


Reactivation of varicella-zoster virus following mRNA COVID-19 vaccination in a patient with moderately differentiated adenocarcinoma of rectum: A case report

SAGE Open Medical Case Reports
Volume 10: 1–4
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2050313X221077737
journals.sagepub.com/home/sco



BM Munasinghe¹ , UPM Fernando², M Mathurageethan¹
and Durga Sritharan¹

Abstract

Herpes zoster which is the reactivation of varicella-zoster virus, a pathogenic human alpha-herpes virus, following primary infection or chicken pox, is known to occur especially in advanced age and in the immunocompromised among other predisposing factors. COVID-19 vaccination-induced immunomodulation is a novel scenario, hypothesized to be a result of shifting of T-lymphocyte population towards vaccine-induced naïve CD8⁺ subset, offsetting the balance of varicella-zoster virus responsive T-helper cells, thereby defecting the cell-mediated immunity which suppresses the latent varicella-zoster virus. The exact mechanism, however, is still elusive. Herein, we discuss a case of reactivation of varicella-zoster virus following BNT162b2 mRNA COVID-19 vaccine in an elderly female on oral medication for long-term diabetes and hypertension with good control who has undergone local radiotherapy for an underlying adenocarcinoma of rectum awaiting surgical resection, highlighting the key features of pathogenesis of the disease in relation to COVID-19 vaccination with a pertinent survey of the literature. This case report highlights the importance of differentiating vaccine-related cutaneous reactions with clinically more significant adverse events, early specific therapy thus preventing poorer acute and chronic outcomes.

Keywords

Varicella-zoster virus, herpes zoster, shingles, COVID-19, vaccination, rectal cancer

Date received: 16 October 2021; accepted: 12 January 2022

Introduction

Varicella-zoster virus (VZV) is a neurotropic virus. It gets reactivated after differing latent periods to produce herpes zoster (HZ).¹ Well-known triggers identified and described in the literature include old age and immunosuppression due to variety of reasons.^{2,3} The pathophysiology basically involves waning cell-mediated immunity (CMI) which otherwise keeps the lifelong dormancy of VZV in check.¹ Vaccines and radiotherapy have been clearly demonstrated in such reactivations probably subsequent to transient generalized and regional immunosuppression, respectively.^{4–6} Even though the primary or varicella infection is generally mild, HZ during reactivation might lead to sinister outcomes involving neurological and ophthalmological systems.^{7,8} HZ resultant of COVID-19 vaccines is being reported in increasing incidence with the prevailing

pandemic where the exact pathobiology is yet to be described, even though assumed to be related to the ineffective T-cell-mediated control of the dormant virus. A variety of clinically mild cutaneous manifestations are also described following COVID-19 vaccines,⁹ necessitating a thorough understanding among clinicians to discern from potentially troublesome vents such as HZ to initiate therapy early and prevent long-term morbidity. Herein, we present one of the few globally reported cases of reactivation of VZV in an elderly South-Asian female with an underlying

¹District General Hospital, Mannar, Sri Lanka

²National Blood Transfusion Service, Colombo, Sri Lanka

Corresponding Author:

BM Munasinghe, District General Hospital, Mannar, Sri Lanka 41000.
Emails: malakafmp@gmail.com; mannaranaesthesia@gmail.com



rectal malignancy following COVID-19 vaccination. This article is primarily focused on the pathogenesis of the disease illustrating most up to date evidence in the literature.

Case presentation

The patient is a 71-year-old Asian female who was admitted to the medical ward of our institution, a District General Hospital in northern Sri Lanka, with the complaint of painful blisters involving left arm for 2 days. Rapid antigen test for COVID-19 was negative on admission. She was vaccinated with BNT162b2 mRNA COVID-19 vaccine (Pfizer) first dose 5 days prior to the onset of symptoms. She disclosed a childhood history of chickenpox where she had not been vaccinated for VZV prior. She was a diabetic and hypertensive for 30 years with good control. The medication included oral hypoglycemics (metformin and sitagliptin) with losartan as the antihypertensive. There was no recent change in her drug regimen and she denied any systemic or cutaneous adverse effects following her routine drug therapy. In addition, she was also diagnosed with moderately differentiated adenocarcinoma of rectum for 18 months without evidence of distant metastasis, received local radiotherapy 38 days before the onset of symptoms and awaiting anterior resection. Due to compromised cardiac functions as a result of past myocardial infarction with dual vessel disease, she was deemed to be unfit for neoadjuvant chemotherapy. Allergy history and family history for recurrent infections were negative. At the time of admission, she was fever free. Further examination revealed crops of pustular vesicles of differing age in postero-lateral aspects of left arm spreading to the anterior forearm in a multi-dermatomal pattern involving C4, C5, C6 and T1 dermatomes sparing mammary and facial dermatomes (Figure 1). Her vitals were stable and systemic manifestations of varicella-zoster were absent. The diagnosis of HZ (shingles) was made clinically. Blood samples were taken for full blood count (FBC), C-reactive protein (CRP), culture and sensitivity and fasting blood sugar, all of which were normal. Retroviral studies were negative. Blister fluid for viral polymerase chain reaction (PCR) was positive for VZV. She was administered oral acyclovir 800mg five times daily for 1 week, antibiotics, topical soframycin cream and potassium permanganate compression dressings after dermatology opinion. She made an uneventful recovery and was discharged from the hospital to continue oral medication at home. Investigations later revealed normal levels of T-cell subsets (CD4+, CD8+ and CD 19+) on flow cytometry and normal immunoglobulin (Ig)A, IgM and IgG levels 1 month following recovery. Subsequent dose of the same vaccine administered 8 weeks after the first dose did not result in any adverse events.

