Original Article

# Complication of Bacillus Calmette-Guerin (BCG) Vaccine in HIV-infected Children

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***Abstract*** Nine of 355 cases of symtopmatic HIV-infected children who admitted to Chiang Mai University Hospital from January 1989 to December 1994 had complication due to BCG vaccination. The median age was 15 months with its range from 8 to 22 monts. Four cases presented with ulceration of the previously-healed BCG scar with ipsilateral enlarged and inflamed axillary nodes. Four cases had ipsilateral enlarged axillary nodes without ulceration of the previously healed BCG vaccination sites. One case had disseminated lesions including multiple lymphadenitis, draining abscess at left supraclavicular node, pulmonary with hilar lymphadenopathy. Although all cases responded initially to antituberculous treatment, four of them finally died. Two cases succumbed from respitatory failure and other two from brain atrophy. Though the outcome of BCG complications in normal hosts are usually favorable, our reported cases demonstrated evidence of aggressiveness of BCG strain used for vaccination. With the AIDS pandemic there is rising incidence of HIV-infected pregnant women and a corresponding rise in the incidence of HIV-infected infants for whom complication of BCG vaccination should be looked for and treated prompt;y. (J Infect Dis Antimicrobial Agents 1995;12:63-7).

## INTRODUCTION

Bacille CaImette-Guerin (BCG) is a strain of *Mycobacterium bovis*, first used as a live attenuated vaccine in human in 1921. In Thailand, BCG vaccine is routinely given, to every newborn at birth including children of HIV-infected mothers as stated in the guidelines on immunization of HIV-infected individuals by World Health Organization (WHO)(1). According to WHO, BCG should also be given to individuals with asymptomatic HIV infection in areas with high risk of TB infection.

Reports of BCG vaccine complications, both local reactions and disseminated diseases in Hl'v-infected infants and children have been extensively reviewed (2). Whether these complications represent an increased risk of BCG vaccination in newborns of HIV-infected women has to be carefully investigated. We reported nine HIV-infected cases who exhibited complication of BCG vaccination.

## PATIENTS AND METHODS

### Patients.

The first pediatric case of symptomatic HIV infection (P2 according to Centers for Disease Control classification) (3) at Chiang Mai University Hospital was diagnosed in February 1989. Between then and December 1994 there were 355 children who were admitted to the hospital because of symptomatic vertical HIV infection. Nine of these children had BCG vaccine complications. HIV infection in four patients were diagnosed because of their HIV seropositivity at the age of 18, 19, 21 and 22 months. Because the other five seropositive cases were children less than 18 months of age, the diagnosis of AIDS was made according to the WHO clinical surveillance definition (4).

### Methods.

Identification of the *Mycobacterium* spp. was done by microscopy of the acid-fast-stained (AFB) clinical

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specimen and/or *Mycobacterium* culture. Identification of the organism as *Mycobacterium bovis* was done at Johns Hopkins Hospital laboratory, Maryland, U.S.A.

