ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA
© 2020 ASBAI

BCG reactivation after COVID-19 vaccine: case report

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

Luis Felipe Ramos Berbel Angulski[1], Ana Laura Mendes Almeida[1], Camila Alves Tonami[1], Jaime Olbrich Neto[1]

ABSTRACT

BCG reactivation can occur in different contexts: associated with infectious conditions, immunosuppression, autoimmunity and post-vaccinations. Also, especially in children below of 5 years of age, should be valued as a finding present in about 50% of cases of Kawasaki disease. In this article, we report the first case published in the literature of a young adult patient, who manifested a reactivation of BCG after receiving the first dose of vaccine against COVID-19 (AztraZeneca/Oxford/Biomanguinhos). Within the first 24 hours after the administration of the vaccine, the patient developed high fever, sweating, local pain, diffuse myalgia and headache. After 2 days, erythema and induration at the site of the BCG vaccine scar began. she has how comorbidity to chronic spontaneous urticaria, but she was asymptomatic without crises for more than 1 year. The relevant family history is maternal death due to the complex syndrome of autoimmunity overlap (systemic lupus erythematosus, Sjögrens syndrome, and anti-phospholipid antibody). After being medicated with NSAID and moderate topical corticosteroid therapy potency for 3 days, there was complete resolution of BCG reactivation. The patient, after 3 months, received the 2nd dose of the vaccine and had no symptoms. It is believed that the reactivation of BCG occurs due to a cross-reaction mechanism between the individuals HSP, elicited as mediators of innate immunity against vaccine inflammation, with some epitopes of *M. bovis*. It is recommended that any immunosuppressive or autoimmune condition be investigated in patients that manifest BCG reactivation, especially in adults, in which Kawasaki disease is quite rare. Vaccines, including those against COVID-19, can also trigger of this immunological phenomenon still poorly understood.

Keywords: BCG vaccine, COVID-19 vaccines, autoimmunity.

RESUMO

A reativação da BCG pode ocorrer em diversos contextos: associada a quadros infecciosos, imunossupressão, autoimunidade e pós-vacinações. Além disso, especialmente em crianças abaixo de 5 anos de idade, deve ser valorizada como um achando presente em cerca de 50% dos casos de Doença de Kawasaki. Neste artigo, relatamos o primeiro caso publicado na literatura de uma paciente adulta jovem, a qual manifestou uma reativação de BCG após receber a primeira dose de vacina contra COVID-19 (AztraZeneca/Oxford/Biomanguinhos). Dentro das primeiras 24h após a administração da vacina, a paciente desenvolveu febre alta, sudorese, dor local, mialgia difusa e cefaleia. Após dois dias, iniciou eritema e enduração no local da cicatriz da vacina BCG. Ela tem como comorbidade a urticária crônica espontânea, porém estava assintomática sem crises há mais de 1 ano. Tem como antecedente familiar relevante o óbito materno por síndrome complexa de sobreposição de autoimunidade (lúpus eritematoso sistêmico, síndrome de Sjögren e síndrome do anticorpo antifosfolípide). Após ser medicada com anti-inflamatórios não esteroides (AINE) e corticoterapia tópica de moderada potência por 3 dias, houve resolução completa da reativação da BCG. A paciente, após 3 meses, recebeu a segunda dose da vacina e não manifestou nenhum sintoma. Acredita-se que a reativação da BCG ocorra devido a um mecanismo de reação cruzada entre HSP do indivíduo, elicitadas como mediadores da imunidade inata frente à inflamação vacinal, com alguns epítopos do *M. bovis*. Recomenda-se que seja investigada alguma condição imunossupressora ou autoimune nos pacientes que manifestem reativação da BCG, principalmente em adultos, na qual a doença de Kawasaki é bastante rara. As vacinas, incluindo as contra COVID-19, também podem desencadear o surgimento deste fenômeno imunológico ainda pouco compreendido.

Descritores: Vacina BCG, vacinas contra COVID-19, autoimunidade.

1. HCFMB - Unesp - Department of Pediatrics - Botucatu, SP, Brazil.

Submitted: 07/08/2021, accepted: 09/20/2021.

