

Two Cases of Subcutaneous Tuberculous Granuloma Associated with BCG Vaccination

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In recent years, BCG vaccination is routinely performed worldwide. The Ministry of Health, Labor and Welfare of Japan reported that the vaccination rate was as high as 92.9% in 2011. Majority of the reported local adverse reactions to BCG vaccination included lymph node swelling, keloid formation, and abscesses. Subcutaneous tuberculous granuloma is a rare local adverse reaction to BCG vaccination. Herein, we report two cases of developing subcutaneous tuberculous granuloma associated with BCG vaccination. Both of them were treated with isoniazid. There is no standard management for BCG-induced subcutaneous tuberculous granuloma, however, treatment with anti-tuberculosis drugs should be considered for cases of BCG-induced subcutaneous tuberculous granuloma with abscesses or ulcerations.

Key words: BCG vaccination, adverse reactions to BCG vaccination, subcutaneous tuberculous granuloma associated with BCG vaccination

INTRODUCTION

More than 100 years have passed since Calmette and Guérin in France developed the Bacille Calmette-Guérin (BCG) vaccine in 1908. In recent years, BCG vaccination is routinely performed worldwide [1]. In Japan, it became compulsory under the Immunization Law in 1948 for all tuberculin-negative individuals aged 30 years or under to receive the vaccine at the governments' expense [2]. Since then Japan has seen a major decrease in the number of patient with onset of tuberculosis [2]. After 2005, the subject of vaccines were reduced to children between the ages of 3 to 6 months, however, in consideration of the increase of adverse reactions such as osteitis, from April of 2013 target age was raised to under 1 year old. The Ministry of Health, Labor and Welfare of Japan (MHLW) reported that 986,844 infants, at 92.9%, received BCG vaccination in 2011 alone.

Intradermal BCG vaccination is a standard method of vaccination used worldwide. In Japan, however, a unique vaccination apparatus with 9 short needles (Fig. 1) was developed for the purpose of reducing hypertrophic scars and ugly keloid formation that were left by accidental subcutaneous injections with the traditional single needle while effectively obtaining vaccine's efficacy [3]. In clinical practice, BCG suspended solution is spread on the left upper arm, then, two pricks using this multiple puncture with 9 short needles are made vertically over the solution. After more than ten years of cooperative studies, in 1967, this multiple puncture method was adopted in Japan [2]. Thereafter, local

adverse reaction lesions noticeably decreased, both in intensity and duration, compared with those produced by intradermal vaccination [2].

CASE REPORTS

Patient 1

An 8-month-old Japanese girl was referred from a private dermatologist with subcutaneous tumor on her left upper arm which rapidly developed within a week. The tumor did not respond to oral antibiotics prescribed at the previous clinic. On our initial dermatological examination, we noticed a soft, painless subcutaneous tumor, 15 mm in size with erythema, near the BCG vaccination site (Fig. 2A) which was injected 45 days prior to visiting our out patients clinic. We suspected it to be an adverse reaction to BCG vaccination or other bacterial abscess. Ultrasound examination detected a lobular and cyst-like subcutaneous lesion with debris-like punctiform echo images. Histopathological examination showed granuloma with infiltrations of eosinophils and Langhans giant cells (Fig. 2B). Skin tissue culture detected *Mycobacterium (M.) tuberculosis* complex. Blood interferon- γ -release assay resulted negative. Together, these findings led to the diagnosis of subcutaneous tuberculous granuloma associated with BCG vaccination. With a treatment of 6 months course of 10mg/kg/day of isoniazid, the tumor healed leaving a scar formation (Fig. 2C). During the treatment, the subspecies of *M. tuberculosis* complex was confirmed as *M. bovis* BCG by polymerase chain reaction (PCR) method.



Fig. 1 A unique apparatus of BCG vaccination in Japan with 9 short needles.

