treatment (Lavan *et al*, 2017; Nasseri *et al*, 1991). There are vaccines for at least 20 human diseases and they are used either routinely or in specific instances (Barboi *et al*, 2020; Maver and Poljak, 2018; Nasseri *et al*, 1991; Smith *et al*, 2004). There are concerns about vaccine safety and efficacy (Jefferson *et al*, 2003; Marin *et al*, 2010) which require monitoring and reporting of adverse reactions (Korger *et al*, 1986).

The Bacille Calmette-Guérin (BCG) vaccine is a live vaccine used to protect against severe tuberculosis in children. Immunocompromised patients vaccinated with the BCG vaccine are more likely to experience adverse vaccine reactions consisting of disseminated infection BCG infection with an inflammatory reaction (Aghamohammadi *et al*, 2010; McCusker and Warrington, 2011; Mittal *et al*, 2014).

The BCG vaccine was introduced by Camille Guerin and Albert Calmette and consists of live attenuated *Mycobacterium bovis* (Hawgood, 1999). An infection due to *Mycobacterium bovis* in an immunocompromised patient may be life-threatening and may include a strong inflammatory response that can also cause pathology (Norouzi *et al*, 2012; Talbot *et al*, 1997). The majority of patients who have an adverse reaction to the BCG vaccine are immunocompromised males (Rezai *et al*, 2008). The majority of patients who have disseminated BCG disease in our area have Mendelian Susceptibility to Mycobacterial Disease (MSMD). MSMD is a rare immunodeficiency syndrome, characterized by a narrow vulnerability to poorly virulent mycobacteria, such as the BCG in the BCG vaccine and environmental mycobacteria; they have severe, recurrent infections due to these organisms (Shahmohammadi *et al*, 2014; Sohani *et al*, 2020). Having immunodeficiency can increase the risk for disseminated BCG disease, a rare, life-threatening complication of BCG vaccination characterized by miliary pulmonary nodules (Smith *et al*, 2015), disseminated infection spread to the lymph nodes, skin or lungs (Smith *et al*, 2015). Treatment of disseminated BCG disease includes a fluoroquinolone, such as moxifloxacin (Kourime *et al*, 2016), needle aspiration, incision and drainage or excision of involved suppurative lymph nodes (Srivanitchapoom and Yata, 2020).

The differential diagnosis of patients with symptoms of disseminated BCG disease typical mycobacteria, typical bacteria, viruses, parasites and mycotic infections, connective tissue disease and neoplasms should be considered accurately (Bhola *et al*, 2018; Ko *et al*, 2019; Kradin, 2018). The diagnosis of disseminated BCG disease must include ruling out other mycobacterial infections, such as through microbiological culture and polymerase chain reaction (PCR) testing. Accurate diagnostic testing is necessary since treatment involves a long course of medication. If a case of disseminated BCG disease is confirmed, it requires an evaluation for causes of immunodeficiency (Aelami *et al*, 2015).

Early diagnosis of disseminated BCG disease relies on a careful parent and family immunodeficiency history, physical examination for bone pain and laboratory testing, which should include a complete blood count (CBC) and liver function testing (Sadeghi-Shanbestari *et al*, 2009).

There are few studies evaluating chest and abdominal computerized tomography (CT) findings during disseminated BCG disease. In this study, we aimed to determine the chest and abdominal CT findings among subjects with disseminated BCG disease in order to identify pulmonary and abdominal consequences of disseminated BCG disease and their frequencies among immunocompromised subjects.

## MATERIALS AND METHODS

This study was conducted among all patients aged <16 years admitted to Masih Daneshvari Hospital, Tehran, Iran, during 2016-2019 with a history of receiving the BCG vaccine followed by developing disseminated BCG disease. The disseminated BCG disease diagnostic criteria used for this study to be included as a study subject were having miliary pulmonary nodules or lymphadenitis or an abscess or a fistula at the BCG vaccination site and having 2 or more of the following: a fever >38.5°C for >2 weeks, a familial history of immunodeficiency, a personal history of weight loss, having recurrent or persistent diarrhea, having recurrent or persistent oral candidiasis, having bone pain, having a hemoglobin level <10 mg/dl, having hepato- or splenomegaly (Bhola *et al*, 2018; Pendharkar *et al*, 2019; Rischmann *et al*, 2000). Exclusion criterion for study subjects was having a history of a lung disease unrelated to disseminated BCG disease or a diagnosis of tuberculosis or other atypical mycobacterial infections.

