Granulomatous hepatitis in a healthy adult after bacillus Calmette–Guérin injection into a plantar wart

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Viral warts are a common skin disease that occurs in 7% to 10% of the entire population. In most cases, the warts disappear spontaneously within 2 years of their onset, but in about one-third of the cases, the warts recur despite repeated treatment.[1] Treatment for warts includes salicylic acid,[2] podophyllin,[3] bleomycin,[4] 5-fluorouracil, laser therapy,[5] interferons, cauterization, cryosurgery,[6] and other surgical methods that usually cause pain and scarring.

To treat warts by strengthening the immune response to the virus,[7] a previous study reported that local immunotherapy in the form of a live bacillus Calmette–Guérin (BCG) vaccine, an attenuated strain of *Mycobacterium bovis* injected within the wart, effectively treated the warts and inhibited relapse.

There have been reports of erythema around the injection site, ulceration, and local lymphadenitis after BCG vaccination, but dissemination of *M bovis* after BCG injection is extremely rare, with an incidence of 0.008 to 0.1 per 100,000 vaccinations.[2] Side effects of intralesional BCG injection in the wart are reported to be similar to those of BCG vaccines. According to a report by Lamm et al,[2] intravesical injection of the BCG vaccine in patients with bladder cancer resulted in granulomatous hepatitis in 0.7% of cases.

Granulomatous hepatitis with pneumonitis as a hypersensitivity systemic reaction after intravesical BCG was also reported, and all the symptoms in that case disappeared within a few days after steroid therapy.[8]

Such systemic complications of BCG inoculation are speculated to be caused by the dissemination of *M bovis* and hypersensitivity reactions.[2,7,9] Granulomatous hepatitis after BCG injection to treat skin warts is rare; in fact, only 1 case of granulomatous hepatitis after intralesional BCG injection in a healthy adult has been reported, in 1977.[10]

We report a case of fever and elevated liver enzyme levels caused by a possible hypersensitivity reaction that developed after a BCG injection to treat skin warts in a healthy adult.

CASE REPORT

A 19-year-old woman presented to our outpatient clinic on September 25, 2014 with the chief complaints of high fever and pain in the upper right region of the abdomen. She had no history of smoking, drinking, and no underlying diseases. The patient visited a local dermatology clinic on September 20 for a recurrent plantar wart on the right foot and received a 0.1-mL BCG injection in the wart area. Three hours after the injection, she began to experience a headache, chills, nausea, vomiting, and pain in the upper right region of the abdomen. She was hospitalized for 2 days at another hospital, during which her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels rose to 195 and 177 (normal range 5-40 U/L), respectively, with a persistent fever (temperature $\geq$38°C). She subsequently presented to our outpatient clinic.

At the time of presentation, the patient's body temperature was 38.9°C, and a physical examination revealed right upper abdominal tenderness and rebound tenderness. No erythema or tenderness were present around the plantar BCG injection site.

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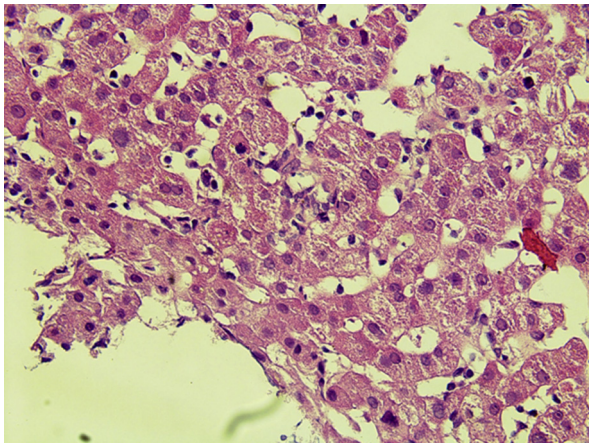

Fig 1. Liver biopsy specimen findings of a 19-year-old woman who presented with the chief complaints of fever and right upper abdominal pain after an intralesional bacillus Calmette–Guérin injection to treat a plantar wart. Noncaseating granuloma comprising epithelial cells are seen within the liver tissue, and eosinophilic infiltration is seen in the surrounding areas.

New local lymphadenopathy or tenderness did not occur after the BCG injection.

Laboratory findings were as follows: hemoglobin, 12.3 g/dL; white blood cells, 3820 cells/μL; platelets, 178,000 cells/μL; blood urea nitrogen, 5.1 mg/dL; and creatinine, 0.58 mg/dL. The prothrombin time and activated partial thromboplastin time were within the normal range, at 9.7 and 29.8 seconds, respectively. The total bilirubin (2 mg/dL), AST/ALT (480.7/359.6 U/L), and alkaline phosphatase (307 U/L) levels were elevated. Additional examinations revealed a normal eosinophil count (60 cells/mm^3) and elevated total immunoglobulin E (IgE) titer (692 IU/mL), with a CD4 count of 560 (39%) cells/μL.