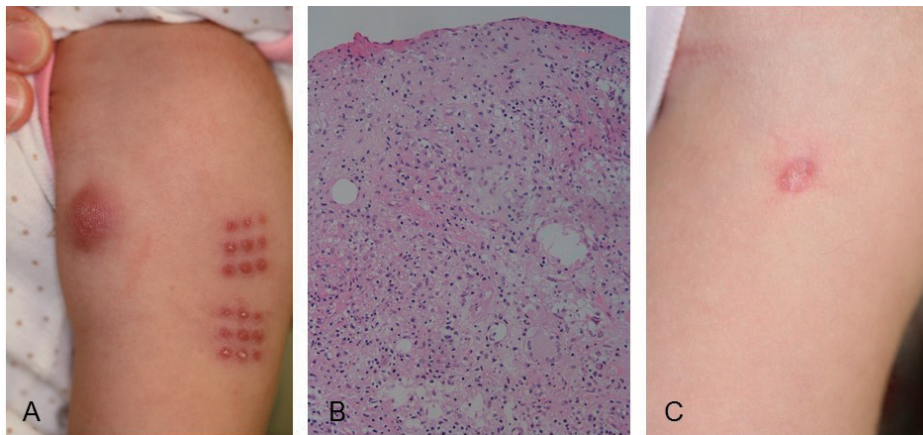


Fig. 2 (A) A soft, painless subcutaneous tumor, 15 mm in size with erythema near BCG vaccination site. BCG vaccination site revealed 3 x 6 artificial red dots. (B) Histopathological examination showed granuloma with infiltrations of eosinophils and Langhans giant cells (HE, x200). (C) The tumor healed with scar formation.

Patient 2

A 9-month-old Japanese boy was referred from a private pediatrician. He was vaccinated with BCG at 6 months of age, before a subcutaneous nodule on his left axilla appeared, 76 days after vaccination. He was diagnosed with reactive lymph node swelling and was treated with oral antibiotics at the previous clinic, but there was no improvement. On our initial dermatological examination, we noticed a subcutaneous nodule, 12mm in size with erythema and ulceration, on his left axilla (Fig. 3A). Histopathological examination showed epithelioid cell granuloma with necrosis (Fig. 3B). *M. tuberculosis* complex was detected by PCR method. He also was diagnosed as subcutaneous tuberculous granuloma associated with BCG vaccination. The tumor healed with scar formation after a treatment of 4 months course of 10mg/kg/day of isoniazid.

DISCUSSION

Few major local adverse reactions to the BCG vaccination includes lymph node swelling, keloid formation, and abscesses [1]. Subcutaneous tuberculous granuloma, which is considered a rare local adverse reaction often occurs at the left axilla or left upper arm but not at the injection site when injected with this multiple puncture apparatus. Reference from MHLW shows that within the 986,844 infants who received the BCG

vaccination in 2011 in Japan, 21 cases with cutaneous tuberculosis-like skin lesion including subcutaneous tuberculous granuloma were registered. According to the registered number, the rate of occurrence of subcutaneous tuberculous granuloma was less than 0.0021%. Another Japanese literature review reported that as few as 13 cases with subcutaneous tuberculous granuloma were confirmed during the 12 years from 1997 to 2008 in Japan (published in Japanese). To confirm the low frequency of adverse reactions to BCG vaccination in clinical practice, we investigated these numbers during the past three years (from January 2014 to December 2016) at Tojo Pediatric Clinic, Kanagawa prefecture, Japan, which is an average sized pediatric clinic in our medical district. Out of 613 BCG-vaccinated infants, there was not a single case of subcutaneous tuberculous granuloma. One case each of lymph node swelling, skin rash, urticaria, and fever was seen. All of them had neither past history nor underlying disease of any kind. Our data from Tojo Pediatric Clinic showed that subcutaneous tuberculous granuloma, as an adverse reaction to BCG vaccination, was indeed rare. This result did not contradict the past data shown by the MHLW and previously mentioned literature.

Distinction between cutaneous manifestations of BCG vaccination and true cutaneous tuberculosis