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 22.0 (International Business Machines Corporation (IBM), Chicago, IL). The chi-square test was used to calculate 95% confidence intervals (CI). The data are presented as means ± standard deviations (SD). A $p$-value ≤ 0.05 was considered statistically significant.

Written informed consent was obtained from the parents of all study subjects prior to inclusion in the study and verbal consent was obtained from older study subjects who were able to provide it. This study was approved by the Ethics Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1397.31).

## RESULTS

A total of 22 subjects were included in the study; 14 males. The mean (+SD) age of study subjects was 68 (+51) (range: 3-192) months. Fifteen subjects had MSMD. The other causes of immunodeficiency were malignancy such as lymphoma and leukemia, immunosuppressive medications and protein loss.

On our examinations, 55% (*n*=12) had a mediastinal mass (Fig1a), a lymphadenopathy was seen at the BCG vaccination site in 23% (*n*=5) (Fig 1b), and 5% of subjects had organomegaly (Fig1c).

On abdominal CT, splenomegaly was seen in 59% (*n*=13) and hepatomegaly was seen in 27% (*n*=6). Hypoechoic lesions were seen in the spleen in 14% (*n*=3), splenic masses in 9% (*n*=2) and liver masses in 5% (*n*=1).

Mesenteric lymphadenitis was seen in 50% (*n*=11), femoral lymphadenitis in 23% (*n*=5) and retroperitoneal lymphadenitis in 14% (*n*=3).

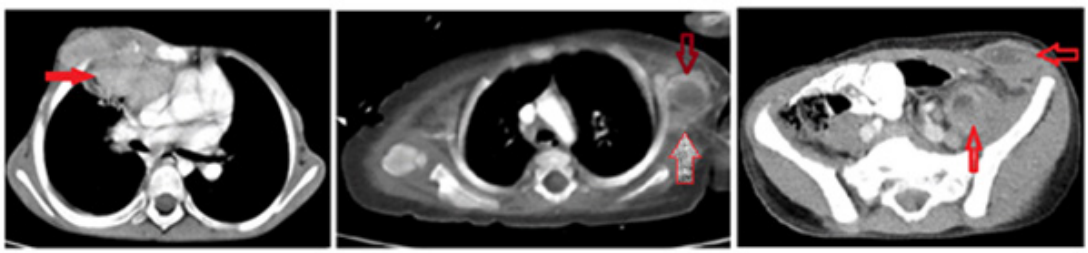
Abdominal wall thickening was seen in 41% (*n*=9), increased attenuation of the mesenteric fat was seen in 27% (*n*=6), ascites in 23% (*n*=5) and infiltration of the omental fat in 5% (*n*=1).

On chest CT, consolidation was seen in 32% (*n*=7), bronchiectasis in 23% (*n*=5), a nodule in 18% (*n*=4), a ground glass opacity (GGO) in 14% (*n*=3), a collapse in 14% (*n*=3), a cavitary lesion in 9% (*n*=2), a tree-in-bud lesion in 5% (*n*=1) scarring in 5% (*n*=1) and miliary lesions in 0% (*n*=0).

On both chest and abdominal CT, lymphadenopathy was seen in the upper abdomen in 59% (*n*=13), in the axilla in 55% (*n*=12), ), in mediastinum in 50% (*n*=11), in the hilum in 36% (*n*=8), in the cervical area in 27% (*n*=6) in the prediaphragmatic area in 23% (*n*=5), and in the retrocrural area in 18% (*n*=4) (Tables 1 and 2).

## DISCUSSION

This study reported the common chest and abdominal CT findings among patients with disseminated BCG disease in the study population.



a b c

Fig 1 - Mediastinal mass (a), lymphadenopathy near the BCG site (b) and abdominal organomegaly (abnormal enlargements) (c) in 3 study subjects

Table 1
Abnormal findings on chest and abdominal computed tomography scans of study subjects

| Findings | Frequency in percent (*n*) |
|---|---|
| Chest computed tomography scans | |
| Mediastinal lesions | 55 (12) |
| Parenchymal lesions | 36 (8) |
| Fusion of lung and mediastinal tissue | 36 (8) |
| Invasion of mediastinum | 36 (8) |
| Lung parenchyma collapse | 32 (7) |
| Invasion of chest wall | 27 (6) |
| Invasion of ribs | 18 (4) |
| Lobulations of soft tissue lesions | 9 (2) |
| Cutaneous tracts | 9 (2) |
| Abdomen computed tomography scans | |
| Splenomegaly | 59 (13) |
| Mesenteric lymphadenitis | 50 (11) |
| Abdominal wall thickening | 41 (9) |
| Hepatomegaly | 27 (6) |
| Mesenteric fat with increased attenuation | 27 (6) |
| Femoral lesions | 23 (5) |
| Ascites | 23 (5) |
| Hypoechoic lesions in the spleen | 14 (3) |
| Retroperitoneal lesions | 14 (3) |
| Spleen masses | 9 (2) |
| Liver masses | 5 (1) |
| Infiltration of omental fat | 5 (1) |