Viral laboratory tests were performed to check for acute hepatitis. The patient's blood tested negative for hepatitis A virus IgM, negative for hepatitis A virus IgG, negative for hepatitis B surface antigen, positive for hepatitis B surface antibody, negative for hepatitis C virus antibody, negative for cytomegalovirus IgM, positive for cytomegalovirus IgG, negative for Epstein–Barr virus capsid IgM, positive for Epstein–Barr virus capsid IgG, and negative for HIV. Blood culture tests yielded negative findings.

A computed tomography scan of the abdomen indicated acute hepatitis with a minimal amount of ascites in the pelvic cavity and a contracted gall bladder with an edematous wall. The patient claimed to have received a BCG vaccine immediately after birth and had a BCG vaccination scar on her left upper arm. The tuberculin test showed positive results with a 12 × 10 mm induration, but the interferon-gamma release assay yielded negative findings. A liver biopsy specimen was obtained and a culture test was performed to confirm hematogenous dissemination, and the histologic findings suggested granulomatous inflammation without caseous necrosis. However, acid-fast bacilli (AFB) were not detected and eosinophil infiltration was observed in the surrounding tissues (Fig 1).

Based on the possibility of *M bovis* dissemination after the intralesional BCG injection in the wart area, real-time polymerase chain reaction (PCR) amplification to detect both *M bovis* and *Mycobacterium tuberculosis* was performed.[11]

M bovis dissemination is clinically and pathologically indistinguishable from *M tuberculosis*, and therefore a primer targeting the *pncA* gene of *M bovis* was also performed, based on the fact that the sequence of the *pncA* gene for the 2 strains differs at the 169C position (C>G).[9,11] The PCR tests performed with the hemoculture samples prepared by culturing blood samples under aerobic and anaerobic conditions, liver tissues, and blood samples all showed negative results. The possibility of *M bovis* dissemination could not be eliminated, and because cultures that would confirm dissemination required more time, treatment was begun with isoniazid (INH) 300 mg, ethambutol 800 mg, and rifampicin 600 mg. On day 4 of the drug therapy, the patient had a systemic maculopapular rash with high fever; therefore, we discontinued administration of all antimycobacterial drugs. The rash improved after discontinuation of the antimycobacterial drugs. We subsequently restarted the antituberculosis medication; nonetheless, even without steroids, the patient developed a fever and demonstrated elevated levels of AST/ALT. Moreover, the right upper abdominal pain underwent repeated cycles of improvement and exacerbation. After 4 weeks of treatment, the symptoms relieved. Liver function markers, such as AST, ALT, and alkaline phosphatase, normalized after 3 months. The patient continued to receive antimycobacterial medication for 6 months.

An AFB culture using blood and liver tissue samples still yielded negative results after 8 weeks.

Because of the adverse effect of the BCG vaccine, the patient's wart was treated with an alternative immunotherapy, the measles, mumps, and rubella vaccine. The patient had lesions on the left foot and left finger; 8 measles, mumps, and rubella (MMR) vaccine injections were administered to the foot. The plantar and digital lesions were treated via stimulation of immune responses (Fig 2).

