Update on cutaneous complications of Bacille Calmette-Guérin immunization

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Bacille Calmette-Guérin (BCG) is an attenuated form of *Mycobacterium bovis* that is used to offer protection against tuberculosis . Usually, 3–4 weeks after vaccination, an inflamed infiltrated papule appears, and then an ulcer develops, which heals by the 13th week. However, sometimes complications occur following BCG vaccination or immunotherapy, including cutaneous complications, which have been discussed in this review. Erythema, soreness, ulceration, blistering, keloid, BCG lymphadenitis, and inoculation site abscess occur frequently. Rare complications include complications directly related to vaccine components such as cold abscess of the chest wall, cutaneous granulomas (early and delayed), lupus vulgaris, sarcoidosis, and reactivation granulomatous skin lesions in patients with Kawasaki disease. Complications related to triggered immune response of the patient rather than to the vaccine itself include papular tuberculids, lichen scrofulosorum-like eruption, fixed drug eruption, and granuloma annulare. *M. bovis* infection of the penis, scrotal abscesses, Reiter's syndrome, and cryoglobulinemia vasculitis were reported during BCG intravesical immunotherapy. Intralesional BCG immunotherapy can induce lupus vulgaris, disseminated BCG, and erythema multiforme. In conclusion, BCG vaccination is to be promoted; however, the use of a less virulent vaccine and proper vaccination techniques to minimize BCG complications is advised. Proper selection of those receiving the vaccines should be considered.

Keywords:
Bacillus Calmette-Guérin, cutaneous complications, immunotherapy, *Mycobacterium bovis*, vaccination

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Introduction

Bacillus Calmette-Guérin (BCG) is an attenuated form of *Mycobacterium bovis* and is used by many developing and developed countries to produce a vaccination against tuberculosis (TB) infection on a national scale. In 1984, Lotte and coworkers analyzed and classified complications associated with BCG vaccination in detail. This classification was based on clinical, bacteriological, histological, and biological information. Category 1 involved extensive local lesions, regional suppuration, and BCG-related lymphadenitis. Categories 2 and 3 comprised more serious complications. Nonfatal cases (localized or multiple changes) were included in category 2, whereas fatal cases (generalized lesions usually associated with immunodeficiency) were included in category 3. Category 4 included complications not definitely confirmed, either bacteriologically or histologically – for example, keloid formation [1]. In 2005, Bellet and Prose classified skin complications of BCG immunization into complications as seen in immunocompetent and immunodeficient hosts. The cutaneous complications in immunocompetent hosts were further subdivided into frequent complications (erythema, soreness, abscess, ulcer, keloid, and blister formation) and rare complications [cutaneous granulomas, BCG granuloma in Kawasaki disease, fixed drug eruption, BCG-induced lupus vulgaris (LV), and BCG infection following mesotherapy]. The cutaneous complications in immunodeficient hosts constitute severe local and systemic infection in the setting of cellular immune deficiency [2]. Now, 5 years later, there have been further reports of complications related to BCG vaccination and/or immunotherapy, including ones involving the skin. These cutaneous complications will be discussed in this review.

The usual cutaneous BCG vaccination site response

Approximately 3–4 weeks after vaccination, a 5–15 mm erythematous, inflamed and infiltrated papule appears. Frequently, a central crust develops, which then falls off leaving an ulcer that usually heals by the 13th week after vaccination. This crusted ulcer then evolves into a small, flat scar [3]. Nonsuppurative involvement of regional or local lymph nodes is also a part of the normal process [4].

Cutaneous complications of BCG vaccination

Cutaneous complications of BCG vaccination can occur with initial vaccination and also with revaccination. Complications in revaccination are unusual but may be more frequent than reactions to the initial dose [5]. Several studies have reported these complications [5–7].

Common complications

Erythema, soreness, ulceration, blistering, and keloid scar occur frequently. These complications usually resolve without intervention or sequelae [1].

BCG lymphadenitis, defined as the development of ipsilateral regional lymph node enlargement after BCG vaccination, is the most common complication resulting from this vaccination [8]. In its natural course, BCG lymphadenitis either undergoes spontaneous regression or enlarges progressively and becomes suppurative, marked by the appearance of fluctuations in the swelling with erythema and edema of overlying skin [9]. Once suppuration has occurred, the treatment should aim at promoting resolution and preventing spontaneous discharge and sinus formation. Suppurative lymph nodes are managed by needle aspiration to prevent sinus formation and to hasten resolution. Surgical excision is only rarely required [10,11]. Medical treatment with antituberculous drugs is not effective in the treatment of BCG lymphadenitis when the involved lymph nodes are around 3.0 cm and have developed fluctuation and inflammation of overlying skin [12].

Inoculation site abscess is another common complication, the management of which is controversial. There is no convincing evidence that medical interventions, including use of antituberculous agents, hasten recovery. Inherent resistance to pyrazinamide, coupled with isoniazide resistance in BCG strains, complicates the issue [4].