Arq Asma Alerg Imunol. 2021;5(4):422-5.

http://dx.doi.org/10.5935/2526-5393.20210062

Introduction

BCG reactivation consists of an inflammatory process located in the region of vaccine administration (in the right deltoid region), which can manifest from mild local hyperemia to more exuberant reactions, with formation of eczema, ulceration with exudation and crusts on the skin. This process can occur temporarily years after the administration of BCG (in Brazil, it is applied to newborns right at birth). Some literature references also call itBCGitis, although this term more commonly encompasses satellite adenomegaly type reactions.

It is described as occurring in various contexts, such as after infectious conditions, usually of viral etiology (upper airways or gastroenteritis, in addition to published reports on measles and HHV-6), in addition to immunosuppressive conditions (use of immunosuppressive drugs, chemotherapy, infection by HIV or post-transplantation). It is also described as a process that occurs after several vaccinations and as a clinical sign indicative of Kawasaki disease in about 50% of cases, despite not being included in the diagnostic criteria for this disease.

In this article we report the first case published in the literature of a young adult patient, who was vaccinated against COVID-19 (AztraZeneca/Oxford) and developed a reactivation of BCG.

Case report

A 23-year-old patient, student of Medicina, received the vaccine against COVID-19 and about 12 hours later, she developed chills and burning in her eyes, but without hyperemia or ocular secretion. Two hours after the onset of the condition, he developed a fever of 39.4°C and sweating, associated with pain at the site of vaccine administration and diffuse myalgia, especially on the back, and frontal headache. The next day, he observed mild hyperemia at the site of the vaccine and started inappetence. After 2 days, he observed redness and induration at the site of the scar from the BCG vaccine (which he had received in childhood, Figure 1). She was seen by the team from the Post-Vaccine Adverse Events Outpatient Clinic of a tertiary referral hospital, and an erythematous plaque measuring 2 cm in diameter was observed at the site of vaccine administration. Other changes were excluded, such as adenomegaly or signs of systemic involvement.

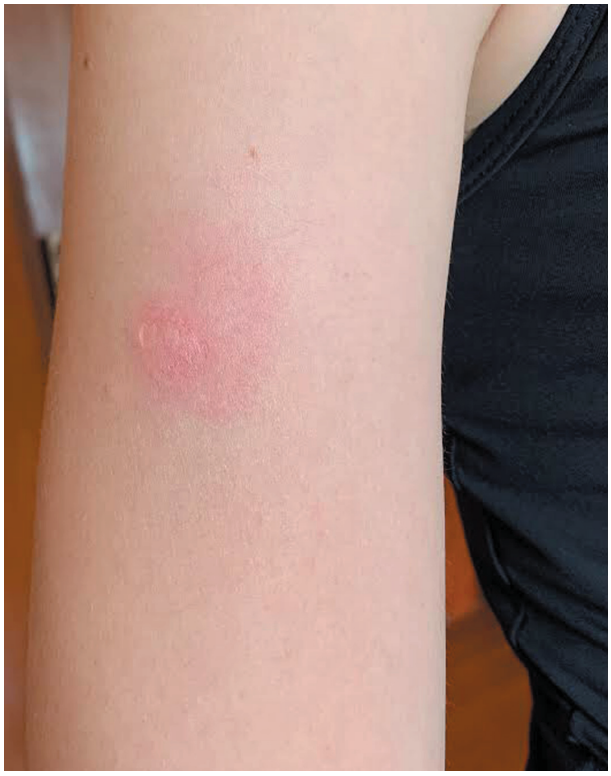

Figure 1
BCG reactivation after COVID-19 vaccine.

She presented from comorbidity a condition of spontaneous chronic urticaria, which had been diagnosed since the age of 10 years, and had been under control, without medication, for more than 1 year. In the reported crises, he presented some episodes of urticaria accompanied by angioedema (on the face and extremities of the hands and feet), associated with arthralgia in the knees. Despite extensive investigation of autoimmune etiologies, the patient did not meet criteria for any other specific disease.