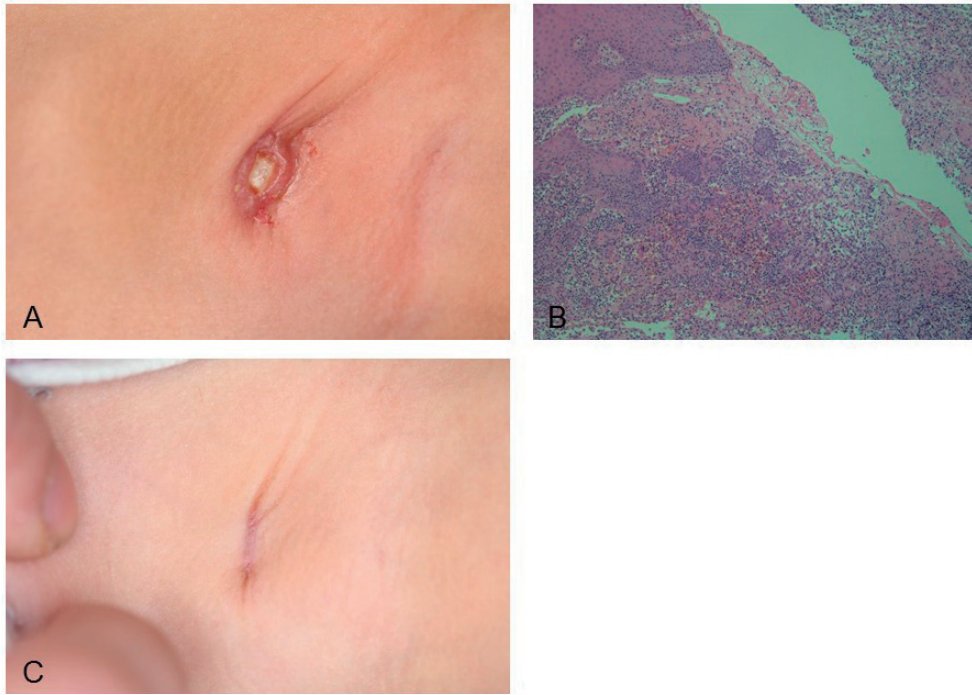


Fig. 3 (A) A subcutaneous nodule, 12 mm in size with erythema and ulceration, on left axilla. (B) Histopathological examination showed epithelioid cell granuloma with necrosis (HE, x100). (C) The tumor healed with scar formation.

was also crucial in these two cases. Both *M. bovis* BCG and *M. tuberculosis* belong to *M. tuberculosis* complex, unable to be differentiated by commercially available molecular assays. In case 1, *M. bovis* BCG was detected by PCR method at the Research Institute of Tuberculosis, Japan Anti-tuberculosis Association. Interferon- γ -release assay, a simple blood test which aids in the detection of *M. tuberculosis*, have excellent specificity that is unaffected by BCG vaccination such as in this case [4]. Principal differential diagnosis in case 2 is the lymph node swelling which often becomes ulcerated. Lymph node swelling is the most frequent local adverse reaction. Forty nine cases were registered on MHLW in 2011. This frequency is calculated at 0.005%, however, other large scale prospective cohort study in Japan reported at 0.73% [5].

Furthermore, there is no standard management for BCG-induced subcutaneous tuberculous granuloma. Although most of the axillary nodule, including subcutaneous tuberculosis granuloma and lymph node swelling, are adverse reactions of BCG vaccination that resolves naturally, other nodules develop abscess formation. It is proposed that anti-tuberculosis drugs should be considered for cases with ulceration in

which *M. tuberculosis* complex are detected. In the case of lymph node swelling, follow-up observation shall be made.

In conclusion, subcutaneous tuberculous granuloma is a rare local adverse reaction to BCG vaccination. Especially in Japan, local adverse reactions by accidental subcutaneous injections are scarce, due to introduction of a unique multiple puncture method. Treatment with anti-tuberculosis drugs should be considered for cases of BCG-induced subcutaneous tuberculous granuloma with abscesses or ulcerations.

REFERENCES

- 1) Hoque SR, Cliff SH. A lesion at BCG vaccination site. *Clin Exp Dermatol* 2009; 34: 117-118.
- 2) Yamamoto S, Yamamoto T. Historical review of BCG vaccine in Japan. *Jpn J Infect Dis* 2007; 60: 331-336.
- 3) Griffith AH. Multiple-Puncture BCG Vaccination. *Postgrad Med J* 1964; 40: 74-77.
- 4) Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008; 149: 177-184.
- 5) Mori T, Yamauchi Y, Shiozawa K. Lymph node swelling due to Bacille Calmette-Guerin vaccination with multipuncture method. *Tuber Lung Dis* 1996; 77: 269-273.