**CASE SUMMARIES**
**(Table 1)**

The mothers of all nine patients acquited HIV

**Table 1. Nine cases of HIV-infected children with Bacille Calmette-Guerin (BCG) complications.**

| NO. | Time of Diagnosis | AGE (mo.) | SEX | HIV status CDC classification | BCG symptoms | Evidence of BCG complications | Treatment (duration) | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | Oct-90 | 8 | M | P2AD2<br>FTT,HS,GL<br>repeated pneumonia | Ulcerated BCG site*<br>Ipsilateral inflammed axillary node<br>Chronic lung infiltrates** | Pus from ulcer smear/stain positive AFB<br>After few weeks of Rx., there were<br>-resolution of ulcer and adenitis<br>-improvement of lung lesion by CXR | INH + RIF<br>(4 wk) | immediate outcome: alive<br>Four mo. later expired at home<br>with respiratory problem |
| 2 | Jul-92 | 21 | F | P2A<br>FTT,HS,GL | Draining abscess at lt.supra<br>-clavicular node (Fig.3)<br>Generalized lymphadenopathy<br>Patchy infiltrate at rt.lung<br>with mild pleural effusion and<br>enlarged rt.paratracheal node | Pus from ulcer smear/stain positive AFB<br>Pus from ulcer culture positive for *M.bovis*** | INH + RIF + PYR<br>(3 wk) | immediate outcome: alive<br>After few weeks of Rx., there were<br>-resolution of abscess and adenitis<br>-improvement of lung symptoms<br>Two mo. later expired at other hospital<br>with respiratory problem |
| 3 | Oct-92 | 11 | M | P2AB<br>FTT,HS,GL<br>delayed development<br>brain atrophy | Ulcerated BCG site*<br>Ipsilateral enlarged axillary node<br>Chronic lung infiltrates** | Pus from ulcer smear/stain positive AFB<br>Pus from ulcer culture positive for *M.bovis**** | INH,RIF,PYR<br>(4 mo.) | immediate outcome: alive<br>After few weeks of Rx., there were<br>-resolution of ulcer and adenitis<br>While on treatment he died from<br>brain atrophy |
| 4 | Nov-93 | 11 | M | P2AB<br>FTT,HS,GL, thrush<br>delayed development<br>brain atrophy | Ulcerated BCG site*<br>Ipsilateral inflamed axillary node<br>Chronic lung infiltrate** | Pus from ulcer smear/stain positive AFB<br>Pus from ulcer culture positive for *M.bovis**** | INH,RIF,PYR<br>(2 mo.) | immediate outcome: alive<br>After few weeks of Rx., there were<br>-resolution of ulcer and adenitis<br>While on treatment he died from<br>brain atrophy |
| 5 | Nov-93 | 11 | M | P2A<br>HS,GL,thrush<br>chronic diarrhea | Ulcerated BCG site*<br>Later developed draining abscess at<br>ipsilateral axillary node (Fig.1)<br>Chronic lung infiltrate** | LN biopsy: AFB infection | INH,RIF,PYR(2mo.)<br>INH,RIF (7 mo.) | Alive<br>After few weeks of Rx., there were<br>-resolution of the abscess<br>CXR: show clearing of the infiltrate |
| 6 | May-94 | 17 | M | P2A<br>FTT,HS,GL<br>chronic fever<br>delayed development | Ipsilateral enlarged axillary node<br>Chronic lung infiltrate** | LN biopsy: AFB infection<br>Pus from LN biopsy smear/stain positive AFB<br>Pus from LN biopsy culture positive for<br>*M. bovis**** | INH,RIF(9 mo.) | Alive |
| 7 | Sep-94 | 15 | M | P2A<br>HS,GL | Ipsilateral enlarged axillary node<br>(Fig.2) | Pus from LN aspiration smear/stain positive AFB<br>Pus from LN aspiration culture positive<br>for *M. bovis**** | INH,RIF<br>still on INH,RIF | Alive : on treatment |
| 8 | Sep-94 | 16 | M | P2A, D1<br>FTT,HS,GL,<br>chronic diarrhea<br>H. influenzae<br>meningitis<br>recurrent pneumonia | Ipsilateral enlarged axillary node | Pus from LN aspiration smear/stain positive AFB<br>Pus from LN aspiration culture positive<br>for *M. bovis**** | INH,RIF<br>still on INH,RIF | Alive : on treatment |
| 9 | Nov-94 | 22 | M | P2A<br>FTT,HS,GL | Ipsilateral enlarged axillary node | Pus from LN aspiration smear/stain positive AFB<br>Pus from LN aspiration culture positive for<br>*Mycobacterium*. Identification of specie:<br>pending | INH,RIF<br>still on INH, RIF | Alive : on treatment |

* : Ulceration of previously healed BCG site (at the right shoulder)

