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BRIEF REPORT

Rapid Diagnosis of Hemophagocytic Lymphohistiocytosis Triggered by Disseminated BCG Infection in Infants With Severe Combined Immunodeficiency: Case Report

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Hemophagocytic lymphohistiocytosis triggered by disseminated Bacillus Calmette-Guerin infection is rare. Targeted next-generation sequencing for tuberculosis can rapidly identify different strains of *Mycobacterium tuberculosis* complex as well as drug resistance genes. Herein we report 2 cases of hemophagocytic lymphohistiocytosis in whom targeted next-generation sequencing rapidly identified Bacillus Calmette-Guerin as the infectious trigger.

Keywords. disseminated BCG disease; hemophagocytic lymphohistiocytosis; *Mycobacterium bovis* BCG; severe combined immunodeficiency; targeted next-generation sequencing.

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening state of immune hyperactivation. It comprises a primary form and a secondary form. The former is related to genetic mutations, while the latter is related to infectious, inflammatory, or neoplastic triggers. Diagnosis of secondary HLH should meet 5 of the following 8 criteria: fever, splenomegaly, cytopenia (affecting ≥2 of 3 lineages in the peripheral blood), hypertriglyceridemia (≥3 mmol/L) and/or hypofibrinogenemia (≤1.5 g/L), hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer (NK) cell activity, elevated ferritin (≥500 μg/L), soluble CD25 (≥2400 U/L) according to the 2004 diagnostic guideline [1]. The most common infectious triggers for secondary HLH are viruses, while bacteria, visceral leishmaniasis, mycobacteria, and fungi can also trigger HLH [1, 2]. Indeed, studies have reported cases of HLH triggered by disseminated tuberculosis (TB) [3, 4]. Easily confused with *Mycobacterium tuberculosis* (MTB), Bacillus Calmette-Guerin (BCG), which consists of attenuated *Mycobacterium tuberculosis* variant *bovis* BCG (*M. bovis* BCG), is a strain of MTB complex that can cause severe disseminated infection in children with immunodeficiency [5]. In China, BCG vaccination (vaccine D_2PB302, introduced from Danish strain-823) is recommended at birth, except in those with immunodeficiency or acute or severe chronic illness. Infants with underlying immunodeficiency that may not be recognized at birth in the absence of newborn screening for severe combined immunodeficiency (SCID) are susceptible to BCG infection. However, HLH triggered by disseminated BCG infection is rarely reported. Timely diagnosis of BCG-triggered HLH is highly challenging, and any delay in diagnosis and treatment is life-threatening. Detection of *M. bovis* BCG by culture is time-consuming and has low sensitivity, while conventional nucleic acid detection cannot identify the strain and provide information on drug resistance. Recently, targeted next-generation sequencing (tNGS) has emerged as a comprehensive alternative to existing methods for drug susceptibility testing (DST) and strain identification for MTB complex [6, 7]. Targeted NGS developed by Hugo Biotech Co., Ltd., for tuberculosis (TB-pro), based on targeted polymerase chain reaction with specific primers and next-generation sequencing, can identify 10 different MTB strains and 17 antituberculous drug-related resistance genes within 48 hours [8, 9]. Typically, the sequencing is performed for cell-free DNA in blood samples, whereas it is performed for whole cells and cell-free DNA in other samples such as cerebrospinal fluid (CSF), sputum, and bronchoalveolar lavage fluid. Herein, we report 2 cases of infants admitted with HLH in whom *M. bovis* BCG in blood and cerebrospinal fluid (CSF) was identified by tNGS.

Ethical Statement

Our study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University.

Case Presentation

Patient 1: A 3-month-old boy with fever and cough for 9 days and rash for 6 days was admitted to the pediatric intensive care unit of West China Second University Hospital on October 14, 2022. The patient was given ceftriaxone for 5 days and cefotaxime for 3 days in a local hospital, but his symptoms did not improve. He was the first baby of nonconsanguineous Chinese parents. There was no known family history of hereditary disorders. The parents denied exposure to TB.

