ORIGINAL PAPER

Nagoya J. Med. Sci. **63**. 123 ~ 128, 2000

SEVERE DISSEMINATED BCG INFECTION IN AN 8-YEAR-OLD GIRL

*KATSUMI YAMANAKA[1], MUTSUO ISHII[2], TOMI AKASHI[3], MASASHI MORI[4], YOSHITSUGU IINUMA[5], SATOSHI ICHIYAMA[6] and TORU MORI[7]

[1]*Nagoya City Central School of Nursing*
[2]*Department of Pediatrics, Nagoya Daini Red Cross Hospital*
[3]*Public Health Bureau, Nagoya City*
[4]*Microbiology Department, Nagoya City Public Health Research Institute*
[5]*Department of Clinical Laboratory, Nagoya University Hospital*
[6]*Department of Clinical Laboratory, Kyoto University Graduate School of Medicine*
[7]*Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association*

ABSTRACT

An 8-year-old girl died of sepsis due to staphylococcal infection one year and 8 months after Bacille Calmette-Guerin (BCG) revaccination. Two months after the vaccination in accordance with the school health program, she was hospitalized with a high fever, skin rash over the face and lower limbs, and leukopenia. Her clinical and laboratory pictures were not compatible with those of any established type of immunodeficiency. The polymerase chain reaction (PCR) test for *M. tuberculosis* complex was positive for bone marrow, pleural fluid, and peripheral blood. The strain recovered from a mycobacterial culture of the blood was identical to the BCG strains with which the patient was vaccinated, based on restriction fragment length polymorphism (RFLP) and a pulse-field gel electrophoresis (PFGE) analyses of DNA. She developed finally a lung abscess due to staphylococcal septicemia, which was the direct cause of her death.

Key Words: BCG, vaccine, complication

INTRODUCTION

The BCG vaccine has been administered in Japan percutaneously using the multiple puncture method since 1967. Every year, about two million infants and children are vaccinated according to the BCG program, out of whom at least one million are under the age of four years. Side effects of the BCG vaccination include a frequency of lymphadenopathy,[1)] of 0.733% in infants aged 0 to 3 years; however, more serious reactions, such as generalized dissemination or osteitis, have been quite rare in Japan. This is a report of such a rare case of disseminated BCG infection that occurred in a school-age female following re-vaccination with BCG.

CASE REPORT

A 6-year-old Japanese female was admitted to the Nagoya Daini Red Cross Hospital on

Correspondence: Katsumi Yamanaka, Nagoya City Central School of Nursing
1-4-7, Aoi, Higashi-ku, Nagoya 461-0004, Japan
Telephone: +81-52-935-1755
Fax: +81-52-935-8344

August 23, 1996, with a fever of around 40°C (104° Fahrenheit), multiple fine red spots scattered over the face and lower limbs, and leukopenia. The fever and spots had first appeared around July 31, 1996.

The girl was born in a normal course in 1989, with a birth weight of 2,570 g, after a gestation period of 38 weeks. She had been vaccinated with BCG at three months, and thereafter with other vaccines according to the established vaccination schedule for infection control in Japan. These vaccinations include poliomyelitis, measles, chickenpox, rubella, mumps (the latter three in a trivalent combined vaccine), Japanese B encephalitis, and diphtheria, pertussis, and tetanus (in another trivalent combined vaccine). No complications were observed related to these vaccinations. When she was five years old, she had acute otitis media, which required six months of medical treatment.

On April 26, 1996, a skin rash without any illness was first noticed, for which no special examination or treatment was arranged. This symptom lasted intermittently until her admission. On June 19, 1996, after a tuberculin skin test with a negative result, the patient was vaccinated with BCG (manufactured by Nihon BCG Co., Tokyo, Japan) on the upper left arm using the routine percutaneous multipuncture method. The patient had no known history of contact with any tuberculosis patients. There was no apparent general or local abnormal reaction following the vaccination. No lymph node enlargement was observed during her entire clinical course.

The family history was noncontributory, without predisposition to infection. Her parents and only brother were alive and well. Her brother took BCG vaccination without any complication. There was no family history of tuberculosis.

The blood examination at the time of her admission revealed slight leukopenia, with a white blood cell count of 1,500 per cubic milliliter. The proportion of lymphocytes among all the white cells was slightly decreased to 14%. There was an increase in the erythrocyte sedimentation rate to 80 mm/h, and the C-reactive protein was also slightly elevated at 5.84 mg/dl. There was no abnormal change in the concentration of immunoglobulins in the serum. Differentiation of the T- lymphocytes revealed that CD4+ cells accounted for only 13.1% and CD8+ cells 74.3%. Thus, the ratio of CD4/8 was markedly reduced to 0.18. Lymphocyte transformations after incubation with phytohemagglutinin and with concanavalin A were within normal limits. The HIV antibody was negative.