Rare complications

Complications directly related to the vaccine components

A number of rare cutaneous complications have been described as rarely occurring in immunocompetent hosts. Cold abscess of the chest wall is an unusual complication of BCG vaccination. Such a complication may be confused with a chest wall tumor, and a surgical intervention may be needed for a definitive diagnosis [13,14].

Cutaneous granulomas (early and delayed) after BCG vaccination seem to be very rare. A unique case of delayed tuberculoid granuloma formation confined to the BCG vaccination site has been reported. Appearing 3 years after vaccination, the lesion was a 3 cm bluish plaque, with surrounding inflamed skin. Pathology in this case showed a granulomatous infiltrate with epithelioid histiocytes, lymphocytes, and Langerhans' giant cells [15]. Failure to isolate BCG mycobacteria from fresh tissue is not unexpected because of the sparsity of organisms in lesions. For similar reasons and because of sampling errors, a negative PCR result also does not exclude their presence [16]. Aluminum was thought to be responsible for some vaccination granulomas [17].

BCG vaccination may produce LV after a single BCG vaccination [18,19]; however, multiple vaccinations seem to markedly increase the risk [20,21]. A similar phenomenon has been described after immunotherapy with BCG vaccination [22]. Previous studies have reported that the time interval between vaccination and the onset of BCG-induced LV ranges from a few months to 4 years, with an average of 1 year [23]. However, reports of cases appearing several years after inoculation are also present [18,19].

The etiology of sarcoidosis is unknown, although *M. bovis* from BCG vaccination was hypothesized to be responsible for its development in one case report [24].

The development of reactivation granulomatous skin lesions at the site of BCG vaccination in patients with Kawasaki disease has been described in a number of patients. Pathologic examination revealed an epithelioid granulomatous inflammatory reaction with negative Ziehl–Neelsen stain, cultures, and PCR [25,26].

Mycobacterial spindle cell pseudotumor is another rare complication of mycobacterial infection, as well as of BCG vaccination. It is characterized by an exuberant spindle cell proliferation, which has been reported in many organs including the skin. The incidence is higher in immunocompromised patients, especially in those with acquired immunodeficiency syndrome [27].

Cutaneous and systemic complications of BCG vaccination in the setting of immunodeficiency have been well described and are specifically related to altered cellular immunity [28,29]. The site of BCG vaccination may be ulcerated with drainage of purulent material and blood [30]. Multiple erythematous to whitish 3–5 mm papules with central umbilication have also been reported [31]. Multiple asymptomatic firm papules and nodules on the face, trunk, and extremities may also be present [30]. A 7-month-old boy with known severe combined immunodeficiency presented with a nontender, firm subcutaneous nodule on his back [31]. In all these cases, histopathological examination revealed acid fast bacilli, and *M. bovis* was identified by culture and/or PCR.

The first case report of acute erythroderma and recurrent BCG abscesses was presented after bone marrow transplant [32].

Idiopathic disseminated BCG infection is a rare but severe complication of BCG vaccination. The infection probably results from an as yet unknown genetically determined immunodeficiency condition that affects the killing of intracellular bacteria [33].

Complications related to triggered immune response of the patient rather than the vaccine itself

A 3-month-old child with a grossly symmetrical monomorphic papular acrally located skin eruption, a voluminous lymphadenopathy after BCG vaccination, and hepatomegaly was reported. The diagnoses of Gianotti–Crosti's syndrome and generalized TB infection were discarded. The appearance of these lesions 48 h after a tuberculin patch test, their tuberculoid structure, and the absence of any systemic involvement favored the diagnosis of papular tuberculids, a rarely reported complication of BCG vaccination [34]. A patient with an unusual lichen scrofulosorum-like eruption localized to a previous multipuncture BCG vaccination site was also reported [35].

A special form of fixed drug eruption with a well-defined hyperpigmented patch present for 1 year at the site of

BCG vaccination was reported in a patient who received oral cotrimoxazole. Each time the patient received the drug, the lesion became erythematous and pruritic [36].

Granuloma annulare following BCG vaccination or tuberculin skin tests has been rarely reported in the literature. Houcke-Bruge and colleagues have described three cases. In the first two cases, granuloma annulare was initially localized at the vaccination site and then generalized. In the third case, diagnosis was deep granuloma annulare localized far from the initial vaccination site, with recurrence following tuberculin test. In the three cases, diagnosis was made on the basis of clinical and histological elements. A possible cause could be injection trauma or a cell-mediated delayed hypersensitivity reaction to a specific antigen contained in the vaccine, leading to development of such skin disorders in predisposed patients [37].