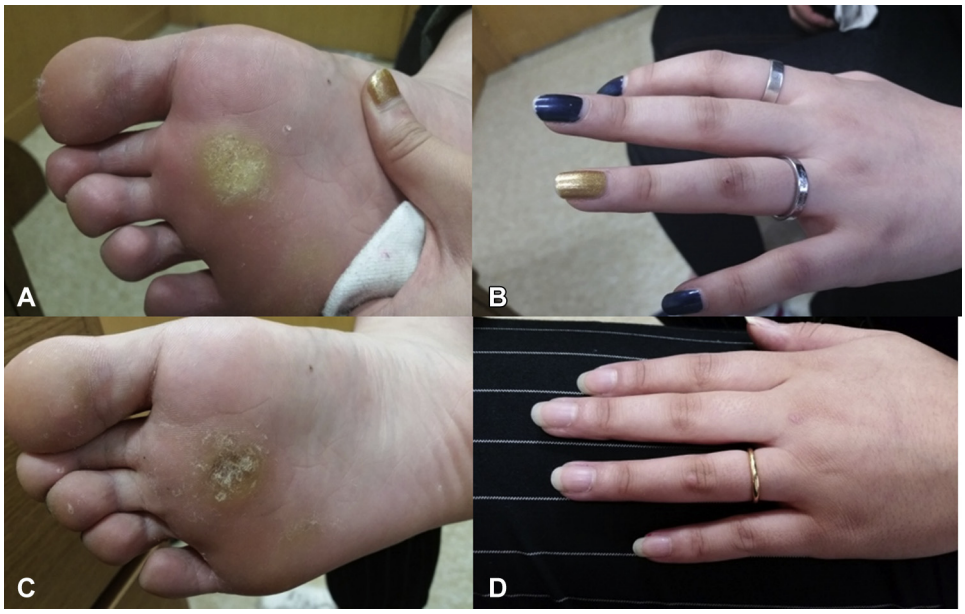

Fig 2. Flat warts on the hand and foot. After the 8 measles, mumps, and rubella (MMR) vaccinations to the foot, the plantar and hand lesions showed improvement. **A**, Flat plantar warts at the time of presentation to the hospital. **B**, Flat warts on the hand at the time of presentation to the hospital. **C**, Flat plantar warts after 10 months. **D**, Flat warts on the hand after 10 months.

DISCUSSION

The possibility of granulomatous hepatitis resulting from dissemination of BCG as a side effect of intravesicular BCG immunotherapy has been suggested in cases wherein mycobacteremia and granulomatous hepatitis were diagnosed based on blood cultures and histology of patients who received an intravesicular BCG injection as immunotherapy to treat bladder cancer.[9] It has also been indicated in cases of granulomatous hepatitis wherein *M bovis* was detected via culture and genetic examination of liver tissues.[12] The reported cases involved bladder cancer patients who received an intravesicular BCG injection, and almost all of the patients were immunosuppressed. However, many cases in the literature report that blood culture, acid-fast stain, and DNA hybridization examinations yield negative results.[13]

Hypersensitivity pneumonitis after intravesical BCG immunotherapy for superficial bladder cancer was also reported.[14] In that report, lung biopsy specimens revealed noncaseating granuloma, and immunoblot analysis of the serum and BCG revealed >10 IgG fractions binding to BCG. Acute hypersensitivity hepatitis with mononuclear cell granuloma accompanied by elevated AST was also documented during systemic injection of the antigen purified protein derivative of tuberculin into an *M bovis*–infected mice model.[15] Therefore, hypersensitivity can be caused by BCG injection.

The response to glucocorticoids administered along with antituberculous drugs has supported the possibility of hypersensitivity against BCG. Early tapering of steroid can result in relapse, suggesting that a type IV hypersensitivity reaction to BCG and dissemination of BCG play critical roles in the pathophysiology of granulomatous hepatitis after BCG injection.[13,16]

There have been multiple cases of granulomatous hepatitis after intralesional BCG injection to treat bladder cancer, but only 1 case of granulomatous hepatitis after BCG immunotherapy for plantar warts in a healthy adult has been reported.[17] In that report, a liver biopsy specimen confirmed noncaseating granuloma, but acid-fast organisms were not detected via staining or cultures. Molecular genetic studies were not performed, but antimycobacterial treatment was initiated upon suspecting dissemination of BCG bacteria, after which the patient's condition showed improvement. In addition, it was reported that deterioration of liver function in that case occurred because of INH-related hepatitis after INH administration. On the other hand, in our case, we performed a molecular genetic study in addition to culture tests, both of which did not show evidence of dissemination. However, because we could not completely eliminate the possibility of dissemination until we received the culture test results, we initiated antimycobacterial treatment without the use of steroids. Our patient developed a fever and demonstrated elevated levels of AST/ALT, and the right upper abdominal pain underwent repeated cycles of

improvement and exacerbation. The symptoms improved after 1 month.

It is highly unlikely that the hepatitis was a result of the INH administered in our case. INH-related hepatitis develops in only about 1% of patients who receive INH, with the incidence being even lower among younger adults ≤ 35 years of age. In addition, the interval between INH-related hepatitis onset and the administration of INH is usually 4 to 8 weeks. Laboratory findings for INH-related hepatitis also show much higher levels of bilirubin and AST than that observed in our case. Therefore, the patient in our case is likely to have had hypersensitivity-mediated hepatitis rather than BCG dissemination or INH-related hepatitis.[18]

Although there have been reports of disease dissemination after intralesional injections in immunosuppressed patients, they are rare; the interval between an intralesional injection to treat malignant melanoma and squamous cell cancer and onset of granulomatous hepatitis generally ranges between 12 hours and 2 weeks.[18] However, our patient received the BCG vaccine immediately after birth, and has been healthy thus far. Severe symptoms were observed only at 3 hours after a single intralesional BCG injection was administrated. There was no evidence of dissemination and local lymphadenopathy. Negative results were obtained for the acid-fast stain, AFB culture, and real-time PCR analysis targeting *M tuberculosis* and *M bovis* using hemoculture, liver tissues, and blood. The histologic findings of granuloma without caseous necrosis together with eosinophilic infiltration indicate granulomatous hepatitis caused by hypersensitivity to the BCG vaccine.