The tuberculin reaction was positive with an erythema diameter of 17 mm. No pathological findings were detected on her chest X-ray film. No lymphadenopathy was seen. No clinically meaningful pathogens were detected in the blood, feces, or CSF, except α-Streptococcus from the throat swab.

On September 19, 1996, about one month after admission, a liver dysfunction was identified, with an elevated level of enzyme activity, i.e., GOT 176 units, GPT 267 units, and LDH 950 units, and this abnormality continued thereafter.

Histologic examination of the bone marrow, which was performed on October 1, 1996, showed epithelioid cell granulomas without Langhans-type giant cell. Soon after this, her chest X-ray film showed an abnormality that suggested atelectasis in the right upper lung field, and a diffuse nebular shadow over the left lung field. Pleural effusion then developed in the right thorax. During this same period, the PCR test for *Mycobacterium tuberculosi*s complex yielded a positive result for the patient's peripheral blood, bone marrow, and pleural fluid. By this time, her tuberculin skin test had turned negative. Anti-tuberculosis therapy using isoniazid, rifampicin, ethambutol, and streptomycin was initiated under the presumptive diagnosis of disseminated tuberculosis. No positive bacteriological findings for mycobacterium were obtained after the introduction of chemotherapy, and the anti-tuberculosis therapy was completed in April 1997, after a total of six months' administration.

However, the patient's general condition did not improve very much. She suffered from episodes of high fever and skin rash, her hepatomegaly persisted, and later cardiomegaly developed. In Dec. 1997, a homogeneous shadow appeared throughout both lungs and the patient developed dyspnea. On March 1, 1998, despite all the trials of antibiotics therapy and symptomatic care, the patient died due to staphylococcal sepsis with abscesses of the lungs, at the age of eight years, one year and nine months after the BCG vaccination.

BACTERIOLOGICAL INVESTIGATION

Two colonies of mycobacteria were recovered from the culture of the blood sample two months following the detection of *M. tuberculosis* complex via the PCR technique. Drug susceptibility testing of this strain revealed that the bacilli were susceptible to all of the anti-tuberculosis medications that she was taking. Genetic investigation was conducted in order to identify this organism, through comparison with the strain from the patient and the BCG strain from the vaccine (Tokyo 156, an international standard BCG strain). Two techniques were employed for the genetic investigation: the restriction fragment length polymorphism (RFLP) analysis,[2] based on the insertion sequence IS6110, and pulse-field gel electrophoresis (PFGE),[3] using the endonucleases of *Xba*I and *Vsp*I. Both techniques revealed that the strain from the patient was identical to the BCG vaccine strain shown in Fig. 1 and Fig. 2.

In a series of biochemical examinations, the strain from the patient showed a positive niacin test, negative photochromogenicity, lack of pyrazinamidase, and no growth on the thiophenecarboxylic acid hydrazid (TCH) plate. These characteristics are all compatible with those of the

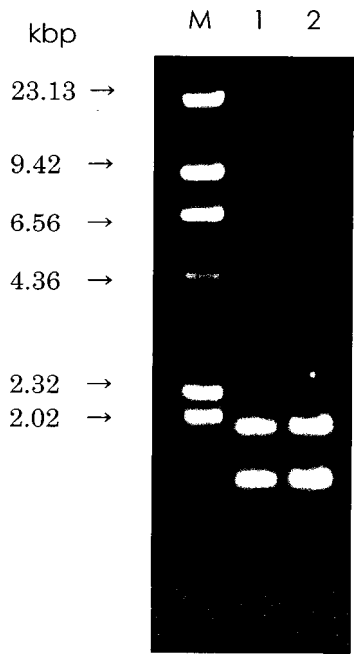

Fig. 1 Restriction fragment pattern with restriction enzyme IS 6110-containing *Puv*II by agarose gel electrophoresis. Lane 1 shows RFLP genotypes of the isolate from the patient. Lane 2 shows genotypes of BCG vaccine strain. Lane M shows λ ladder size standard. *Hin*III digest.