The patient had been investigated, when she was diagnosed with chronic urticaria, with biochemical tests, search for some tumor markers and serological tests to search for autoantibodies – she had a family history of a mother who died of complex autoimmune overlap syndrome (systemic lupus erythematosus, Sjögren's syndrome and anti-phospholipid syndrome). At the time it was evaluated by BCG reactivation, some of these tests were repeated (Table 1). The use of oral NSAID (nimesulide) and topical corticotherapy (mometasone cream 0.1%) were prescribed for 3 days, with complete resolution of the skin condition.

She did not have a recurrence of urticaria or any other systemic manifestation, with follow-up and subsequent contact being carried out until 1 month after vaccination. The patient received the second dose, scheduled after 3 months, and did not develop any reaction, remaining asymptomatic.

Discussion

The pathophysiological mechanism involved in BCG reactivation is still controversial in the literature. A mechanism is suggestedimmune-mediated, through cross-reactions between mycobacterial epitopes with certain chaperones called HSP (heat shock protein).

Tabela 1
Exams performed in the diagnosis of chronic urticaria and BCG reactivation.

Initial exams (2018-2019)	Current exams (2021)
Hb: 13.4 g/dL Ht: 40.9% Platelets: 354 thousand/mm^3 Leukocytes (/mm^3): 11530 - Neutrophils: 6930 - Lymphocytes: 3430 - Monocytes: 820 - Eosinophils: 310 - Basophils: 40	Hb: 12.7 g/dL Ht: 36.1% Platelets: 283,000/mm^3 Leukocytes (/mm^3): 5920 - Neutrophils: 2469 - Lymphocytes: 2611 - Monocytes: 480 - Eosinophils: 349 - Basophils: 12
Anti-nucleus ac (Hep2) NR Ac gastric parietal cells NR Anti-native DNA Ab (double helix) NR Anti-endomysial IgA ac NR Antimitochondrial Ac NR Anti-smooth muscle ac NR Antithyroglobulin NR Ab Anti-Sm Ac/RNP NR Ac anti-Ro and anti-La NR Anticardiolipin NR IgG Anticardiolipin NR IgM Ab C3=90 (VR 67-149 mg/dL) C4=16 (VR 10-38 md/dL) C 15.3=8.2 (VR < 28 IU/mL) C 19.9=6.5 (VR < 37 IU/mL) CA-125=11 (VR < 35 IU/mL)	Anti-nucleus ac (Hep2) NR 1st hour VHS=1 C-reactive protein=negative D-dimer 0.45 (VR < 0.5 µg/mL) Antithyroglobulin NR Ab Anti-TPO Ab (microsomal) NR C4=18.4 (VR 12-36 mg/dL) Autologous Serum Test=negative
IgA=266 mg/dL IgG=827 mg/dL IgM=187 mg/dL IgE=31 kU/L	IgA=262.5 mg/dL IgG=782 mg/dL IgM=161.5 mg/dL IgE=25.02 IU/mL Immunophenotyping: - CD3/CD4=1176 (40.3%) - CD3/CD8=821 (28.1%) - CD4/CD8=1.4 - CD19=325 (11.2%) - CD16/56=413 (14.2%)
Free T4: 0.9 nd/dL Basal TSH: 1.3 mIU/L	T4L: 1.17 ng/dL Basal TSH: 2.33 mIU/mL

Chaperones are a family of proteins that are involved in the post-translational processing of proteins synthesized in cells, ensuring the correct folding of the polypeptide chain, preventing aggregation and ensuring that disulfide bonds are established between the sulfated amino acids. Among the chaperones, there are the so-called HSP (heat shock protein) – heat shock proteins, involved in the folding, assembly and transport of essential proteins for cell survival. Its synthesis increases in the presence of cellular stress, including infections, ischemia and other physical stresses. Its role has been included within the innate immune response.

In the illness of Kasawaki, the cross-reaction between HSP 63 and HSP 65 with mycobacterial antigens is cited explaining the BCG reactivation described in this disease. Another possible mechanism described in the literature is the reactivation of quiescent M. bovis maintained adjacent to the site of vaccine administration under certain conditions of immunosuppression, including a theoretical risk of systemic dissemination of the infection, called BCGose.