In our study, 55% of subjects had mesenteric lymphadenopathy while in a previous study with 7 disseminated BCG disease cases, 86% (*n*=6) of the patients had mesenteric lymphadenopathy as revealed by CT scan (Shrot *et al*, 2016). Constant and co-workers reported five cases disseminated BCG disease with 80% (*n*=4) mesenteric lymphadenopathy using imaging (Constant *et al*, 2011).

Table 2
Locations of lymphadenopathy seen on computed tomography scans of study subjects

| Location | Frequency in percent (*n*) |
|---|---|
| Axillary | 55 (12) |
| Hilar | 36 (8) |
| Mediastinal | 50 (11) |
| Prediaphragmatic | 23 (5) |
| Retrocrural | 18 (4) |
| Upper abdominal | 59 (13) |
| Cervical | 27 (6) |

In our 3-year study, 59% of subjects had splenomegaly similar to a previous 9-year study that found 53% of their patients had splenomegaly (Paiman *et al*, 2006).

In our study, none of the subjects had boney involvement with their disseminated BCG disease. This is in contrast to the results of previous studies that found boney involvement (Alavi and Safavi, 2008; Twine *et al*, 2007).

No miliary pattern was observed in this study; this is in accordance with the World Health Organization who recommends BCG vaccination of newborns in countries with a high TB burden to prevent miliary TB (World Health Organization, 2018).

In our study, 5% of subjects had organomegaly but a previous study reported finding organomegaly in 70% of subjects with disseminated BCG disease demonstrated a prevalence rate of nearly 70% (*n*=30) (Sharifi Asadi *et al*, 2015).

In summary, we report here the chest and abdominal CT findings of subjects with disseminated BCG disease. Chest and abdominal CT scan abnormalities were common in our study population. We had a large proportion of subjects with MSMD, a genetic condition predisposing patient to developing disseminated BCG disease upon vaccination. We conclude that due to the not uncommon problem of immunocompromised patients in the study population and relatively common problem of disseminated BCG disease, these CT results should be considered as possible manifestations of disseminated BCG disease. Further studies are needed to determine if any of these chest and abdominal CT findings can be used for the early diagnosis of disseminated BCG disease.

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## CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

## REFERENCES


Aelami MH, Alborzi A, Pouladfar G, Geramizadeh B, Pourabbas B, Mardaneh J. Post-vaccination disseminated bacillus calmette guérin infection among children in Southern Iran. *Jundishapur J Microbiol* 2015; 8: e25663.

Aghamohammadi A, Moin M, Rezaei N. History of primary immunodeficiency diseases in Iran. *Iran J Pediatr* 2010; 20: 16-34.

Alavi M, Safavi S. The bone scan in disseminated BCGitis. *Hell J Nucl Med* 2008; 11: 46-7.

Barboi A, Gibbons CH, Axelrod F, *et al*. Human papillomavirus (HPV) vaccine and autonomic disorders: a position statement from the American Autonomic Society. *Auton Neurosci* 2020; 223: 102550.

Bhola RK, Sarangi R, Dey P, Samal P. Disseminated BCG-osis with haemophagocytosis, tubercular bacteraemia, and unusual haematological findings with its haematology analyser-based expression. *J Hematopathol* 2018; 11: 87-92.

Constant C, Figueiredo A, Brito MJ. Bacille Calmette-Guérin adenitis: diagnostic and therapeutic guidelines. *Acta Med Port* 2011; 24 (Suppl 2): 263-8. [in Portuguese]

Hawgood, BJ. Doctor Albert Calmette 1863-1933: founder of antivenomous serotherapy and of antituberculous BCG vaccination. *Toxicon* 1999; 37: 1241-58.

Jefferson T, Price D, Demicheli V, *et al*. Unintended events following immunization with MMR: a systematic review. *Vaccine* 2003; 21: 3954-60.

Ko JP, Girvin F, Moore W, Naidich DP. Approach to peribronchovascular disease on CT. *Semin Ultrasound CT MR* 2019; 40: 187-99.