** : Chronic lung infiltrate: because tissue diagnosis was not done, the etiology was unknown

*** : Culture proved *M. bovis* (BCG stain) done at Johns Hopkins Hospital, U.S.A.

AFB: acid-fast bacilli, BCG: Bacillus Calmette-Guerin (BCG), CDC: Centers for Disease Control, CXR: chest roentgenogram, FTT: failure to thrive, GL: generalized lymphadenopathy, HS: hepatosplenomegaly, INH: isoniacid, LN: lymph node, PYR: pyrazinamide, RIF: rifampicin, Rx: treatment

infection heterosexually either by working as prostitute or from husbands ho had sexual affair with prostitutes. Eight cases were Thai and one was hill tribe. They all lived in Chiang Mai or neighboring provinces. The patients' ages ranged from 8 to 22 months. The median age was 15 months. Eight were male and one was female. All received routine BCG vaccination at birth on the right arm. Four had ulceration of the previously-healed BCG site with ipsilateral enlarged and inflamed axillary node (Fig. 1). Four had ipsilateral enlarged axillary node without ulceration of the previously-healed BCG site (Fig.2). One patient (case no.2), who did not have ulcerated BCG site, had a draining abscess at left supraclavicular lymph node (Fig.3) as well as generalized enlarged and inflamed lymph nodes. She also had patchy infiltration in the right lung with a small pleural effusion and enlarged right paratracheal lymph node. Pus from the draining abscess grew *Mycobacterium bovis.* Her lung lesions responded within 3 weeks to treatment with isoniazid, rifampicin and pyrazinamide. She lost to follow-up and died two months later with respiratory failure. It is very likely that she developed disseminated disease with *Mycobacterium bovis.* In eight cases who presented with enlarged right axillary lymph node, five cases had chronic lung infiltrate. Tissue diagnosis of the lung lesion was not obtained, as invasive procedures were not clinically indicated.

All patients had signs and symptoms of HIV infection which included failure to thrive, generalized lymphadenopathy, hepatosplenomegaly and oral thrush. Two patients also had brain atrophy detected by computed tomography. Two other patients had recurrent severe bacterial infections.

The causative organisms in six cases (case no. 2, 3, 4, 6, 7, 8) were comfirmed as *Mycobacterium bovis* (BCG strain). In the last case (case no. 9) pus from lymph node aspiration grew *Mycobacterium spp.* The identification was pending. In two patients culture for *Mycobacterium bovis* was not done but AFB were seen in pus from ulcer of the previously-healed BCG scar in one case (case no. 1). His enlarged and inflamed ipsilateral axillary lymph node responded to treatment with isoniazid and rifampicin. In the other patient (case

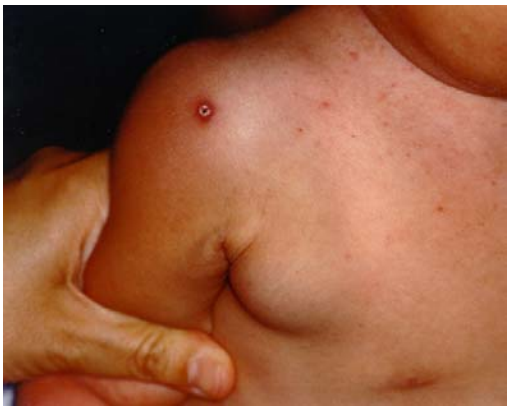

**Fig. 1 Enlarged and inflamed right axillary node (same side with ulceration of the previously-healed BCG site)**

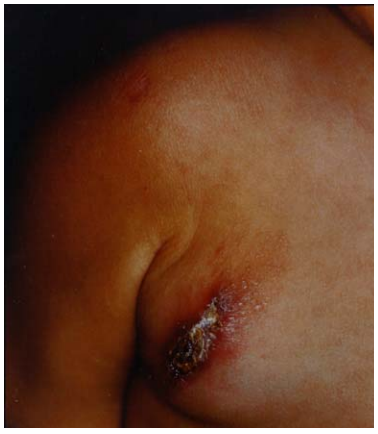

**Fig. 2 Enlarged right axillary node (same side with BCG scar)**

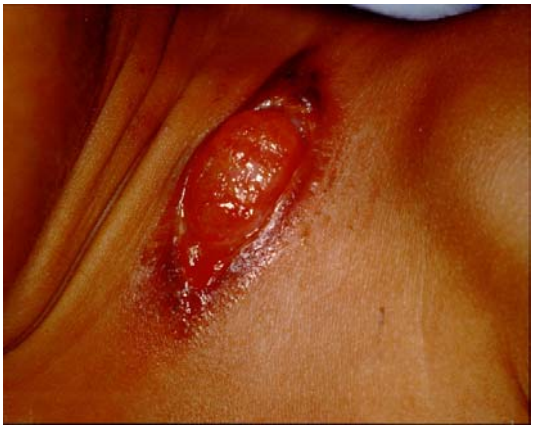

**Fig. 3 A draining abscess at the left supraclavicular lymph node of patient no.2**

no. 5), isoniazid and rifampicin were begun several days prior to the diagnosis. Culture taken from biopsy of the ipsilateral axillary lymph node showed no growth, but histopathology confirmed AFB infection.

