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CASE REPORT

BCG vaccine reactivation after mRNA immunization against COVID-19: case report

Reativação de vacina BCG após imunização contra COVID-19: relato de caso

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ABSTRACT

The Bacillus Calmette-Guérin (BCG) vaccine is a live attenuated pathogen vaccine used to prevent severe types of tuberculosis. A related immunological event is its scar reactivation. It is usually associated with Kawasaki disease and the use of other immunizers. In this report, we aim to describe the case of a 24-year-old woman with BCG vaccine scar reactivation after administering a Messenger RNA (mRNA) vaccine against COVID-19, BNT162b2. The pathophysiology involved in the scarring reactivation of the BCG vaccine is related to the chaperone proteins. There are still no cases reported in Brazil of BCG scar reactivation after mRNA vaccines. Nevertheless, we conclude that there is no evidence that such a reaction contraindicates a new dose of the vaccine.

Keywords: BCG vaccine; COVID-19; Adverse effects.

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RESUMO

A vacina do Bacilo Calmette-Guérin (BCG) é uma vacina de patógeno vivo atenuado utilizada para a prevenção de formas graves da tuberculose. Um evento imunológico relacionado é a reativação da cicatriz, usualmente associada à doença de Kawasaki e ao uso de outros imunizantes. Objetivamos descrever nesse relato, o caso de uma mulher de 24 anos com reativação da cicatriz da vacina BCG após administração do imunizante de RNA-mensageiro (mRNA) contra COVID-19, BNT162b2. A fisiopatologia envolvida na reativação cicatricial da vacina BCG tem relação com as proteínas chaperonas. Ainda não existem casos relatados no Brasil de reativação da cicatriz BCG após vacinas de mRNA. Apesar disso, concluímos que não há evidências de que tal reação contraindique nova dose da vacina.

Palavras-chave: Vacina BCG; COVID-19; Efeitos adversos.

Introduction

The Calmette-Guérin bacillus vaccine is a live attenuated vaccine used for preventing severe forms of tuberculosis such as tuberculous meningitis and miliary tuberculosis[1]. Widely used in Brazil, the national immunization program offers the vaccine to all newborns. The vaccination rate of the Brazilian population between 2006-2016 was over 90%[1]. The BCG vaccine, known for over 100 years, is considered safe and effective. However, the immunological pathways triggered by its inoculation are not fully understood[2]. The vaccine is also linked to immunizing against other mycobacteria, reducing overall viral infections and treating bladder cancer[2,3].

One of the immunological effects related to BCG is its scar reactivation. This reaction appears commonly in Kawasaki's disease (KD), viral infections, and the administration of other vaccines[4,5]. The explanation involves the chaperones HSP (*heat shock protein*) which are intracellular and mitochondrial molecules essential to cellular homeostasis[6]. The HSPs are part of folding, carrying and producing intracellular proteins, preventing aggregation or malformation. In situations of cellular stress, its synthesis rises as a form of innate immunological response[6].

During the COVID-19 pandemic, two messenger-RNA vaccines were approved with emergency status and were made available to slow the pandemic's impact. This paper brings the first published case report of the BCG's scar's reactivation after administering an mRNA vaccine.

Case Report

We report the case of a 24 years old female medical student, previously healthy, suffering from attention deficit hyperactivity disorder (ADHD), currently on escitalopram and methylphenidate, without other systemic or cutaneous conditions. The patient has healthy parents and a sister with Hashimoto's disease. She took two doses of inactivated virus vaccine against COVID-19 and presented no adverse effects. The day following her third dose, this time with an mRNA vaccine made by Pfizer/BioNTech, she developed mild pruritus, edema, erythema and heat on the BCG scar site (Figure 1). She did not present fever, adenomegaly or any other symptoms. She denied presenting similar episodes after the previous administration of other vaccines, including the vaccine against Influenza she took in the same year. The condition did not require any treatment and had complete remission after seven days.

