Granulomatous hepatitis as a rare complication of Bacillus Calmette-Guérin vaccination

Maryam Shoaran, Mehri Najafi, Rozita Jalilian, Nima Rezaei

From the Department of Pediatric Gastroenterology, Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Correspondence: Dr. Maryam Shoaran · Department of Pediatric Gastroenterology, Pediatric Health Research Center, Tabriz University of Medical Sciences, Children Hospital, Sheshgelan Street, Tabriz, Iran · T: 00984115262250 · maryamshoaran@yahoo.com

Ann Saudi Med 2013; 33(6): 627-629
DOI: 10.5144/0256-4947.2013.627

Bacillus Calmette-Guérin (BCG) vaccine, which is a widely practiced vaccine in some regions, could lead to a variety of complications. Herein, a 2-month-old infant is presented who was referred because of hepatosplenomegaly and diarrhea. Liver biopsy indicated multiple small and large granulomas composed of epithelioid histiocytes; granulomas resided in portal or lobular areas. The diagnosis of granulomatous hepatitis was made, and treatment with isoniazid, rifampine, and ethambutol were started. Liver function tests were normalized and hepatosplenomegaly was reduced in an 8-month follow-up. The presence of epithelioid cell granuloma in the liver may indicate a diagnosis of disseminated BCG as a rare complication of vaccination. Prompt diagnosis and appropriate treatment could prevent further complications in the affected patients.

Tuberculosis (TB), as one of the most important infectious diseases in developing countries, is still a health challenge and a leading cause of mortality.1 Bacillus Calmette-Guérin (BCG) vaccine (strain of Mycobacterium bovis) has been used widely against human TB. However, as of live-attenuated nature of the vaccine, complications occasionally occur, including ulcers and abscesses at the site of injection, regional lymphadenitis, and even disseminated disease (BCGosis).2 Serious complications occur mostly in immunodeficient patients, while BCGosis has been described in immunocompetent patients.3 Herein, a rare complication of BCG is presented in an infant who suffered from granulomatous hepatitis.

CASE

A 2-month-old infant boy was referred to the Children’s Medical Center Hospital, Pediatrics Center of Excellence, with hepatosplenomegaly and mild diarrhea. He was the first child of related parents. His birth and medical histories were unremarkable. The baby was well until 1.5 months of age when he became symptomatic. He did not have a family history of similar problem, immunodeficiency, or any other specific disease. On physical examination, the liver was palpable 5 to 6 cm and spleen 6 to 7 cm below the costal margin. No fever and respiratory symptoms were reported; a non-tender painless mass (2×2 cm) was found in his left axilla, which could not be aspirated.

Laboratory data showed abnormal liver function tests, including elevated levels of alanine aminotransferase (ALT): 114U/L (normal range <40 U/L), aspartate aminotransferase (AST): 136U/L (normal range <40 U/L), gamma-glutamyltransferase: 279 U/L, which was above the normal range. Bilirubin total and direct levels were 1.5 and 0.3 mg/dL, respectively. Erythrocyte sedimentation rate was 21. Other laboratory findings, including complete blood count, blood sugar, blood urea nitrogen, creatinine, coagulation profile, serum protein, albumin, triglyceride, cholesterol, serum lactate and ammonia, alpha-1-antitrypsine, and serum and urine chromatography were all within normal range. Stool examination was unremarkable. Abdominal sonography revealed splenomegaly (77 mm) with hypoechoic areas, hepatomegaly (73 mm), and several celiac and para-aortic lymph nodes, which were highly suggestive for infiltrative lesions, especially BCGosis.

The patient subsequently underwent a liver biopsy that showed multiple small and large granulomas composed of epithelioid histiocytes, some with clear and plump cytoplasm, surrounded by few lymphocytes and fibroblasts. In one granuloma, Langhans giant cell was evident. No caseative necrosis was seen; granulomas resided in portal or lobular areas. There was also evi-
case report

GRANULOMATOUS HEPATITIS AND BCG VACCINE

dence of portal fibrous expansion, portal inflammation, lobular inflammation, and interface hepatitis. Ziehl–Neelsen staining demonstrated a few acid-fast bacilli (Figures 1 and 2). Tissue culture and polymerase chain reaction (PCR) for mycobacteria were negative.

The diagnosis of granulomatous hepatitis was made; and the mycobacterial infection was considered on top of the diagnostic list. Other infections or drug causes leading to granuloma formation in the liver were excluded. Human immunodeficiency virus antibody and autoantibodies were negative; no evidence of primary immunodeficiency disease was reported through screening tests (immunoglobulin assays, B-cell and T-cell enumeration, and nitroblue tetrazolium test). To evaluate more specific immunologic pathways including IL-12 and IFN-α receptor deficiency, the samples had to be sent to a referral laboratory for analysis. Unfortunately, the parents did not agree to a comprehensive evaluation of immunologic function.