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No abnormality was noticed at birth; then he received BCG vaccination. On admission, his height and weight were 60 cm and 6.8 kg, respectively. His temperature was 38.6 °C, heart rate 190 bpm, respiratory rate 56 bpm, and blood pressure 73/59 mmHg. He had scattered red macules and papules all over his body. A BCG scar was noted on his left upper arm. Superficial lymph nodes were not enlarged. Abdominal palpation demonstrated hepatomegaly and splenomegaly; his liver was palpable to 6 cm under the right costal margin, and the spleen was palpable to 8 cm under the left costal margin. Laboratory examinations revealed decreased hemoglobin (Hb, 79 g/L) and platelet count (Plt, 38 000/μL), elevated triglycerides (3.49 mmol/L), elevated ferritin (3022.7 ng/mL), and elevated sCD25 (14 784 pg/mL). NK cell activity was normal (24.25%). Nucleic acid tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV), coronavirus disease 2019 (COVID-19), adenovirus, respiratory syncytial virus, rhinovirus, influenza virus, parainfluenza virus, metapneumovirus, bocavirus, mycoplasma, and chlamydia were all negative. Immunoglobin M (IgM) tests for herpes simplex virus and rubella virus were negative. Mycobacterial cultures of blood, gastric juice, and CSF were negative after 6 weeks of incubation. Other bacterial and fungal cultures of blood, CSF, and sputum were negative. The interferon-gamma release assay (IGRA) was indeterminate, with decreased positive control. The Xpert MTB/RIF tests of sputum and gastric juice performed on admission were negative. A second Xpert MTB/RIF of sputum performed 1 week after admission revealed "MTB detected with very low quantity and RIF resistance not detected." The main laboratory examinations performed during the first week of hospitalization are summarized in Supplementary Table 1. The bone marrow smear showed active hyperplasia without hemophagocytosis. Computed tomography (CT) of the thorax and abdomen revealed exudation and ground glass shadow in both lungs (Figure 1*A*) and hepatosplenomegaly (Figure 1*B*). Brain magnetic resonance imaging (MRI) showed bilateral ventricular enlargement. With fever, splenomegaly, decreased hemoglobin and platelet count, and elevated triglycerides, ferritin, and sCD25, a diagnosis of HLH was made according to the HLH-2004 criteria (6/8 criteria). A chemotherapy regimen of dexamethasone and etoposide was initiated, and imipenem and cilastatin were used as anti-infectious agents. Pathogen metagenomic next-generation sequencing (mNGS; Hugo Biotech Co., Ltd.) of blood and CSF was performed searching for infectious agents, and MTB complex was identified 48 hours later in both blood (reads: 27 138) and CSF (reads: 15 710). Antituberculous treatment with isoniazid, rifampin, pyrazinamide, and ethambutol was immediately started, while another sample of blood was sent for tNGS (TB-pro) to identify the strain of MTB complex and drug resistance genes. Another 48 hours later, tNGS identified pyrazinamide-resistant *M. bovis* BCG in blood (reads: 4459). Pyrazinamide was discontinued, and levofloxacin was introduced. Whole-exome sequencing (WES) was subsequently conducted. One month later, WES revealed a pathogenic mutation of IL2RG (c.391C > T, p.Gln131Ter) in the X chromosome, which indicated X-linked SCID. The primary HLH-related genes were all negative. After 1 month of antituberculous treatment, a second tNGS of blood was performed, and *M. bovis* BCG was still detected (reads: 47); a tNGS of CSF was also performed, and pyrazinamide-resistant *M. bovis* BCG was identified (reads: 487). After 2 months of antituberculous treatment, a second mNGS was performed, and MTB complex was still detected (reads: 30). The patient underwent hematopoietic stem cell transplantation (HSCT) after 2 months of intensive antituberculous treatment with isoniazid, rifampin, levofloxacin, ethambutol, and chemotherapy. He continues the consolidation period of antituberculous treatment with isoniazid and rifampin, which will last for 10 months and will be completed in October 2023. He has regular follow-ups in the pediatric hematology department and pediatric infectious diseases department.

