



**Astrid Herzum, Ilaria Trave,
Federica D'Agostino, Martina
Burlando, Emanuele Cozzani,
Aurora Parodi**

Department of Dermatology, Di.S.Sal., University
of Genoa, San Martino Polyclinic Hospital IRCCS,
Genoa, Italy

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Corresponding author: Astrid Herzum, MD
 Department of Dermatology, Di.S.Sal., University
of Genoa, San Martino Polyclinic Hospital IRCCS,
Largo Rosanna Benzi 10, 16132 Genoa, Italy
 Tel: +39-0105555756, Fax: +39-0105556509
 E-mail: astridherzum@yahoo.it

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Epstein-Barr virus reactivation after COVID-19 vaccination in a young immunocompetent man: a case report

We present the case of a 24-year-old Caucasian man, who developed a scaly erythematous skin rash after the second dose of coronavirus disease 2019 (COVID-19) vaccination with Comirnaty (BNT162b2, BioNTech/Pfizer; Pfizer, New York, NY, USA) and proved positive for Epstein-Barr virus (EBV) reactivation. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines have been associated with an up-regulated T helper type 1-cell response, possibly favoring an immune system imbalance. Also, EBV reactivation has been postulated after COVID-19 vaccination, but only in the immunosuppressed. Noteworthy we report the first case of EBV viral reactivation associated with cutaneous manifestations in an immunocompetent patient after the COVID-19 vaccine.

Keywords: COVID-19, COVID-19 vaccine, Epstein-Barr virus, Exanthema, Case report

Introduction

In response to the recent coronavirus disease 2019 (COVID-19) pandemics, newly developed gene-therapy-based vaccines are being routinely administered worldwide, and accompanying adverse effects, including viral reactivations, are being increasingly reported [1].

Interestingly, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines have been associated with an up-regulated T helper type 1 (Th1)-cell response, which probably increments inflammatory cytokines involved in a systemic inflammatory syndrome favoring an immune system imbalance [2].

Viral reactivations, especially of herpesviruses comprising human herpesvirus (HHV)6, HHV7, and virus zoster varicella (VZV), have been described after COVID-19 vaccination, possibly inducing clinical manifestations as pityriasis rosea (PR) and PR-like eruptions and herpes zoster [3-6]. Also, Epstein-Barr virus (EBV) reactivation has been postulated after COVID-19 vaccination, but only in the immunosuppressed, where viral reactivation has been linked to monomorphic posttransplant lymphoproliferative disorder [7].

Herein we report the first case of EBV reactivation associated with cutaneous manifestations in an immunocompetent patient after the COVID-19 vaccine.

Case Report

A 24-year-old man presented at the Dermatology Department with a faint maculopapular rash, scaly, erythematous, and non-itchy on his limbs and trunk (Fig. 1). He referred the first lesion had appeared for 1 week on his arm, 3 weeks after the SARS-CoV-2 mRNA vaccine Comirnaty (BNT162b2, BioN-Tech/Pfizer; Pfizer, New York, NY, USA). The rash had successively spread on his trunk and lower limbs.

The patient, otherwise in good health, referred only to modest fatigue and malaise, sore throat, and was afebrile. He was not taking any medications and his medical history was unremarkable.

On physical examination, a faint rash consisting mainly of mildly erythematous and desquamative macules and papules was observed on his trunk, especially the hips (Fig. 1), inner upper arms, and thighs. Also, a well-demarcated, intensely erythematous, and scaly plaque was evidenced on his upper arm, which he referred being the primary skin lesion (Fig. 2). Also, asymptomatic, barely hinted oral and genital lesions were evidenced, consisting of lightly undermined round to oval areas (Fig. 3). Erythema of the urethral meatus and erythema and pasty exudate of the pharynx were detected.