Discussion

The pathophysiology regarding BCG scar reactivation remains unclear. One of the proposed mechanisms is the immune-mediated reactions due to the cross between the epitopes of the Mycobacterium Bovis and the HSP chaperones. The cross-link between the HSP 63 and HSP 65 produced in the peripheral bloodstream and the reminiscent *M. bovis* antigens on the scar site explains the mechanism present in Kwasaki's Disease BCG scar reactivation[4]. When this disease is in place, cellular stress produces the corresponding chaperones, eventually leading to the cutaneous reaction. Another already reported mechanism is the inflammatory reaction of the scar against quiescent *M. bovis* particles in the vaccine after situations of immunosuppression, with the risk of systemic dissemination[2].

Like the BCG vaccine, COVID-19 displays inflammatory pathways not fully established. During the pandemic, the BCG vaccine was also subject to studies for a possible protective factor against the disease[7]. The inflammatory cascades set by the SARS-CoV-2 infection



Figure 1. Reactivation of BCG vaccination scar after COVID-19 vaccine.

are multiple and affect systems beyond the respiratory tract. One example is the severe inflammatory disorder called Pediatric Inflammatory multisystem syndrome (PIMS), which has similar features to KD and affects children and teenagers[8].

There are still no published cases in Brazil of BCG scar reactivation with messenger RNA vaccine (Pfizer/BioNTech). These vaccines are different because they do not use attenuated viruses or viral vectors but a synthetic mRNA that stimulates the production and expression of endogenous SARS-CoV-2 S protein, responsible for binding the virus to the surface of human cells. It culminates in the development of antibodies against the virus, even without previous exposure[9].

Reports of adverse reactions associated with the reactivation of this scar were already published. In 2021 a Danish study aimed to assess BCG's response to COVID-19 and subjected health professionals to a new dose. Later after the emergence of specific vaccines against COVID-19, there were observed two cases of patients with symptoms in the new BCG scar site but no symptoms in the old scar from the vaccine taken after birth[5]. Another case reported in Brazil described reactivation after the first viral vector dose vaccine (AstraZeneca/Oxford) in a young female patient with chronic urticaria and significant family history of autoimmune disease. That individual was treated with topical corticosteroid therapy until resolution[4]. In this study, the patient had no diagnosed autoimmune or autoinflammatory disorders besides Hashimoto's thyroiditis in a first-degree relative.

Also, in 2021, two case reports of BCG scar reactivation in previously healthy patients were published. The first report is the case of two healthcare professionals, one from Puerto Rico and the other from Mexico. They presented reactivation of the scar after taking the second dose of the mRNA vaccine (Pfizer/BNT162b2 and Moderna/Cambridge, respectively). Both improved with symptomatic treatment[10]. The second report also shows two patients that presented BCG scar site reactivation after mRNA vaccination (Pfizer/BNT162b2 and Moderna/Cambridge). The patient that took the Pfizer immunizer displayed the condition after the first dose, while the patient that took the Moderna's after the booster dose. In both cases, edema and erythema on the BCG scar site improved spontaneously after seven days requiring no specific treatment[11]. The natural history of the cases already reported is similar to the one presented in this report, all with spontaneous improvement and no aggravating factors.

Vaccines against COVID-19 are still in phase 3 and 4 studies, so new adverse effects and elucidations of their phenomena may still emerge. Knowing this possible reaction and its differential diagnosis, such as KD, is of great value to health professionals. We also emphasize that there is no evidence that this reaction contraindicates a new dose of the vaccine.

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Authors' Contribution

We describe contributions to the papers using the taxanomy (CRediT) provide above: Conceptualization, Investigation, Methodology, Writing – original draft & Writing – review & editing: Ribeiro JP. Investigation & Writing – original draft: Flor AF; Dantas CWM. Supervision & Writing – review & editing: Queiroz MCAP.

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