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Hematopoietic stem cell transplantation in a patient with X-linked chronic granulomatous disease and BCGosis: A case report and review of literature

Dear editor,

The Bacillus Calmette-Guérin (BCG) vaccine, a live attenuated strain of *Mycobacterium bovis*, is used to prevent tuberculous meningitis and miliary tuberculosis. The Tokyo-172 BCG strain is administered to infants in Taiwan.[1] BCG vaccination can lead to adverse events ranging from local inflammation and regional lymphadenitis (BCGitis) to distant or disseminated BCG infection (BCGosis), especially in immunocompromised children.[2] Chronic granulomatous disease (CGD) is caused by defects in genes encoding subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[3] Patients with CGD have impaired phagocyte function and increased susceptibility to infections, including mycobacteria.[3,4] Allogeneic HSCT may be curative for CGD.[3]

We report a five-year-old Taiwanese boy who received a BCG vaccination at five months old and has suffered from recurrent infections since he was 16 months old. He was diagnosed with X-linked CGD by decreased respiratory burst activity, decreased gp91phox protein expression on monocytes (30.5% of healthy controls), and a hemizygous splice site mutation in the *CYBB* gene, c. 897G > A at the age of 2.8 years (Supplementary Figures 1A, 2, and 3).

The patient was found to have two calcified nodules over the left axillary region on chest radiography and a positive result on a purified protein derivative skin test at the age of 3.5 years. Multiple axillary, mesenteric, and inguinal lymph nodes were identified on neck-to-pelvic computed tomography (CT) (Fig. 1A and B). BCG lymphadenitis was confirmed by an excisional biopsy of a left axillary lymph node (Supplementary Figure 4). Interferon-γ was administered regularly until one month before hematopoietic stem cell transplantation (HSCT). He was treated with anti-mycobacterial therapy with isoniazid (INH) and rifampin (RIF) for nine months for BCGitis. Triple therapy with INH, RIF, and ciprofloxacin was administered for another three months because of lung opacities on chest CT, which could indicate disseminated BCG infection (Fig. 1C).

After BCG lung infection was controlled (Fig. 1D), anti-mycobacterial therapy was changed to INH, ethambutol, and levofloxacin before transplantation to avoid drug–drug interactions, and this triple therapy was continued after transplantation. Allogeneic HLA-matched unrelated donor HSCT was performed at the age of four years and eight months, while the patient remained fully engrafted with no signs of graft-versus-host disease five months post-HSCT.

BCG infection is the most documented mycobacterial infection in 11.1–82% of patients with CGD who have received BCG vaccination.[2,4] The most common sites of BCG infection are the local injection site, left axillary lymph nodes, and lungs.[2] In a recent meta-analysis by Fekrvand S et al., BCG disease had an infection-related mortality rate of 12.4% in CGD patients.[5] We summarized nine published cases with BCG infections that occurred before HSCT in Supplementary Table 1. Six cases (66.7%) were disseminated BCG infections. One patient with disseminated BCG infection died, while 88.9% of patients were alive while receiving one to four anti-mycobacterial agents from 15 to 47 months (Supplementary Table 1).

In conclusion, BCG infection in patients with CGD has a good prognosis. Multiple anti-mycobacterial agents should

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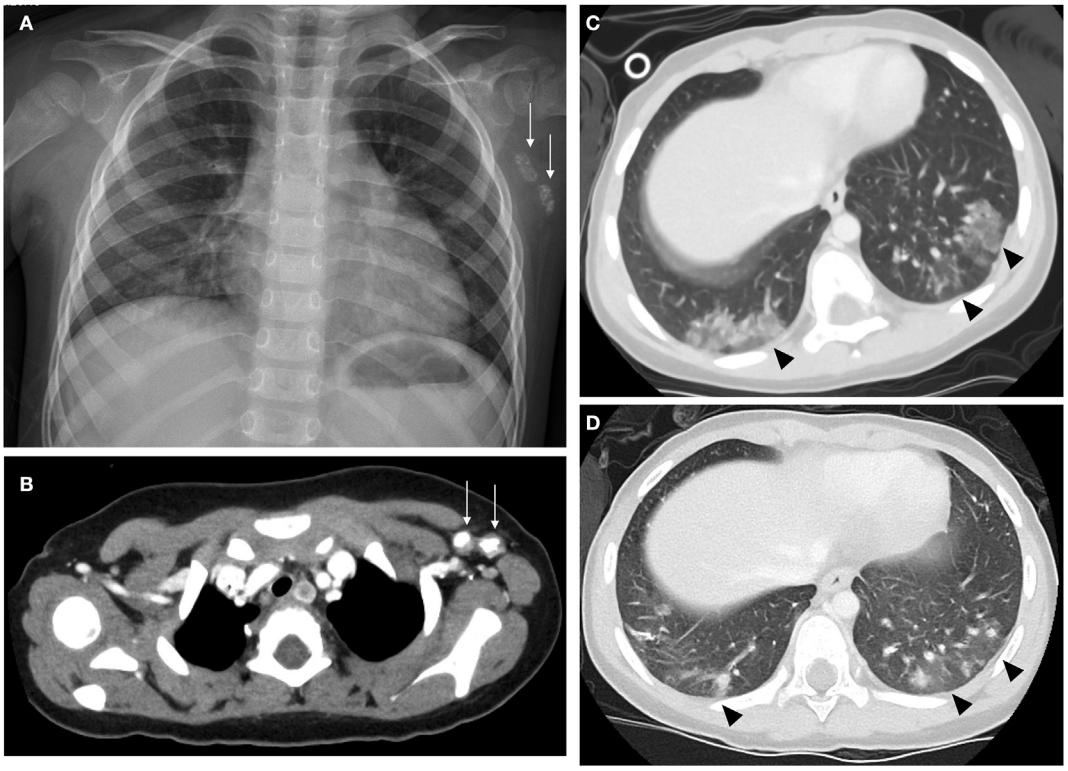

Figure 1. Chest radiograph and Chest CT images of BCG infection in our patient with CGD. Left axillary calcified lymphadenitis (indicated by arrows) at age of 3.5 years before anti-mycobacterial treatment (A, B), progressive ground glass opacities with consolidations over bilateral posterior lower lung fields (indicated by arrowheads) after nine months of isoniazid and rifampin therapy (C), improved lung consolidations (indicated by arrowheads) after triple anti-BCG therapy (isoniazid, rifampin, and ciprofloxacin) for three months (D).

control BCG infection before HSCT until patients achieve immune reconstitution post-HSCT.

Disclosure of conflict of interests

The authors declare that they have no conflict of interests.

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Author contributions

PCH designed the project, collected, analyzed the data, and drafted the manuscript. TYY collected and analyzed the data. MYL performed hematopoietic stem cell transplantation and data collection. BLC revised the manuscript with data interpretation. HHY designed the project, drafted the manuscript for submission. All authors have read and approved the manuscript.

Data availability

Please contact the corresponding author Dr. Hsin-Hui Yu at yuhsinhui0121@ntu.edu.tw if you wish to request further information on the data.

Ethics approval and consent to participate

This study was approved by the Institutional Research Ethics Committee at National Taiwan University Hospital, Taipei, Taiwan. All procedures were performed with the prior informed consent of the parents/legal guardian.

Consent to publication

Patient's parents provided informed consent for this case report to be published.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.01.002.

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