Korger G, Quast U, Dechert G. Tetanus vaccination--tolerance and prevention of side effects. *Klin Wochenschr* 1986; 64: 767-75. [in German]

Kourime M, Akpalu EN, H Ouair, *et al*. BCGitis/BCGosis in children: diagnosis, classification and exploration. *Arch Pédiat* 2016; 23: 754-9. [in French]

Kradin RL, editor. Diagnostic pathology of infectious disease. 2nd ed. Philadelphia, PA: Elsevier; 2018.

Lavan RP, King AIM, Sutton DJ, Tunceli K. Rationale and support for a One Health program for canine vaccination as the most cost-effective means of controlling zoonotic rabies in endemic settings. *Vaccine* 2017; 35: 1668-74.

Marin M, Broder KR, Temte JL, Snider DE, Seward JF. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010; 59 (RR-3): 1-12.

Maver PJ, Poljak M. Progress in prophylactic human papillomavirus (HPV) vaccination in 2016: a literature review. *Vaccine* 2018; 36: 5416-23.

McCusker C, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol* 2011; 7 (Suppl 1): S11.

Mittal H, Faridi MMA, Kumar P, Aggarwal A. Disseminated bacillus calmette guerin disease in a twin infant with severe combined immunodeficiency disease. *J Glob Infect Dis* 2014; 6: 132-4.

Nasseri K, Sadrizadeh B, Malek-Afzali H, *et al*. Primary health care and immunisation in Iran. *Public Health* 1991; 105: 229-38.

Norouzi S, Aghamohammadi A, Mamishi S, Rosenzweig SD, Rezaei N. Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases. *J Infect* 2012; 64: 543-54.

Paiman SA, Siadati A, Mamishi S, Tabatabaie P, Khotaee, G. Disseminated *Mycobacterium bovis* infection after BCG vaccination. *Iran J Allergy Asthma Immunol* 2006; 5: 133-7.

Pendharkar D, Hassan MJ, Khan S, Khetrapal S, Ahmad N, Jetley S. Cytological diagnosis and management of Bacille-Calmette-Guerin(BCG) induced lymphadenitis in infants. *Indian J Pathol Oncol* 2019; 6: 63-6.

Rezai MS, Khotaei G, Mamishi S, Kheirkhah M, Parvaneh N. Disseminated bacillus Calmette–Guerin infection after BCG vaccination. *J Trop Pediatr* 2008; 54: 413-6.

Rischmann P, Desgrandchamps F, Malavaud B, *et al*. BCG intravesical instillations: recommendations for side-effects management. *European urology*, 2000; *37*(Suppl. 1), 33-36.

Sadeghi-Shanbestari M, Ansarin K, Maljaei SH, *et al*. Immunologic aspects of patients with disseminated bacille Calmette-Guerin disease in north-west of Iran. *Ital J Pediatr* 2009; 35: 42.

Shahmohammadi S, Saffar MJ, Rezai MS. BCG-osis after BCG vaccination in immunocompromised children: case series and review. *J Pediatr Rev* 2014; 2: 62-74.

Sharifi Asadi P, Aghamohammadi A, Mahmoudi S, Pourakbari B, Saboui F, Mamishi S. Clinical, laboratory and imaging findings of the patients with disseminated bacilli Calmette–Guerin disease. *Allergol Immunopathol (Madr)* 2015; 43: 254-8.

Shrot S, Barkai G, Ben-Shlush A, Soudack M. BCGitis and BCGosis in children with primary immunodeficiency - imaging characteristics. *Pediatr Radiol* 2016; 46: 237-45.

Smith LL, Wright BL, Buckley RH. Successful treatment of disseminated BCG in a patient with severe combined immunodeficiency. *J Allergy Clin Immunol Pract* 2015; 3: 438-40.

Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? *Pediatrics* 2004; 114: 187-95.

Sohani M, Habibi S, Delavari S, *et al*. Evaluation of patients with primary immunodeficiency associated with Bacille Calmette-Guerin (BCG)-vaccine-derived complications. *Allergol Immunopathol (Madr)* 2020; 48: 729-37.

Srivanitchapoom C, Yata K. Suppurative cervical lymphadenitis in adult: an analysis of predictors for surgical drainage. *Auris Nasus Larynx* 2020; 47: 887-94.

Talbot EA, Perkins MD, Silva SFM, Frothingham R. Disseminated bacille Calmette-Guerin disease after vaccination: case report and review. *Clin Infect Dis* 1997; 24: 1139-46.

Twine C, Coulston J, Tayton K. Bony lesions in BCG-vaccinated children: consider BCG osteitis. *J Paediatr Child Health* 2007; 43: 307-9.

World Health Organization. BCG vaccine: WHO position paper, February 2018 - recommendations. *Vaccine* 2018; 36: 3408-10.