Nonetheless, it is not easy to identify the role of BCG in the development of systemic reactions after BCG injection because mycobacteria strains are not easily detected on acid-fast smears and may not be cultured using lesion, blood, or bone marrow samples or DNA hybridization.

This study is the second report in English literature to confirm granulomatous hepatitis in a patient with normal immune function who presented to the hospital for fever after receiving BCG immunotherapy to treat plantar warts. The findings of this case report suggest that hypersensitivity to BCG, in addition to BCG dissemination, may be a potential cause of granulomatous hepatitis after an intralesional BCG injection in a healthy adult with normal immune function. The findings of this study also call for additional systematic studies to shed light on the mechanisms of BCG hypersensitivity and granulomatous hepatitis.

In conclusion, granulomatous hepatitis was confirmed in an adult with normal immune function after receiving immunotherapy to treat plantar warts. We suggest that clinicians be aware of the possibility of granulomatous hepatitis as a side effect of intralesional BCG injection.

REFERENCES

1. Sterling JC, Gibbs S, Haque Hussain SS, Mohd Mustapa MF, Handfield-Jones SE. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. *Br J Dermatol*. 2014;171:696-712.
2. Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. *J Urol*. 1992;147:596-600.
3. Marcus J, Camisa C. Podophyllin therapy for condyloma acuminatum. *Int J Dermatol*. 1990;29:693-698.
4. Amer M, Diab N, Ramadan A, Galal A, Salem A. Therapeutic evaluation for intralesional injection of bleomycin sulfate in 143 resistant warts. *J Am Acad Dermatol*. 1988;18:1313-1316.
5. Hruza GJ. Laser treatment of epidermal and dermal lesions. *Dermatol Clin*. 2002;20:147-164.
6. Torrelo A. What's new in the treatment of viral warts in children. *Pediatr Dermatol*. 2002;19:191-199.
7. Aldahan AS, Mlacker S, Shah VV, et al. Efficacy of intralesional immunotherapy for the treatment of warts: a review of the literature. *Dermatol Ther*. 2016;29:197-207.
8. Molina JM, Rabian C, D'Agay MF, Modai J. Hypersensitivity systemic reaction following intravesical bacillus Calmette-Guerin: successful treatment with steroids. *J Urol*. 1992;147:695-697.
9. Spositto FL, Campanerut PA, Ghiraldi LD, et al. Multiplex-PCR for differentiation of *Mycobacterium bovis* from *Mycobacterium tuberculosis* complex. *Braz J Microbiol*. 2014;45:841-843.
10. D'Alessandria RM, Khakoo RA. Granulomatous hepatitis in a healthy adult following BCG injection into a plantar wart. *Am J Gastroenterol*. 1977;68:392-395.
11. Jung YJ, Kim JY, Song DJ, et al. Evaluation of three real-time PCR assays for differential identification of *Mycobacterium tuberculosis* complex and nontuberculous mycobacteria species in liquid culture media. *Diagn Microbiol Infect Dis*. 2016;85:186-191.
12. Proctor DD, Chopra S, Rubenstein SC, Jokela JA, Uhl L. Mycobacteremia and granulomatous hepatitis following initial intravesical bacillus Calmette-Guerin instillation for bladder carcinoma. *Am J Gastroenterol*. 1993;88:1112-1115.
13. Leebeek FW, Ouwendijk RJ, Kolk AH, et al. Granulomatous hepatitis caused by Bacillus Calmette-Guerin (BCG) infection after BCG bladder instillation. *Gut*. 1996;38:616-618.
14. Um SJ, Lee SK, Yang DK. Hypersensitivity pneumonitis following intravesical bacille Calmette-Guerin immunotherapy for superficial bladder cancer. *J Investig Allergol Clin Immunol*. 2009;19:230-232.
15. Ferluga J. Tuberculin hypersensitivity hepatitis in mice infected with *Mycobacterium bovis* (BCG). *Am J Pathol*. 1981;105:82-90.
16. Gonzalez OY, Musher DM, Brar I, et al. Spectrum of bacille Calmette-Guerin (BCG) infection after intravesical BCG immunotherapy. *Clin Infect Dis*. 2003;36:140-148.
17. Leung L. Hyfrecation for recalcitrant nongenital warts. *J Family Med Prim Care*. 2013;2:141-144.
18. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 34-1975. *N Engl J Med*. 1975;293:443-448.