CASE REPORT

Disseminated cutaneous BCG infection following BCG immunotherapy in patients with lepromatous leprosy

GEETI KHULLAR*, TARUN NARANG*, KUSUM SHARMA**, UMA NAHAR SAIKIA*** & SUNIL DOGRA*
*Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh – 160012, India
**Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh – 160012, India
***Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh – 160012, India

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Summary Cutaneous complications of Bacillus Calmette-Guerin (BCG) vaccine, especially in the form of generalised disease, are uncommon and mostly occur in immunocompromised individuals. There is a paucity of data on the cutaneous adverse reactions secondary to BCG immunotherapy in leprosy. We report two unique cases of disseminated cutaneous BCG infection following immunotherapy in patients with lepromatous leprosy. To our knowledge, cutaneous BCG infection presenting as widespread lesions after immunotherapy and confirmed by isolation of Mycobacterium bovis by polymerase chain reaction (PCR) has not been described. A high index of suspicion is required when leprosy patients who receive BCG immunotherapy develop new lesions that cannot be classified as either reaction or relapse, and diagnosis may be confirmed on histopathology and PCR.

Introduction

Bacillus Calmette-Guerin (BCG), a live attenuated vaccine prepared from a strain of Mycobacterium bovis, is routinely administered to neonates for the prevention of serious infections by Mycobacterium tuberculosis in endemic countries. Cutaneous complications secondary to BCG vaccination may either be localised or distant from the injection site.
Immunotherapy with BCG vaccine is often used as an adjunct to the WHO multidrug therapy multibacillary regimen (MB-MDT) in the treatment of multibacillary leprosy patients. BCG immunotherapy leads to faster clearance of Mycobacterium leprae and also decreases the incidence of Type 2 leprosy reaction. In most studies it has been found to be safe, the only adverse effect being ulceration at the injection site and to the best of our knowledge, there is only a single case report on the cutaneous manifestation (lichen scrofulosorum) of BCG vaccine in leprosy. We describe two patients with lepromatous leprosy (LL) who developed disseminated cutaneous BCG infection after immunotherapy.

**Report of Cases**

**PATIENT 1**

A 35-year-old male, diagnosed to have sub-polar LL [pre-treatment bacillary index (BI) of 6+ and morphological index (MI) 5% from the ear lobe and arms] was treated with WHO MB-MDT for 1 year and four doses of BCG vaccine were given intradermally as immunotherapy at 3 monthly intervals during the same year. Two months after the 4th dose of the vaccine, the patient developed asymptomatic erythematous papules and plaques on the trunk, buttocks, upper arms and persistent ulceration of the vaccination site [Figure 1(a) and (b)]. The lesions were non-tender and progressively increased in number and size. This was treated as an upgrading reaction with prednisolone 40 mg/day for 2-3 weeks, however there was no improvement and new lesions continued to occur.

**PATIENT 2**

A 27-year-old male with LL was started on WHO MB-MDT (pre-treatment BI 4+ and MI 0%) and BCG vaccine at 3 monthly intervals. However, after the 3rd dose of the vaccine he developed multiple asymptomatic skin-coloured to erythematous papules which coalesced to form plaques on the trunk and upper limbs.

In both the patients, the scar from BCG vaccine administered at birth was present on the left upper arm. There was no neuritis, fever, loss of weight or appetite, abdominal or chest complaints, or any past history of tuberculosis in the patients or their family members. There was no regional lymphadenopathy and systemic examination was within normal limits. Mantoux test measured 16 × 20 mm and 24 × 18 mm in patients 1 and 2 respectively. The skin biopsy in both the cases showed non-caseating perivascular and periappendageal

![Figure 1](image1.png)

**Figure 1.** (a) Multiple erythematous papules and plaques scattered on the chest and abdomen. (b) Vaccination site on the left upper arm showing punched out ulcers with yellowish-brown adherent crust and erythematous papules and plaques in the vicinity of vaccine induced ulceration.
granulomas composed of epithelioid cells and lymphocytes in the superficial and mid-dermis [Figure 2(a)].

Staining for acid fast bacilli (AFB) was positive in both the cases, the stain being retained after discolouration with both 5% and 20% H$_2$SO$_4$ [Figure 2(b) and (c)] in patient 1 and only with 20% H$_2$SO$_4$ in patient 2 [Figure 2(d)].

Polymerase chain reaction (PCR) from the skin biopsy specimens was carried out using the hup B gene primers for _M. bovis_ as described previously.$^3$ Mycobacterial DNA extracted from the vaccine strain was used as a positive control and PCR grade water as negative control. The DNA extracted from the skin biopsy samples of both the patients was positive for 618 bp band specific for _M. bovis_ (Figure 3). In order to confirm the identification of _M. bovis_, the amplified products from both the skin biopsy specimens and the vaccine vial were sequenced. The alignment of the DNA sequence between the patient specimens and the

![Figure 2](image_url)

**Figure 2.** (a) Microphotograph showing perifollicular and perivascular non-caseating granulomas composed of epithelioid cells and lymphocytes in the dermis (H&E $\times$ 10). (b) Lepra stain showing beaded bacilli in patient 1 [Ziehl – Neelsen stain (5% H$_2$SO$_4$) $\times$ 100]. (c) AFB stain showing solid staining bacillus in patient 1 [Ziehl – Neelsen stain (20% H$_2$SO$_4$) $\times$ 100]. (d) AFB stain showing solid staining bacillus in patient 2 [Ziehl – Neelsen stain (20% H$_2$SO$_4$) $\times$ 100].
vaccine showed 99% homology, thus confirming that the skin biopsies were positive for *M. bovis*. No focus of tuberculosis was identified on chest radiograph, ultrasonography of abdomen and urinalysis for AFB. The total lymphocyte count, T and B lymphocytes and serum immunoglobulins were in the normal range. Based on the clinical presentation and investigations, a diagnosis of disseminated cutaneous BCG infection was made in both the cases. The patients were started on Category 1 (four drugs) anti-tubercular therapy (ATT), and the lesions subsided completely after 6 months of treatment.