Patient Consent

Our study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University. Before the study enrollment, written informed consent was obtained from the guardians of this patient for the publication of this case report and all information contained in it.

Patient 2: A 3.5-month-old boy with fever for 1 week and abdominal distension, wheezing, and shortness of breath for 1 day was admitted to the pediatric intensive care unit of West China Second University Hospital on December 5, 2022. He received ceftriaxone and penicillin for 6 days in a local hospital, but his symptoms did not improve. He was the first baby of nonconsanguineous Chinese parents. The parents were healthy, and there was no known family history of hereditary disorders. His parents denied exposure to TB. No abnormality was found at birth; then he received BCG vaccination. On admission, his height and weight were 60 cm and 7.1 kg, respectively. His temperature was 36.1 °C, heart rate 176 bpm, respiratory rate 56 bpm, and blood pressure 101/67 mmHg. The BCG scar had swelling and redness. Abdominal palpation demonstrated an enlarged liver, palpable to 5 cm under the right costal margin, as well as an enlarged spleen, palpable to 7 cm under the left costal margin. A routine blood count revealed pancytopenia (white blood cell 2000/μL, Hb 83 g/L, Plt 18 000/μL). Other laboratory examinations showed decreased fibrinogen (102 mg/dL) and elevated triglycerides (5.09 mmol/L) and ferritin (4318.0 ng/mL). NK cell activity (20.7%) and sCD25 (5187 pg/mL) were normal. Nucleic acid tests of EBV, CMV, COVID-19, adenovirus, respiratory syncytial virus, rhinovirus, influenza virus, parainfluenza virus, metapneumovirus, bocavirus, mycoplasma, and chlamydia were all negative. Mycobacterial cultures of blood and gastric juice were negative

