

A Review of Cutaneous Granulomas and Lupus Vulgaris Following BCG Vaccination in a Skin Hospital in Singapore

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Abstract

Introduction: Since the introduction of BCG vaccination in 1921, there have been numerous reports of cutaneous complications. Although common local effects such as erythema, soreness and local abscesses are well known, the incidence of cutaneous granulomas and BCG-induced lupus vulgaris is rare. **Patients and Methods:** This is a retrospective analysis of our local experience in dealing with cases of cutaneous granulomas following BCG vaccination. Cases were seen at a local tertiary level dermatological referral centre. **Results:** There were 14 cases seen over an 8-year period. Of these cases, 4 were clinically suggestive of BCG-induced lupus vulgaris, but only 1 of these cases was confirmed by culture. All but one of these cases had developed these complications after multiple BCG vaccinations. The 3 suspected but unconfirmed cases were treated with isoniazid. The 1 case of confirmed BCG-induced lupus vulgaris was treated with rifampicin and ethambutol, as sensitivity testing revealed resistance to isoniazid. All 4 cases responded well to treatment. The other 10 cases of vaccine-induced cutaneous granulomas responded to local symptomatic treatment. **Conclusions:** Although local effects such as induration and pustule formation at the injection site are not rare, the development of cutaneous granulomas is uncommon. Incidence of complications increases with multiple vaccinations. Cases usually respond to local symptomatic therapy, while more aggressive lesions responded to the use of oral isoniazid. Confirmed cases of BCG-induced lupus vulgaris should be treated based on antibiotic sensitivity profile.

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Introduction

BCG vaccines are live vaccines derived from a strain of *Mycobacterium bovis* that was attenuated by Calmette and Guérin at the Pasteur Institute in Lille, France.¹ In Singapore, all newborn babies are given the vaccination at birth, and until recently, a second vaccination was given to children at the end of their primary school studies, at the age of 12. Common local effects include the development of induration and pustule formation at the injection site, which can persist for up to 3 months after vaccination, and muscle soreness, erythema and purulent damage are more likely to occur if the vaccine is given subcutaneously.² A permanent scar results, occasionally with keloid formation. The development of cutaneous granulomas is rare, and the development of BCG vaccine induced lupus vulgaris even more so, in the context of the vaccine being given to a person who is not immunocompromised. These complications increase with multiple vaccinations.

We report a case series of 14 patients seen over an 8-year period at the National Skin Centre (NSC), a tertiary dermatological referral skin hospital in Singapore.

Patients and Methods

Fourteen patients (9 males and 5 females) attending the

clinic at NSC were seen over the past 8 years, from 1993 to 2000. Their ages ranged from 1 to 30 years. The majority of cases (11 out of 14) were in children aged between 11 and 12 years, as this is the age when they have repeat BCG immunisation in school. There was 1 patient who presented at the age of 1. Two patients, aged 30 years old, were seen at our clinic for cutaneous granulomas following a vaccination given to them by their company's doctor. They were workers in a garment factory in Singapore, and when one of their colleagues developed pulmonary tuberculosis (TB), the workers were all given BCG vaccination without a Mantoux test being done prior to the injection. In all cases, the granulomas occurred over the left deltoid region, which is the standard site for BCG vaccination in Singapore.

Results

The patients were predominantly Chinese (13 out of 14). One other affected patient was a 1-year-old Malay female child. The time between vaccination and the development of a granulomatous reaction ranged from 1 to 12 weeks, with an average duration of 4.2 weeks. The most common reactions were the development of vesiculopustules on a granulomatous plaque (Fig. 1); 8 patients developed this reaction. The next most common reaction was the

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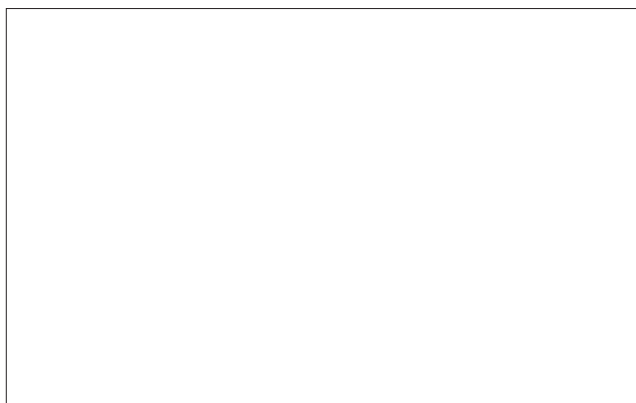