In the case reported in this work, the only comorbidity presented by the patient is spontaneous chronic urticaria, a disease now considered autoimmune in more than 50% of cases. Two possible current mechanisms to explain the onset of the disease are described: first, there is the abnormal synthesis of IgG against specific IgE molecules or their receptors, present on the surface of mast cells and basophils (autoimmune urticaria); second, there is the possibility that the individual will develop specific IgE molecules that recognize a particular autoantigen (autoallergic urticaria). Regardless of the associated mechanism, mast cells and basophils end up being activated, culminating in the release of pre- and newly formed inflammatory mediators, responsible for the symptoms of the condition and the emergence of wheals.

It is suggested that the COVID-19 vaccine may have caused an unspecific stimulation of innate immunity, which interfered with the balance maintained between the presence of bovisquiescent and the individual's immune system. In the literature, it is speculated that infections associated with transient immunosuppression, such as measles, may disrupt this balance, explaining the reported cases of BCG reactivation after this wild virus infection. Interestingly, the patient did not have urticaria exacerbation and/or angioedema, keeping her underlying disease under control, suggesting that BCG reactivation itself may not have a direct relationship with spontaneous chronic urticaria. She also did not meet criteria for Kawasaki disease, which is rare over 5 years old.

Therefore, it is imperative to investigate any immunosuppressive/autoimmune condition in individuals who present BCG reactivation after different contexts, such as infections or vaccine reactions, although there is none in the literature suggested investigation protocol. In children, especially under 5 years of age, especially infants, it is essential to remember the possibility of Kawasaki disease in the presence of this immunological phenomenon that is still poorly understood.

References

1. Novais C, Fortunato F, Bicho A, Preto L. Bacillus Calmette-Guérin reactivation as a sign of incomplete Kawasaki disease. BMJ Case Rep. 2016 Mar;2016:bcr2015213875. doi: 10.1136/bcr-2015-213875. PMID: 27033285; PMCID: PMC4840603.
2. Ladeira I, Carvalho I, Correia A, Carvalho A, Duarte R. Erratum to "BCGitis in children". Rev Port Pneumol (2006). 2016 Nov-Dec;22(6):e1. doi: 10.1016/j.rppnen.2016.10.001. Epub 2016 Nov 17. Erratum for: Rev Port Pneumol. 2014 May-Jun;20(3):172-3. PMID: 27867082.
3. Moreira TN, Moraes-Pinto MI, Costa-Carvalho BT, Grumach AS, Weckx LY. Clinical management of localized BCG adverse events in children. Rev Inst Med Trop Sao Paulo. 2016;58:84. doi: 10.1590/S1678-9946201658084. PMID: 27828625; PMCID: PMC5096638.
4. Diniz LMO, Castanheira RG, Giampietro YG, Silva MS, Nogueira FD, Pessoa PD, et al. Diagnostic value of the reaction at the bacillus Calmette-Guérin vaccination site in Kawasaki disease. Rev Paul Pediatr. 2021;39:e2019338. doi: 10.1590/1984-0462/2021/39/2019338. Epub 2020 Aug 28. PMID: 32876305; PMCID: PMC7457469.
5. Rezai MS, Shahmohammadi S. Erythema at BCG inoculation site in Kawasaki disease patients. Mater Sociomed. 2014 Aug;26(4):256-60. doi: 10.5455/msm.2014.26.256-260. Epub 2014 Aug 26. PMID: 25395889; PMCID: PMC4214810.
6. Suliman OS, Abdelnasser M. Incomplete Kawasaki disease: The usefulness of BCG reactivation as a diagnostic tool. Sudan J Paediatr. 2012;12(1):84-8. PMID: 27493333; PMCID: PMC4949825.
7. Muthuvelu S, Lim KS, Huang LY, Chin ST, Mohan A. Measles infection causing Bacillus Calmette-Guérin reactivation: a case report. BMC Pediatr. 2019 Jul 24;19(1):251. doi: 10.1186/s12887-019-1635-z. PMID: 31340782; PMCID: PMC6652017.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Luis Felipe Ramos Berbel Angulski
E-mail: lf.angulski@unesp.br