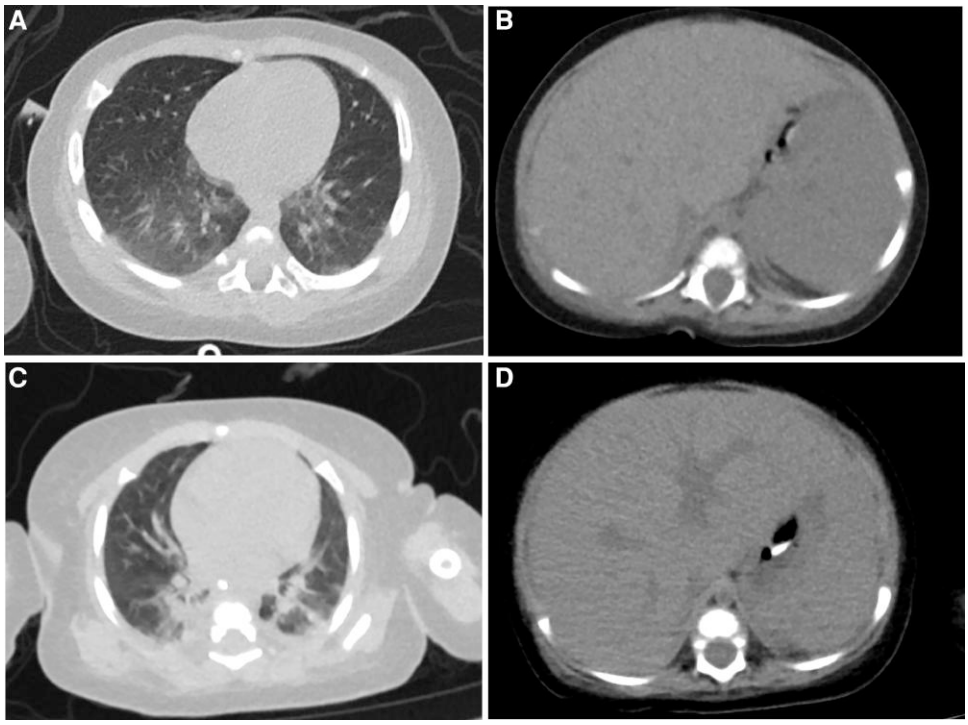

Figure 1. CT images of the thorax and abdomen for patient 1 and patient 2. *A*, CT image of the thorax for patient 1. *B*, CT image of the abdomen for patient 1. *C*, CT image of the thorax for patient 2. *D*, CT image of the abdomen for patient 2. Abbreviation: CT, computed tomography.

after 6 weeks of incubation. Other bacterial and fungal cultures of CSF, blood, and sputum were normal. The Xpert MTB/RIF tests of sputum and gastric juice were negative. The IGRA was indeterminate, with decreased positive control. All results are summarized in Supplementary Table 2. Bone marrow smear did not show hemophagocytosis. CT of the thorax revealed exudation and consolidation in the lower lobes of both lungs (Figure 1*C*). Abdominal CT demonstrated enlargement of the liver and spleen (Figure 1*D*). A head CT was normal. With fever, splenomegaly, pancytopenia, hypertriglyceridemia and hypofibrinogenemia, and elevated ferritin, a diagnosis of HLH was made according to the 2004-HLH criteria (5/8 criteria). Chemotherapy with dexamethasone and etoposide was initiated, and meropenem and vancomycin were administered as anti-infectious agents. Intravenous immunoglobin G (IVIG) was also given for supportive treatment. Due to poor response to anti-infective treatment and chemotherapy for 2 weeks, BCG infection was suspected, and tNGS (TB-pro) of blood was sent to identify the pathogen. *M. bovis* BCG was identified 48 hours later, and it was resistant to pyrazinamide. Antitubercular treatment with isoniazid, rifampin, levofloxacin, and ethambutol was immediately started. Concurrently, WES for primary HLH and immunodeficiency genes was sent. Three weeks later, the WES showed that a novel mutation of IL2RG (c.758-1G > A) was found in the X chromosome, which is inferred pathogenic in Clinvar, indicating X-linked SCID. A diagnosis of disseminated BCG infection-triggered HLH and X-linked SCID was made. The parents rejected further treatment and took the infant home without follow-up.

Patient Consent

Our study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University. Before study enrollment, written informed consent was obtained from the guardians of this patient for the publication of this case report and all information contained in it.

DISCUSSION

We report 2 patients in whom HLH caused by disseminated BCG infection was rapidly diagnosed using the new method of tNGS. Targeted NGS, based on specific primers and targeted amplification, can distinguish 10 different MTB strains including *M. Bovis* BCG. In patient 1, detection of the MTB complex in blood, CSF, and sputum, then identification of the MTB complex as *M. bovis* BCG in blood and CSF, and repeated detection of *M. bovis* BCG in blood (2 samples 1 month apart) in conjunction with clinical manifestations may be indicative of definite disseminated BCG infection in patients with inborn error of immunity according to the European Society for Immunodeficiencies. In patient 2, only a single detection of *M. bovis* BCG in the blood in combination with systemic symptoms is indicative of probable disseminated BCG