Fig. 1. Vesiculopustules on a granulomatous plaque.

development of ulceration; 7 patients had this reaction. Amongst these cases, there were 4 patients whose lesions behaved in a manner suggestive of BCG-induced lupus vulgaris. They comprised two 30-year-old females, a 12-year-old boy and an 11-year-old girl. These patients had plaques, which continued to enlarge progressively while on follow-up. These plaques developed ulcers from which serosanguineous fluid was discharged. All 4 patients complained of varying degrees of local itch as well as mild tenderness. All of these 4 patients had biopsies done, and specimens were sent for cultures as well. Cultures were negative in 3 of these cases. Histology in these cases revealed features of chronic granulomatous and suppurative inflammation. The appearance of aggregates of epithelioid histiocytes with small central necrosis, surrounded by a lymphocytic infiltrate, was typical of these cases. Acid-fast bacilli (AFB) stain in all cases was negative. Chest X-rays for all patients were normal.

The 3 patients, who had clinical features of lupus vulgaris, but where cultures were negative for *M. bovis*, were treated with isoniazid (5 mg/kg daily) for 3 to 6 months. They all responded well to drug therapy, with the ulcerations healing, and exudation stopping. The average time to healing with drug therapy was 4 months. They were classified as BCG granulomas without confirmed evidence of lupus vulgaris.

There was only 1 case of confirmed BCG-induced lupus vulgaris. This occurred in a 30-year-old Chinese woman who was working in a garment factory in Singapore. When one of her colleagues developed pulmonary TB, the factory doctor decided to implement mass BCG vaccination for the workers. There was no prior Mantoux test done. She subsequently developed a progressively enlarging granulomatous plaque, which was ulcerated and discharging serous fluid (Fig. 2). Biopsy showed features of a granulomatous reaction, with no AFB seen. Cultures from the tissue section were negative, but the swab culture from the exudate isolated *M. bovis*, which was sensitive to rifampicin, ethambutol and streptomycin. It showed resistance to pyrazinamide, which is innate to *M. bovis*, as

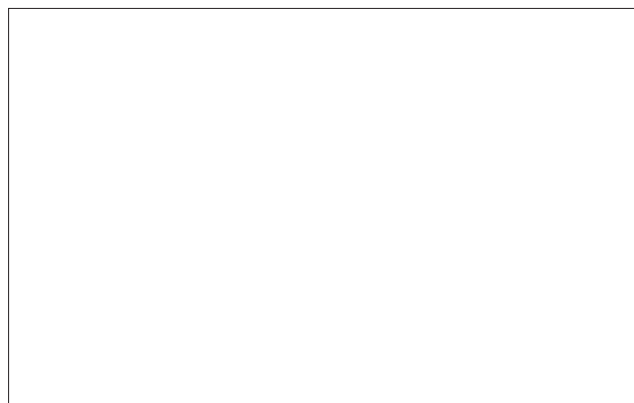


Fig. 2. BCG granuloma exhibiting more aggressive behaviour, with an ulcerated, enlarging plaque.

well as to isoniazid. This patient was investigated for evidence of immunocompromise, and was found to be otherwise well. She was treated with a 6-month course of rifampicin and ethambutol, which resulted in healing and subsequent scar formation.

The other 10 patients who developed cutaneous granulomas following the vaccination did not require aggressive therapy, as the lesions were not progressively enlarging. Although vesiculopustules developed in some of them, these resolved within 2 to 3 weeks following the use of saline dressings and topical steroids. The commonest complaint was that of itching. The average time to complete healing and scar formation in this group of patients who were managed conservatively was 2.1 months.

Discussion

BCG was first administered to humans in 1921. Many BCG vaccines are available worldwide, although all currently used vaccines were derived from the original *M. bovis* strain. *M. bovis* is part of the *M. tuberculosis* complex, which also consists of 3 other species, which are: 1) *M. tuberculosis*, 2) *M. africanum*, and 3) *M. microti*. Under Runyon's original classification, which differentiates Mycobacteria according to their ability to produce pigment as well as their rate of growth, *M. bovis* is a non-chromogen and a slow grower, requiring a minimum of 4 to 6 weeks to form colonies.

