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Case Report

Reactivation of BCG vaccination SCAR after influenza vaccination: a case report

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Abstract

The Bacillus Calmette-Guerin (BCG) vaccine, a live attenuated vaccine derived from *Mycobacterium bovis*, is widely used for tuberculosis prevention and has been linked to various immunological responses beyond its intended purpose. A 23-years-old healthy and allergy-free man was vaccinated for the current year's influenza on his left arm. Two days after inoculation, the patient's BCG scar on his left arm was erythematous, while the influenza vaccination site (located 3 cm from the BCG scar) remained unchanged. A possible ipsilateral relationship between the BCG scar and the influenza vaccine site is suggested. BCG vaccination influences the increase in TNF-α and IL-6 production following influenza vaccination. In BCG-vaccinated subjects, hemagglutinin-inhibition antibody responses against the A(H1N1)pdm09 vaccine strain is markedly enhanced, with a trend toward more-rapid seroconversion. Understanding this BCG and influenza vaccines interaction is crucial for healthcare providers to differentiate between benign post-vaccination reactions and those that may require further clinical evaluation.

Keywords: bacillus Calmette-Guerin vaccine; BCG; influenza vaccine; BCG scar reactivation; erythema

Introduction

Bacillus Calmette-Guerin (BCG) vaccine is a live attenuated vaccine derived from *Mycobacterium bovis*. It is one of the most widely used vaccines in the world, and is primarily used for the prevention of tuberculosis [1–3]. Also, it has been associated with various immunological responses beyond its intended purpose. BCG vaccine also offers protection against non-tuberculous mycobacterial infections like leprosy and Buruli ulcer, nonspecific protective effects against protozoan infections, including tegumentary leishmaniasis and malaria. It is also used in the treatment of superficial carcinoma of the bladder [2–4]. There are also reports of the reactivation of a BCG vaccination scar following measles infection, as well as COVID-19 and influenza vaccinations [5–13]. The reactivation of the BCG scar, characterized by erythema and/or crust formation, is one of the pathognomonic features of Kawasaki disease and occurs in approximately 30-50% of Kawasaki disease patients [4, 14–17]. Here, we present a case report of a 23-years old man who presented with erythema at the BCG inoculation site following influenza vaccination. This article is important for understanding mechanisms of BCG scar reactivation after influenza vaccination, the clinical implications of this response, and the potential impact on vaccination strategies in populations with prior BCG immunization. Understanding this interaction is crucial for healthcare providers to differentiate between benign post-vaccination reactions and those that may require further clinical evaluation.

A case report

A 23-years-old healthy and allergy-free man was vaccinated for the current year's influenza on his left arm. Two days after inoculation, the patient presented with erythema on the deltoid muscle of the left arm at the site of a previous BCG vaccine scar. The BCG scar was erythematous, while the influenza vaccination site (located 3 cm from the BCG scar) remained unchanged. The erythema around the BCG scar measured 2 cm in diameter on the second day after the influenza vaccination (Fig. 1). By the fourth day, the erythema started to diminish and disappeared by day seven without any treatment. The patient reported receiving the influenza vaccine every two years and had not experienced any side effects previously. He was born in Lithuania and received the BCG vaccine on his left arm at two days of age. Our patient received a quadrivalent influenza vaccine containing the following strains: A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022 IVR-238), A/Darwin/9/2021 (H3N2)-like strain (A/Darwin/9/2021 IVR-228), B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild-type), B/Phuket/3073/2013-like strain (B/Phuket/3073/2013, wild-type).

Discussion

Our case report discusses an adult who experienced BCG scar reactivation following influenza vaccination. The erythema resolved within 7 days without treatment. Previous cases have

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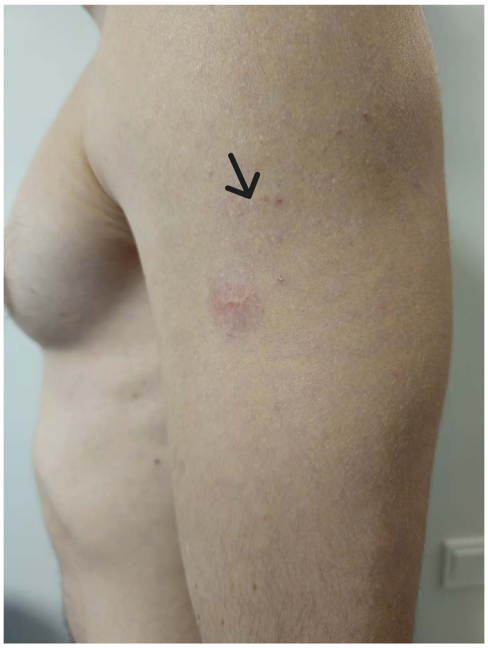

Figure 1. The erythema around the BCG scar. An arrow indicates the influenza vaccination site.