Table 1. Clinical Characteristics in BCG-Triggered HLH in IEIs

	P1	P2	P3	P4	P5	P6	P7
Year	2019	2020	2021	2022	2020	2023	2023
Sex	F	F	M	M	M	M	M
HLH onset age, mo	4	2	3.9	5	4	3	3
Origin	Morocco	Iran	United Arab Emirates	United States	China	China	China
Gene	*IFNGR1*	*IFNGR1*	*CYBB*	*1L2RG*	*1L2RG*	*1L2RG*	*1L2RG*
Mutation	p.W99R, hom	c.514T > G, hom	c.676C > T, hemi	c.596_598delinsTGGATTAT, hemi	c.854G > A, hemi	c.391C > T, hemi	c.758-1G > A, hemi
BCG detection method	NA	Molecular study	NA	CBNAAT	mNGS and PCR-RDB	tNGS	tNGS
BCG infective location	Local	Disseminated	Local	Disseminated	Disseminated	Disseminated	Disseminated
BCG resistance gene	NA	NA	NA	Rifampin negative, others NA	NA	Pyrazinamide positive, others negative	Pyrazinamide positive, others negative
HLH criteria	6/8	5/8	6/8	5/8	6/8	6/8	5/8
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Splenomegaly	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ANC, cells/μL	Normal	8130	2400 ± 500	1890	410	4890	1260
Hb, g/dL	5	5.5	7.1 ± 0.6	4.6	5.2	7.9	8.3
Plt, cells/μL	30 000	38 000	79 000 ± 64 000	4000	23 000	38 000	18 000
Ferritin, ng/mL	1043	2800	>8000	1703	3235	3022.7	4318.0
Triglyceride, g/L	2.11	2.73	1.77 ± 0.42	NA	NA	3.49	5.09
Fibrinogen, mg/dL	420	398	Decreased	212	91	342	102
NK activity	Decreased	NA	NA	NA	NA	24.25% (normal range: ≥15.11%)	20.07% (normal range: ≥15.11%)
Scd25, pg/mL	NA	NA	5386 pg/mL (normal range: 175–858 pg/mL)	89.47 IU/mL (normal range: 27–189 IU/mL)	5182.51 pg/mL (normal range: 410–2623 pg/mL)	14 784 pg/mL (normal range: < 6400 pg/mL)	5187 pg/mL (normal range: < 6400 pg/mL)
Hemophagocytosis	No	No	NA	Yes	No	No	No
ATT treatment	HREA	HREA	None	4-drug ATT	HRZE	HREL	HREL
Outcome	Resolved	Deceased	Deceased	Deceased	Deceased	Cured	Lost to follow-up
Reference	[10]	[11]	[12]	[14]	[13]	Current patient 1[a]	Current patient 2[a]

Abbreviations: A, amikacin; ANC, absolute neutrophil count; ATT, antituberculous treatment; BCG, Bacillus Calmette-Guerin; CBNAAT, cartridge-based nucleic acid amplification test; E, ethambutol; H, isoniazid; Hb, hemoglobin; hemi, hemizygous mutation; hom, homozygous mutation; HLH, hemophagocytic lymphohistiocytosis; IEIs, inborn errors of immunity; L, levofloxacin; mNGS, metagenomic next-generation sequencing; NA, not accessible; NK, natural killer; PCR-RDB, polymerase chain reaction–reverse dot blot; Plt, platelet; R, rifampin; tNGS, targeted next-generation sequencing; Z, pyrazinamide.

[a]The results for current patient 1 and patient 2 were performed on the first day of hospitalization.

infection. A positive result of tNGS from recent BCG vaccination cannot be excluded for this patient. Additional investigation is needed to determine how long BCG can be identified in blood by metagenomics after vaccination.

To date, only 5 patients with BCG-triggered HLH have been reported, 3 with disseminated BCG infection and 2 with local BCG infection (Table 1) [10–14]. HLH is mediated by cytotoxic lymphocytes and macrophage hyperactivation, and chemotherapy with cytotoxic drugs is the first-line treatment [2, 15]. However, for patients with HLH secondary to infection, chemotherapy without targeted anti-infectious therapy may cause the disease to worsen [11]. Treatment of disseminated BCG-triggered HLH is challenging. Disseminated BCG-triggered HLH did not resolve in 3 previously reported patients, and all died. Our patient 1 underwent early treatment with antituberculous agents combined with chemotherapy, resulting in resolution of HLH and allowing for further HSCT. The effective response to antitubercular treatment and chemotherapy supports the diagnosis of BCG-triggered HLH. This case shows that timely identification of BCG is critical for subsequent treatment and better prognosis.