Gastric lavage was negative for TB, but tuberculin skin test (PPD) was positive (17 mm induration). Chest x-ray showed prominence of perihilar markers, right hilum enlargement, and splenomegaly. With the presence of BCG scar and positive PPD, a triple therapy was initiated (isoniazid: 10 mg/kg/d, rifampine: 15 mg/kg/d, and ethambutol: 15 mg/kg/d) for 2 months; It was then recommended to continue isoniazid and rifampine for 7.

In a follow-up, liver function tests were normalized (ALT: 25U/L and AST: 35U/L), hepatosplenomegaly was reduced and no axillary mass was existed within 8 months of starting therapy. Now, he is under a regular follow-up every 2 months. He was well on his last visit; the liver was 2 cm below costal margin and the spleen was just palpable.

DISCUSSION

Granulomas can be present in the liver in a variety of conditions. The detection of granulomatous hepatitis could be the first clue for an underlying systemic disease. The granuloma is a central accumulation of macrophages brought to the site of inflammation, and it is surrounded by a rim consisting of inflammatory cells, mainly T lymphocytes and fibroblasts. The granuloma is usually due to chronic inflammatory reaction in response to the persistence of exogenous agent (infectious or foreign agents or minerals). In these cases, the granuloma is an example of a delayed hypersensitivity reaction to certain antigenic stimuli. Primary biliary cirrhosis, TB, sarcoidosis, viral hepatitis B and C, and drug related are considered as 5 main causes of liver granulomatosis.4

The clinicians must consider the possibility of TB in the existence of granulomatous hepatitis as an uncommon complication of the BCG vaccine.5 Although disseminated, BCG is a very rare condition. Patients with certain primary immunodeficiency diseases could experience such complications after BCG vaccination.6,7 The patients show a well-developed granulomatous response in various sites, mainly in the lungs and liver, though these granulomas may demonstrate a natural immune response to the vaccine.8,9

In the presented patient, the miliary TB was excluded because no tuberculous lesions in other organs were found. There was no active systemic infection due to Mycobacterium tuberculosis because no acid-fast bacilli were observed in the gastric specimen and no caseative necrosis was seen. Although caseous necrosis is the characteristic of TB infection, it is not always present and its absence cannot exclude TB. Acid-fast bacilli are difficult to culture, and the results of PCR studies

Figure 1. Liver tissue showing large granuloma, with collection of epithelioid histiocytes and giant cell formation (Hematoxylin and eosin stain, ×200)

Figure 2. Liver tissue showing large granuloma, with collection of epithelioid histiocytes and giant cell formation (Hematoxylin and eosin stain, ×400)
Granulomatous hepatitis and BCG vaccine

In liver, blood, and other tissue specimens are usually negative. With no evidence of lung disease, congenital TB was ruled out in this case; no other pathological changes were found in liver to indicate other causes of hepatitis or biliary tract disease. Thus, the hepatic granuloma due to BCG vaccination was the most probable diagnosis in this presented patient.

The presence of epithelioid cell granuloma in the liver may indicate a diagnosis of disseminated BCG infection, as a rare complication of vaccination or miliary TB; the diagnostic tests and anti-TB therapy should be promptly initiated to avoid further complications.

References

1. Skevaki CL, Kafetzis DA. Tuberculosis in neonates and infants: epidemiology, pathogenesis, clinical manifestations, diagnosis, and management issues. Paediatr Drugs. 2005;7(4):219-34.
2. Grange JM. Complications of bacillus Calmette-Guérin (BCG) vaccination and immunotherapy and their management. Commun Dis Public Health. 1998;1:84-8.
3. Casanova JL, Jouanguy E, Lamhamedi S, Blanche S, Fischer A. Immunological conditions of children with BCG disseminated infection. Lancet. 1995;346:581
4. Geri G, Cacoub P. Hepatic granulomas. Rev Med Interne. 2011;32:560-8
5. Hristea A, Neacșu A, Ion DA, Streinu-Cercel A, Stînceanu F. BCG-related granulomatous hepatitis. Pneumologia. 2007;56:32-4.
6. Sadeghi-Shabestari M, Rezaei N. Disseminated bacille Calmette-Guérin in Iranian children with severe combined immunodeficiency. Int J Infect Dis. 2009;13:428-3.
7. Movahedi Z, Norouzi S, Mamishi S, Rezaei N. BCGiosis as a presenting feature of a child with chronic granulomatous disease. Braz J Infect Dis. 2011;15:83-6.
8. Tajima Y, Takagi R, Nakajima T, Kominato Y. An infant with asymptomatic hepatic granuloma probably caused by bacillus Calmette-Guérin (BCG) vaccination found incidentally at autopsy: a case report. Cases J. 2008;20:1337.
9. Gormsen H. On the occurrence of epithelioid cell granulomas in the organs of BCG-vaccinated human beings. Acta Pathol Microbiol Scand Suppl. 1998;29:117-20.
10. Lim EJ, Johnson PD, Crowley P, Gow PJ. Granulomatous hepatitis: tuberculosis or not? Med J Aust. 2008;188:166-7.