All patients responded well to treatment with isoniazid and rifampicin with or without pyrazinamide. All ulcers, abscesses and lymphadenitis subsided. Lung lesions improved in four cases and were stable in two cases. Two patients (case no. 1,2) who received only four and three weeks of treatment died after loss to follow-up four and two months later. Two patients (case no. 3,4) died of brain atrophy but their lung lesions had been stable. Five patients (case no. 5,6,7,8,9) were still alive. Two of these had completed 9 months course of *anti-Mycobacterium* drugs and their lung lesions improved. The others were still on the treatment with clinical improvement.

## DISCUSSION

In this report, only one patient (case no. 2) could be confirmed as having disseminated *Mycobacterium bovis* infection. Pulmonary lesions of the other five cases could not be definitely proved to be caused by *Mycobacterium bovis*. These were due to lack of adequate specimen obtained by gastric washing or lack of post-mortem verification. Lung lesions in two cases improved with anti-tuberculous therapy. When the treatment in these patients was terminated after 4 weeks, as recommended for HIV-non-infected patients with BCG complication, they later died from respiratory failure. Disseminated disease could not be entirely ruled out in these two patients. The other two cases died of brain atrophy, probably due to neurological manifestation of HIV infection.

Preliminary data from epidemiologic studies in Rwanda (5) and Uganda (6) did not indicate that there was an increased risk of adverse effects of BCG immunization in infants of HIV-seropositive mothers. These studies followed infants only up to the age of 6 and 11 months respectively. Such follow-up period may be too short for the authors to come to that conclusion. Eight of nine patients who had adverse effect of BCG vaccination in out report were 11 months or more of age and they had the vaccination shortly after birth. However two other reports with denominator data and longer duration of follow-up (7,8) did not show any increased risk.

The risk and benefit of BCG immunization in infants of HIV-seropositive mothers has been discussed widely. The efficacy of BCG vaccination in HIV-infected people has not been established, and will be difficult to study, given the highly variable efficacy of BCG vaccine in various HIV-infected populations (9).

According to the U.S. Immunization Practices Advisory Committee (ACIP), BCG should not be given at all to HIV-infected individuals in areas with low risk of TB infection. The article from the U.S. Center for Disease Control states that in the populations where tuberculosis is common, routinely given BCG vaccination at birth make sense from a public health perspective because the risk of exposure to tuberculosis is high in children of HIV-infected mothers (10). This is in accordance with WHO recommendation that BCG can be given to individuals with asymptomatic HIV infection in areas with high risk of TB infection (1).

In several reviews (2,11) about the safety of BCG vaccination in newborn with HIV-infected mothers, the conclusion was that there was insufficient evidence at this time to prove or disprove an association between BCG complications and HIV infection. Until further information becomes available, the current WHO and ACIP guidelines should be followed.

Although these nine patients accounted for only a small proportion of symptomatic HIV-infected children who were admitted to Chiang Mai University Hospital (9/355 cases), cases of BCG complication might be underdiagnosed. It is possible that persistent or disseminated BCG infection presents in a clinically. unusual manner in HIV-infected infants. Further evaluation of the appropriateness of current practices could be provided by autopsy studies, including mycobacteriology, in infants dying of AIDS in areas where BCG immunization is routine.

Finally Thai clinicians should be alert about this adverse effect of BCG vaccination. Increased attention to the diagnosis of BCG complications is necessary. In the future, larger epidemiologic studies as well as autopsy studies may be particularly useful in defining the roles of tuberculosis and BCG vaccination in HIV infected children. These studies could provide data needed for more precise risk-benefit evaluation of BCG immunization in the AIDS era.

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