BCG vaccination is widely given at birth in countries with endemic tuberculosis. However, BCG infection cannot be avoided in children with underlying immunodeficiencies in the absence of newborn screening for SCID. Differentiating tuberculosis and BCG infection in infants is confusing, as the clinical symptoms of the 2 conditions are atypical and may be overlapping. Of the 5 patients whose cases have been previously reported, 2 were clinically diagnosed [10, 12], 1 detected MTB complex without strain identification [14], and another 2 were confirmed by molecular diagnostic methods to have BCG infection[11, 13]. No patient underwent the full range of antituberculous drugs related to resistance gene testing. Nucleic acid detection methods commonly applied in clinical settings, including Xpert MTB/RIF, TB-DNA polymerase chain reaction, and mNGS, cannot identify the specific strain or the entire range of drug resistance genes for MTB complex. The new method of tNGS can not only distinguish different strains of MTB complex, but also identify 4 first-line and 13 second-line antituberculous drug resistance genes. As BCG infection is atypical and the pathogen is intrinsically resistant to pyrazinamide and sometimes resistant to isoniazid and rifampin, timely identification of the strain and drug resistance genes is important [16]. We used tNGS to rapidly identify both the BCG strain and antituberculous drug resistance genes, allowing for early diagnosis of BCG disease and provision of drug resistance information for targeted therapy planning. However, this is the first instance of the utility of tNGS in identifying drug resistance genes for BCG. The detection of a pyrazinamide resistance gene is consistent with a BCG strain, but the other drug resistance genes need to be verified by phenotypic resistance in the future.

Disseminated BCG infection is usually an indicator of immunodeficiency [17]. Inborn errors of immunity could predispose a patient to HLH after an uncontrolled infection [2]; thus early identification of both the inborn errors of immunity and specific pathogens is important for these patients. Mutations in IL2RG result in typical X-SCID with absent T and NK cells and functionally abnormal B cells [18]. It is fatal without HSCT. Most of the previously reported patients died due to delayed diagnosis and uncontrolled infections before HSCT for HLH with SCID [14, 19, 20]. For patient 1, X-linked SCID was expeditiously identified after early identification of disseminated BCG infection. Thus, preparation for HSCT was undertaken as soon as possible. This is the first case of BCG-trigged HLH with SCID who successfully received an HSCT. This successful treatment with targeted antituberculous treatment, chemotherapy, and HSCT can be valuable in guiding therapy for future patients.

CONCLUSIONS

Targeted NGS with more verification will be a valuable tool for early identification of the specific strain and drug resistance genes in patients with MTB complex infection. Rapid identification of BCG by tNGS may ensure timely treatment and favorable outcomes for BCG-triggered HLH in patients with SCID.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. T.T.Z. and Y.Z.: concept design and writing the original draft. Q.L., Y.L., and Q.G.: resources and validation. Y.Z. and C.M.W.: supervision and funding acquisition.

Ethical approval. This study protocol was approved by the Ethic Committee of West China Second University Hospital, Sichuan University.

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Potential conflicts of interest. All authors: no reported conflicts.

References

1. Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer **2007;** 48: 124–31.
2. Griffin G, Shenoi S, Hughes GC. Hemophagocytic lymphohistiocytosis: an update on pathogenesis, diagnosis, and therapy. Best Pract Res Clin Rheumatol **2020;** 34: 101515.
3. Hauch H, Skrzypek S, Woessmann W, et al. Tuberculosis-associated HLH in an 8-month-old infant: a case report and review. Front Pediatr **2020;** 8:556155.
4. Kessler M, Reinig E. HLH associated with disseminated tuberculosis. N Engl J Med **2020;** 382:1749.
5. Al-Hammadi S, Alsuwaidi AR, Alshamsi ET, Ghatasheh GA, Souid AK. Disseminated Bacillus Calmette-Guérin (BCG) infections in infants with immunodeficiency. BMC Res Notes **2017;** 10:177.