been observed in children. In two of these cases, BCG scar induration and erythema lasted for 48-72 h and also disappeared without treatment [12, 13]. In another case, a day after vaccination, swelling, erosion, and blister formation were observed at the BCG scar site, which resolved 6 days post-vaccination following treatment that included an intravenous anti-allergic drug, topical corticosteroid, and antibiotic ointment [11]. More similar cases were observed after COVID-19 vaccination, where there was no pain or redness at the injection site, but these symptoms were observed exclusively at the BCG wheal. The symptoms following both the first and second doses resolved spontaneously without intervention after administration of both viral vector and mRNA vaccines [6, 8–10]. Our patient had also previously received three doses of the Covid-19 mRNA vaccine, but did not experience any BCG scar reactions. Some articles suggest a possible ipsilateral relationship between the BCG scar and the influenza or COVID-19 vaccine site [8, 11]. In other reports, no link was found between the side of the body where the COVID-19 or influenza vaccine was administered and the side of the body where the BCG scar became reactivated. However, BCG scar reactivation was also observed on the ipsilateral side [6, 12]. In our case, the influenza vaccine was administered in the same arm as the BCG scar. In one study, the reactivation of the BCG scar was observed on the contralateral side. However, during that study, the patients were revaccinated with the BCG vaccine and received the Covid-19 vaccine 6-8 months later, after which two individuals experienced reactivation of the new BCG scar. Both individuals had been vaccinated with BCG during childhood, and no reactivation was noted in the older scars. No treatment was needed or provided [7].

BCG vaccination is associated with enhanced cytokine responses after influenza, and also partially associated after SARS-CoV-2 stimulation. BCG vaccination influences the increase in TNF-α and IL-6 production induced by the influenza vaccination [3, 18]. Also, in animal models, a significant adjuvant effect of BCG cell wall skeleton (BCG-CWS) on the immune response to influenza vaccination has been observed, including decreased viral loads. BCG-CWS has a stimulating effect on antigen-presenting cells, inducing inflammatory cytokines through Toll-like receptors 2 and 4 signaling pathways. BCG-CWS exhibits multifunctional effects including protective humoral and cellular immune responses, control of excessive pathological inflammation, and Th1 cell proliferation upon influenza challenge [19, 20]. Also in BCG-vaccinated subjects, hemagglutinin-inhibition antibody responses against the A(H1N1)pdm09 vaccine strain is markedly enhanced, and there is a trend toward more-rapid seroconversion [3, 21]. It has also been observed in animal models that not only is BCG used to enhance immunization against the influenza virus, but influenza virus vectors can also induce a specific Th1 immune response against *Mycobacterium tuberculosis* [22].

One of the mechanisms proposed in the literature underlying BCG scar reactivation involves the mycobacterial heat shock protein (HSP)65 [10]. The amino acid sequences of mycobacterial HSP65 and those of the COVID-19 S (spike) and N (nucleocapsid) proteins are very similar. Both the COVID-19 S and N proteins support the possibility of a cross-immune reaction between BCG HSP65 and COVID-19 [23]. Furthermore, the BCG vaccine contains similar 9-amino acid sequences to those found in COVID-19; four sets of these similar peptides have been shown to have weak to high binding affinity for common HLA class I molecules. Thus, the BCG vaccine has the potential to generate cross-reactive T cells against COVID-19 [24].

Regarding BCG scar reactivation after influenza vaccination, the literature primarily discusses the nonspecific effects of BCG vaccination related to the enhanced function of myeloid antigen-presenting cells. It has been reported that BCG vaccination prior to influenza vaccination results in a more pronounced and accelerated induction of functional antibody responses against the 2009 pandemic influenza A(H1N1) vaccine strain [21]. Additionally, after influenza vaccination, increases in IL-6 and TNF-α are observed [3, 18]. Positive correlations have been found between serum levels of HSP70 and the inflammatory markers IL-6 and TNF-α, and a homology between HSP70 and mycobacterial antigens has been demonstrated [5, 25]. HSP70 enhances the cross-presentation of exogenous antigens on MHC class I, resulting in better antigen-specific T-cell stimulation [26]. When cytokines or increased levels of HSP70 are present, resident memory T cells (TRM) in the BCG scar can become reactivated. TRM cells rapidly activate local immune cells to mount a response that protects against infections by unrelated pathogens [27, 28]. The potent inflammatory effects of TRM reactivation may have pathological consequences, potentially contributing to the exacerbation of tissue-specific autoimmune or inflammatory diseases [28]. However, many studies report that BCG scar reactivation is typically benign and self-limiting, with no significant long-term adverse effects [6, 8–10, 12, 13]. Thus, BCG scar reactivation could be caused by the nonspecific immunological effects induced by the BCG vaccine and by the influenza vaccine–induced increase in HSP70 that is homologous to mycobacterial antigens.

The limitation of this case is that no laboratory tests were conducted to determine the pathogenesis causing the symptoms. However, this case could strengthen the idea proposed by other authors that the BCG vaccine reactivation response occurs when the influenza vaccine is administered in the ipsilateral arm. Understanding this could help clinicians reduce unwanted reactions to the influenza vaccine in individuals previously vaccinated with BCG and guide them in responding to such bodily reactions.

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Conflict of interest

The authors declare no conflicts of interest regarding the publication of this article.

Ethics statement

The authors declare that all procedures were performed in compliance with the relevant laws.

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Consent

A written consent for publication has been obtained from the patient.

Guarantor

Augustinas Stasiunas is the guarantor of this article.

Contributions

All authors contributed significantly to the conception, design, execution, or interpretation of the reported study.

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