Cutaneous complications of BCG immunotherapy

BCG intravesical immunotherapy is indicated in the management of residual superficial bladder cancer and urothelial carcinoma in situ and for prophylaxis of multiple and/or early recurrent bladder tumors [38]. Even when there are no contraindications to BCG, side effects are common. These consist primarily of local irritative voiding symptoms in the majority of patients. Low-grade fever, arthralgias, and mild constitutional symptoms develop in many patients. Granulomatous reactions to BCG occur commonly in the bladder and prostate of treated patients [39]. There are only a few cases in the literature of *M. bovis* infection of the penis as a complication of intravesical BCG therapy [39–43]. The development of moderate systemic symptoms and multiple penile papules after BCG immunotherapy suggests *M. bovis* infection [39]. Diagnosis is based on history and histological examination [42]. Traumatic catheterization and BCG spillage may be risk factors for penile infection with *M. bovis* [39].

An 86-year-old patient who presented with carcinoma of the bladder was treated with several transurethral endoscopic resections and with repeated instillations of BCG into the bladder. He developed increasing redness and swelling of the right scrotal compartment and inguinal lymphadenopathy. Histological analysis revealed a granulomatous inflammation consistent with a mycobacteriosis. This is a rare complication with potentially serious consequences and requires rapid diagnosis and urgent treatment by a multidisciplinary team [44]. In addition, Kanamori *et al.* [45] reported a case of chest wall abscess caused by *M. bovis* BCG that arose as a complication 1 year after intravesical BCG instillation [45].

Reiter's syndrome during intravesical BCG therapy for bladder carcinoma was rarely reported. Two cases developed fever, conjunctivitis, cystitis, and arthritis after the fourth course of intravesical BCG therapy. Reiter's syndrome in the context of BCG therapy was diagnosed, and intravesical immunotherapy was discontinued [46,47].

Immune-mediated reactions were reported after intravesical instillation of BCG for the treatment of bladder carcinoma, including cryoglobulinemia vasculitis. Biological evaluation revealed autoimmune thrombocytopenia, hypergammaglobulinemia, low C3 and C4 complement fraction levels related to mixed cryoglobulinemia, and lupus anticoagulant [48].

Methanol extraction residue (MER), a cell wall fraction of BCG, has been reported to exhibit immunomodulating properties that permit its successful use as an adjuvant of immunotherapy in cancer patients. Its beneficial immunostimulatory effects are generally thought to be due to nonspecific stimulation of cell-mediated immunity. A patient undergoing treatment with adjuvant immunotherapy with MER for malignant lymphoma developed a cutaneous plasma cell tumor at the injection site of the drug. This complication may represent the result of enhanced humoral immunity induced by the MER treatment. The development of this condition may constitute an indication for the discontinuation of treatment with this agent [49]. Granulomatous lymphangitis is another complication of intralymphatic immunotherapy with MER of BCG in patients with melanoma [50].

In addition to LV following intralesional BCG immunotherapy [22], there is a case report of BCG dissemination with ulceration, skin necrosis, lymphadenitis, and abscess formation after the first intralesional injection of a minimal dose of BCG in a purified protein derivative (PPD)-negative patient with melanoma. The case demonstrated that severe complications can occur in patients who are not hypersensitized, anergic, or debilitated, or who have been treated multiple times. This patient's complication further suggested that migration of BCG after intralesional therapy may play a role in the regression of uninjected nodules seen in some patients [51].

Another complication of BCG immunotherapy for malignant melanoma is erythema multiforme. It occurred in a 31-year-old woman as a complication of BCG administration by scarification technique [52].

'Accidental' BCG inoculation sequelae

Two cases of BCG cutaneous abscesses following mesotherapy have been reported. Mesotherapy is the injection of small amounts of medication or vitamins into the mesoderm. Infectious complications after mesotherapy may result from bacterial or atypical bacterial infections [53].

Conclusion

In conclusion, with the increasing incidence of TB and multidrug resistance of the organism, the promotion of BCG vaccination is gaining importance. In addition, administration of BCG vaccine as an adjuvant immunotherapy against cancer is being widely implemented. However, the use of a less virulent vaccine and proper vaccination techniques to minimize BCG complications is advised [54]. Proper selection of those receiving the

vaccines should be considered. In case of revaccination, prior tuberculin tests and screening for active TB are indicated. Vaccination should be restricted to those who are tuberculin negative and lack active TB focus. Screening of TB with an interferon γ (IFN-γ) assay using an enzyme-linked immunospot assay, which detects antigen-specific IFN-γ-secreting cells in peripheral blood mononuclear cells, was successfully used for detection of *M. tuberculosis* infection [55]. In case of suspected *M. bovis* disease, quantification of IFN-γ-producing lymphocytes, activated with PPD from *M. bovis* (PPD-B) or live mycobacteria, by flow cytometric analysis of intracellular IFN-γ expression [56] would provide a more accurate discrimination of *M. bovis*-infected persons from those vaccinated with BCG.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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