The technique of BCG vaccination requires reconstitution of freeze-dried vaccine afresh for each session. The vaccine is to be given strictly intradermally into the skin of the left upper arm, in the sulcus over the insertion of the deltoid muscle. The dose is 0.1 mL (0.05 mL for infants). A local reaction usually occurs 2 to 6 weeks after vaccination as a small papule that may slowly enlarge and discharge purulent material to leave a shallow ulcer. Tuberculin conversion usually takes place within 12 weeks.

Common local effects may also include muscle soreness, erythema, and moderate axillary or cervical lymphadenopathy. Local abscesses seem to occur more frequently

with a jet injector, compared with needle vaccinations. In one review, there were 19 cases of local abscesses occurring in 10,800 persons vaccinated (0.18%) with a jet injector, compared to only 1 case out of 27,000 needle vaccinations (0.003%).³

A case of ulceration occurring 6 months after vaccination in a 1-year-old Japanese boy who had Kawasaki's disease has been reported.⁴ The authors believed that the granulomatous reaction occurred as a result of hypersensitivity to proteins in the BCG vaccine, which appeared after the onset of Kawasaki's disease. The use of BCG immunotherapy for treatment of some malignancies has also resulted in development of cutaneous granulomas, where evidence of infection could not be obtained. These have been observed in cases of malignant melanoma⁵ and multiple myeloma.⁶

Cases of true tuberculosis at the BCG vaccination site have been described. However, the presence of tubercle bacilli has rarely been demonstrated in these lesions by culture, or by DNA-PCR examination. Some authors are of the opinion that if tubercle bacilli cannot be demonstrated, then some of these cases do not represent true TB. In our series, we have adopted the same approach. Lesions, which show features suggestive of lupus vulgaris but where we are unable to confirm the diagnosis either by demonstrating AFB in the tissue section or by cultures, were treated with isoniazid monotherapy and followed-up closely for evidence of response to treatment.

Lupus vulgaris following BCG vaccination is rare. It can occur over the vaccination site after a latency of 6 months to 3 years. Lomholt⁷ reported the first case of inoculation tuberculosis resembling lupus vulgaris in 1946. Horwitz and Meyer⁸ studied 33 cases of suspected BCG-induced lupus vulgaris and cultures were positive in 7 of these cases. The duration of the lesions ranged from less than 6 months to 3 years, and there was no clear gender predisposition. Hartson⁹ studied 20 cases of unusual site reactions following BCG, but no cultures were done. Izumi and Matsunaga¹⁰ did a review of 56 cases of lupus vulgaris following BCG vaccination in 1982. This review included the series by Horwitz and Meyer, as well as Hartson's series. From the review, the authors found that the incidence of BCG-induced lupus vulgaris is increased following multiple BCG vaccinations, but is rare following a single vaccination. This is in agreement with our findings, as 13 out of the 14 patients studied had had at least 2 vaccinations. The woman who developed BCG-induced lupus vulgaris had received the vaccination at birth, at the age of 12, and was then given a third vaccination. The incidences of BCG-induced complications increase with multiple vaccinations. With the recent decision to cease BCG vaccinations at the age of 12, the incidence of such vaccine-induced problems would be expected to be reduced.

The management of most local reactions to BCG vaccine requires only symptomatic relief, and prevention of secondary infection. Most cases will resolve well, with resultant scarring. However, lesions which show evidence of progressive enlargement, severe ulceration, or exudates that are slow to heal, should be managed more aggressively, along the lines of a suspected lupus vulgaris. Histology is necessary, and the demonstration of AFB is an indication to initiate anti-TB treatment. Although a positive culture is absolutely confirmatory, it is rare to isolate the organism in the majority of these suspected cases.

There is no definite consensus as to the ideal treatment, although we have found isoniazid as monotherapy to be very effective. However, we emphasise the need for close follow-up to monitor response to therapy, as well as a thorough systemic screen. In the only 1 case of culture confirmed lupus vulgaris in our series, the isolated *M. bovis* strain was resistant to isoniazid. Since *M. bovis* shows innate resistance to pyrazinamide, this drug should not be used. Where possible, treatment should be guided by sensitivity tests. A 9-month regimen has been used for cases that have occurred after traumatic intravesical instillation in cases of carcinoma of the bladder, using 2 months of isoniazid, rifampicin and either ethambutol or streptomycin, followed by 7 months of isoniazid and rifampicin.¹¹ However, this situation is quite different from a local cutaneous complication. Any situation where there is a greater risk of dissemination probably warrants the use of multiple drug therapy.

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