Discussion

BCG vaccine is being administered as an adjunct to WHO MB-MDT in MB leprosy patients to enable more efficient killing of the bacilli, including persisters and faster clearance of dead bacilli.\(^1\) A recent study showed that administration of BCG vaccine along with MDT results in increased levels of TNF-\(\alpha\) in multibacillary, IL-17 and IFN-\(\gamma\) in paucibacillary leprosy patients, with improvement in immunological response and a reduction in the frequency and severity of reactions and relapses.\(^4\) Lakshmi *et al.* emphasised the advantage of combining BCG vaccine with MDT in recalcitrant cases of LL, in whom the anergic state may render the chemotherapy ineffective, with persistence of MI positivity even after treatment completion.\(^5\) The normal expected reaction to BCG vaccine comprises of the development of a 5-15 mm sized erythematous indurated area at 3-4 weeks, followed by crust formation that falls off leaving an ulcer that heals with a scar by 12 weeks.\(^6\) Complications of BCG vaccination are uncommon and vary depending on the immune status of the host. According to the revised classification of BCG disease in children, local disease is confined to the site of vaccination; regional disease refers to the involvement of regional lymph nodes or other regional lesions away from the site of vaccination. Distant disease is defined as *M. bovis* isolated from a site distant from the vaccination site such as lung, bone, skin, urine or brain, and disseminated

![Figure 3. PCR showing 618 bp band positivity in both the patients along with positive and negative controls [L1-100 bp Molecular Marker, L2- positive control, L3 and L6 (DNA of patient1), L7 and L8 (DNA of patient 2), L9- negative control].](image-url)
disease as *M. bovis* isolated from more than one distant site and/or from blood or bone marrow culture.\(^7\) In immunocompetent individuals, the reactions are usually infrequent, mild, localised to the injection site and subside spontaneously. These occur at a rate of 0·4 per thousand vaccinations and include erythema, ulceration, blistering, abscess, keloid and regional supplicative lymphadenitis.\(^6,8\) Less commonly, sarcoidosis and fixed drug eruption have been reported to occur.\(^8\) Specific cutaneous reactions caused by *M. bovis*, known as BCG-itis, characteristically demonstrate a granulomatous pattern on histology and can occur either localised to the injection site or as a generalised eruption. Generalised cutaneous and disseminated BCG infections are rarer, with the latter reported in 1 to 3·4 per million children vaccinated.\(^9\) Widespread skin lesions may occur as a part of disseminated BCG infection mostly in immunocompromised individuals with human immunodeficiency virus (HIV) infection and primary immunodeficiencies such as severe combined immunodeficiency and chronic granulomatous disease.\(^10\) They present as numerous asymptomatic umbilicated papules, nodules and abscesses. Other specific reactions include lupus vulgaris, scrofuloderma, lichen scrofulosorum, papulonecrotic tuberculid, erythema induratum of Bazin and granulomatous vasculitis.\(^11\) The risk factors for adverse effects to BCG vaccine include age less than 1 year, subcutaneous administration, injection into the volar aspect of forearm instead of deltoid, number of live bacilli in the dose and the strain of the vaccine used.\(^12\)

The histopathological findings of BCG-itis differ depending on the immune status of the patient. Those with normal immunity reveal multiple well-defined epithelioid granulomas with giant cells and lymphocytes, with or without suppuration and minimal caseous necrosis. Ziehl-Neelsen staining on biopsy and culture specimens may not always demonstrate bacilli, and hence PCR is an important tool to confirm the diagnosis in immunocompetent cases. Immunosuppressed patients show ill-defined granulomas and a diffuse infiltrate of histiocytes with abundant cytoplasm loaded with AFB, few giant cells and lymphocytes.\(^12\)

The present cases are unusual as disseminated cutaneous BCG infection after immunotherapy in leprosy has not been described in the literature. So far only a single case of lichen scrofulosorum has been reported as a complication of BCG vaccination in one leprosy patient.\(^2\) Secondly, our patients did not have any underlying congenital or acquired immunodeficiency. This is in contrast to majority of the reported cases, where disseminated skin lesions occurred along with systemic manifestations in the setting of immunosuppression. A study evaluating immunological conditions in children with disseminated BCG infection showed that at least 50% of these were associated with immunodeficiency syndromes and 50% were idiopathic.\(^10\) The clinical presentation in the form of plaques was also unusual in our cases, as papules, pustules and subcutaneous nodules have been reported in the literature.\(^13\) Interestingly, the skin biopsies in both our cases showed AFB that retained stain with 20% H\(_2\)SO\(_4\), suggesting the presence of *M. bovis*, in contrast to the infrequent detection of bacilli on histopathology in immunocompetent cases reported previously.

**Conclusions**

Disseminated cutaneous BCG infection may infrequently occur in immunocompetent individuals. A high index of suspicion is needed when leprosy patients treated with BCG immunotherapy develop cutaneous lesions that cannot be categorised as reaction or relapse. Detection of *M. bovis* using PCR aids in the confirmation of the diagnosis.
References