6. Cabibbe AM, Spitaleri A, Battaglia S, et al. Application of targeted next-generation sequencing assay on a portable sequencing platform for culture-free detection of drug-resistant tuberculosis from clinical samples. J Clin Microbiol **2020;** 58: e00632-20.
7. Georghiou S, Rodwell T, Colman R, Denkinger C. *The Use of Next-Generation Sequencing Technologies for the Detection of Mutations Associated With Drug Resistance in* Mycobacterium tuberculosis *Complex: Technical Guide*. World Health Organization; **2018**.
8. Mansoor H, Hirani N, Chavan V, et al. Clinical utility of target-based next-generation sequencing for drug-resistant TB. Int J Tuberc Lung Dis **2023;** 27:41–8.
9. Wu X, Liang R, Xiao Y, et al. Application of targeted next generation sequencing technology in the diagnosis of *Mycobacterium tuberculosis* and first line drugs resistance directly from cell-free DNA of bronchoalveolar lavage fluid. J Infect **2023;** 86:399–401.
10. Humblet-Baron S, Franckaert D, Dooley J, et al. IFN-γ and CD25 drive distinct pathologic features during hemophagocytic lymphohistiocytosis. J Allergy Clin Immunol **2019;** 143:2215–26.e7.
11. Razaghian A, Parvaneh L, Delkhah M, et al. Bacillus Calmette-Guérin (BCG)-associated hemophagocytic lymphohistiocytosis in the setting of IFN-γR1 deficiency: a diagnostic dilemma. EJHaem **2020;** 1:334–7.
12. Al-Hammadi S, Yahya AM, Al-Amri A, et al. Case report: BCG-triggered hemophagocytic lymphohistiocytosis in an infant with X-linked recessive Mendelian susceptibility to mycobacterial disease due to a variant of chronic granulomatous disease. Front Pediatr **2021;** 9:687538.
13. Shi B, Chen M, Xia Z, et al. Hemophagocytic syndrome associated with *Mycobacterium bovis* in a patient with X-SCID: a case report. BMC Infect Dis **2020;** 20:711.
14. Vignesh P, Anjani G, Kumrah R, et al. Features of hemophagocytic lymphohistiocytosis in infants with severe combined immunodeficiency: our experience from Chandigarh, North India. Front Immunol **2022;** 13:867753.
15. de Saint Basile G, Sepulveda FE, Maschalidi S, Fischer A. Cytotoxic granule secretion by lymphocytes and its link to immune homeostasis. F1000Res **2015;** 4:930.
16. Ritz N, Tebruegge M, Connell TG, Sievers A, Robins-Browne R, Curtis N. Susceptibility of *Mycobacterium bovis* BCG vaccine strains to antituberculous antibiotics. Antimicrob Agents Chemother **2009;** 53:316–8.
17. Pöyhönen L, Bustamante J, Casanova JL, Jouanguy E, Zhang Q. Life-threatening infections due to live-attenuated vaccines: early manifestations of inborn errors of immunity. J Clin Immunol **2019;** 39:376–90.
18. Kumrah R, Vignesh P, Patra P, et al. Genetics of severe combined immunodeficiency. Genes Dis **2020;** 7:52–61.
19. Bode SF, Ammann S, Al-Herz W, et al. The syndrome of hemophagocytic lymphohistiocytosis in primary immunodeficiencies: implications for differential diagnosis and pathogenesis. Haematologica **2015;** 100:978–88.
20. Cetinkaya PG, Cagdas D, Gumruk F, Tezcan I. Hemophagocytic lymphohistiocytosis in patients with primary immunodeficiency. J Pediatr Hematol Oncol **2020;** 42:e434–9.