Laboratory investigations, including complete blood cell count, liver, and kidney function, were within normal ranges. Antibodies against cytomegalovirus, hepatitis A virus, HHV6, HHV7, and parvovirus B19, at times causing Mononucleosis-

like syndromes, as well antibodies against VZV, Coxsackie A and B, and *Treponema pallidum*, were negative or suggestive of past immunity. Venereal Disease Research Laboratory test and *Treponema pallidum* hemagglutination assay were negative. The pharyngeal swab and serum antistreptolysin O titer were negative. Serology for EBV revealed a viral reactivation, testing positive for immunoglobulin M antibodies against vi-



Fig. 2. Erythematous, scaly plaque on the upper inner arm, representing the primary skin lesion. Written informed consent for publication of this image was obtained from the patient.



Fig. 1. Mildly erythematous and scaly, round and oval macules and papules of the hips. Written informed consent for publication of this image was obtained from the patient.



Fig. 3. Lightly undermined round to oval lesions of the glans accompanied by erythema of the urethral meatus. Written informed consent for publication of this image was obtained from the patient.

ral capsid antigen and for immunoglobulin G antibodies against Epstein-Barr nuclear antigen. We diagnosed an EBV viral reactivation associated with cutaneous manifestations.

The present research complies with the guidelines for human studies and includes evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient gave written informed consent to publish the case (including publication of images).

Discussion

EBV is a ubiquitous HHV4, infecting more than 90% of adults worldwide, mostly transmitted in childhood by contact with saliva [8]. EBV mostly causes primary asymptomatic infection or only mild non-specific symptoms, especially in infants and children, whereas in adolescents and young adults the primary EBV infection often presents as infectious mononucleosis (IM) [8]. IM is characterized by fatigue, fever, pharyngitis, and lymphadenopathy. Also, in 5%–15% of untreated patients, a faint erythematous maculopapular skin eruption, can occur [8]. Moreover, EBV acute infection has been related to oral ulcers, urethritis, and genital ulcers, especially vulvar; the so-called “EBV-associated ulcer vulvae acutum” also known as Lipschütz’s ulcers [8,9].

Of note, the herein reported case of faint maculopapular exanthema, with serological evidence of EBV reactivation, occurred after administration of the COVID-19 vaccine in a young immunocompetent patient.

EBV viral reactivation after the COVID-19 vaccine has been documented up to date only in an immunocompromised patient and successively linked to an EBV-positive diffuse large B-cell lymphoma [7]. The patient had been administered Oxford-AstraZeneca vaccination 1 week before detecting viral reactivation.

In immunocompetent patients, EBV reactivation had been previously related only to COVID-19 disease itself, rather than to the vaccination, also in association to HHV6 and HHV7 reactivation, possibly linked to SARS-CoV-2-infection immune-mediated inflammatory syndrome [10,11]. Interestingly, high EBV viremia levels were detected in COVID-19 hospitalized patients compared to non-COVID-19 patients and the level of EBV viremia was associated with systemic inflammation in COVID-19 patients [11].

What is more, reactivation of Gamma-herpesviruses has been already associated with transfection of SARS-CoV-2 spike

protein S, the target antigen encoded by the COVID-19 vaccine in vitro [12]. Analogously, other types of vaccinations, such as influenza vaccination have been already linked to skin rashes, PR-eruptions with detection of HHV6 and HHV7, and non-Hodgkin lymphoma probably secondary to EBV reactivation [13,14].

Though in the presented case, the link between COVID-19 vaccine administration and EBV reactivation with clinically manifest exanthema, remains just a hypothesis, an alteration in the T cell balance after vaccination, favoring tissue EBV reactivation, cannot be excluded and needs to be addressed in further studies.

ORCID

Astrid Herzum <https://orcid.org/0000-0001-6373-8801>

Ilaria Trave <https://orcid.org/0000-0002-5469-4517>

Federica D’Agostino <https://orcid.org/0000-0002-8045-6125>

Martina Burlando <https://orcid.org/0000-0002-4381-6718>

Emanuele Cozzani <https://orcid.org/0000-0003-3108-4123>

Aurora Parodi <https://orcid.org/0000-0002-6622-2226>

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