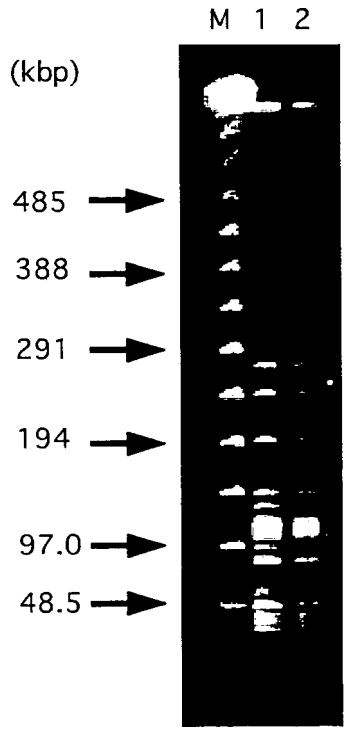

Fig. 2 Large-restriction-fragment patterns with restriction endonuclease *Vsp*I digestion by PFGE. Electrophoresis was performed at 200 V for 20 h with pulse times of 1–4 s. Lane 1 shows PFGE genotypes of the isolate from the patient. Lane 2 shows genotypes of BCG vaccine Strain. M: λ ladder size standard.

BCG strain as shown in parallel. *M. tuberculosis* differs in photochromogenicity, the presence of pyrazinamidase, and growth of the TCH plate.

DISCUSSION

The primary BCG vaccination is given in Japan to children under four years of age, most commonly after the age of three months. There are opportunities for re-vaccination upon entry to primary school (six years) and junior high school (12 years). The coverage of the primary BCG vaccination is as high as or greater than 95%, and currently about one million babies and young infants are vaccinated. Disseminated BCG infection has been extremely rare in Japan. The authors reviewed the literature from 30 years prior and up to 1969 and found that only four fatal BCG infection cases had been reported in Japan. Thus, the incidence of fatal BCG infection in children aged 0 to 3 years is estimated to be one out of 7 to 10 million vaccinations. This low rate of incidence may be mainly attributed to the time of the primary vaccination, only after three months postnatally, as has long been practiced in Japan. In European countries, where neonatal primary vaccination is common, the frequency of a fatal generalized lesion after BCG vaccination is far higher, estimated at 1.56 per one million.[4)]

In the four fatal cases of BCG infection mentioned above, the ages at the time of BCG vaccination were 3 years,[5)] 9 months,[6,7)] 8 months,[7)] and 4 months,[8,9)] No predisposing factor was

detected in the first case. The second and third cases had chronic granulomatous disease (CGD), and the fourth case was known to have a severe combined immunodeficiency (SCID). All were primary vaccination cases. The immunoglobulin level of the case under study was normal, and therefore any underlying immunological defects may not be classified as SCID,[10] a well-known cause related to fatal BCG dissemination. In addition, her adenosine deaminase (ADA) and purine nucleoside phosphrylase (PNP) were at normal levels, which excludes ADA deficiency and PNP deficiency. Mackay and colleagues[11] analyzed immunodeficiency diseases related to fatal outcomes of adverse reactions to the BCG vaccination and distinguished three types; SCID, chronic granulomatous disease and others with cellular immunity abnormalities, and those with normal immunoglobulin levels or with an isolated deficiency of IgA. Our case may belong to the last type. According to the WHO's classification,[10] it is close to "a CD4 T-cell deficiency under a predominantly T-cell defect."

Recently, four children with severe mycobacterial infection were reported[12] to have a mutation in the gene for interferon-γ (IFN-γ) receptor 1. Interleukin-12 (IL-12)-dependamt IFN-γ secretion in humans seems essential in the control of mycobacterial infections,[13] and three unrelated individuals with severe, idiopathic mycobacterial and Salmonella infection were found to lack IL-12Rβ1 chain expression.[14] However, nothing is clear now concerning IL-12 or INF-γ in this case.

The cause of this adverse BCG reaction in the 8-year-old female in this report was presumed to be acquired cellular immunodeficiency not due to HIV, and of unknown nature. Talbot EA[15] *et al.* analyzed 28 cases of disseminated BCG infection in the literature from 1980 through 1995 and discovered that 86% of them had an immunodeficiency of some type, and that there were several cases of revaccination.

We are not certain whether the BCG re-vaccination triggered the development of the immunological defect or caused deterioration so as to eventually culminate in death. It is possible that the process of immunodeficiency started insidiously around the time of the re-vaccination, as suggested by the negative tuberculin test at that time. In conclusion, it is very difficult to anticipate and avoid the possibility of such a serious adverse reaction as in this case with only a routine pre-vaccination check-up consisting of a questionnaire and physical examination, as currently practiced in Japan.

ACKNOWLEDGMENTS

The authors express sincere gratitude to Dr. I. Toida (Japan BCG Laboratory) and Dr. M. Takahashi (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association) for their support of this work. Also, special thanks to Dr. V. Romanus, Swedish Institute for Infectious Disease Control, and Prof. A. Fasth, University of Goteborg, for their kind advice in the management of this case.

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