Discussion

COVID-19 pandemic continues to spread globally, claiming 4.79 million lives to date,¹⁰ threatening the very existence of



Figure 1. Multidermatomal involvement (C4–C6 and T1) with pustular vesicles in left upper limb clinically suggestive of zoster.

human race after the last major scale outbreak of Spanish flu in 1918. To counter the unforeseen threat, the developed countries are toiled with the task of manufacturing a vaccine to battle against COVID-19 while the developing countries are in a relentless battle to purchase vaccines to ramp up the vaccine coverage to their people. According to the World Health Organization statistics, the status quo of COVID-19 vaccines is that there are over 300 investigational vaccines in total to be used under emergency user authorization (EUA) upon success.¹¹ Relatively short time span since the initiation of vaccination programmes and EUA hinders the availability of data on intermediate and long-term adverse events following immunization (AEFI) for COVID-19 vaccines, including the relatively new occurrence of varicella-zoster reactivation in the form of HZ or shingles, on which this case report is based on. That being said, the safety profile of the recently developed vaccines is well-established and the benefits of COVID-19 vaccines greatly outweigh the risks.¹²

Of note, there is an array of cutaneous reactions reported in the literature following COVID-19 vaccines which are reported during clinical trials as well as during post-marketing surveillance. As expected, the allergic and urticarial reactions, local reactions such as redness or swelling of the inoculation site, and severe forms of allergies such as anaphylaxis take precedence over others such as, COVID arm, a delayed type hypersensitivity reaction, delayed large local reactions, morbilliform exanthem and erythromelalgia.⁹ Reactivation of VZV or varicella flare is commonly a mild adverse event, reported sparsely in the literature even though acute or chronic

morbidity due to neurological or ophthalmological adverse events are also documented.^{7,8,13,14}

VZV is a neurotropic virus which can go into decades of latency in the dorsal root ganglia, cranial nerve ganglia and autonomic ganglia of the host following primary infection (varicella or chickenpox).¹⁵ The VZV responder T-cell depletion as a result of natural immunosenescence with ageing or due to immunosuppression secondary to disease, drugs, trauma, radiation, infection, malignancy or even transient stress, can be triggering factors.^{16,17} Although malignancies, in particular the haematological cancers leading to defective CMI and immunosuppression are known to trigger HZ, the reactivation of herpes itself may be a heralding sign of underlying occult cancer.¹⁸

Reactivation of VZV in post-vaccinated patients is multifactorial in nature yet the most important risk factors are advancing age and immunocompromised state of the host.^{2,3} In line with the above findings, older age (>70 years) and moderately differentiated adenocarcinoma of the rectum posed increased risk in developing HZ upon exposure to any other triggering factor in the case of our patient. Post-vaccination HZ albeit rare is not unheard of. Several cases of HZ have been reported in the literature following vaccination of inactivated influenza, hepatitis A, rabies, Japanese encephalitis, yellow fever and 2009 H1N1 influenza vaccines^{10–12} in addition to COVID-19 vaccines.^{19–21} The hallmark of the underlying immunopathology of post-vaccinated patients is the defective CMI, which makes them predisposed to developing HZ is hypothesized to be a result of shifting of T-lymphocyte population towards vaccine-induced naïve CD8+ subset, offsetting the balance of VZV responsive T-helper cells, thereby defecting the CMI which suppress the latent VZV.^{19,22} Transient lymphopenia caused by the vaccines is also suggested as a causative factor.²³ Another explanation resorts to the sentinel toll-like receptors (TLRs) 3 and 7 of the innate immunity where by the mRNA vaccine-induced expression of type 1 interferons and potent inflammatory cytokines, which instigate the T- and B-cell-mediated response, however, may hinder the antigen sensing by TLRs due to weakened antigen presentation. This may cause to reactivation of HZ.²⁴ Radiotherapy has also been discussed in detail by Ramirez-Fort et al.,²⁵ as a trigger of reactivation of VZV, by its regional immunomodulatory properties, predominantly suppression of CMI and promoting replication of viral DNA with worse short-term and long-term sequel (e.g. increased risk of post-herpetic neuralgia) identification of high-risk patients and empirical therapy with proper antivirals during the course of radiotherapy is suggested. In the case of our patient, there was no recurrence of VZV at the region (pelvic) of ionizing radiation she was subjected. During the follow-up, there were no manifestations of herpetic neuralgia.

The cause–effect relationship of the events, the flow cytometry analysis of T-lymphocytes subsets and normal Ig levels following recovery, suggests, not the persistent immunosuppression due to malignancy and related radiotherapy, but the vaccine-induced transient immunomodulation leading to HZ in this patient, although this hypothesis cannot be excluded in entirety, due to the lack of baseline flow cytometry report or during the flare (due to practical difficulties of transporting samples to a remote centre where these sophisticated and costly tests are carried out sparingly but for free).

Conclusion

With the escalation of COVID-19 vaccination, the challenges faced by the clinicians are ever-changing in terms of educating the public, and managing the vaccine-related adverse events which will eventually enhance the acceptance of vaccination campaign and help to curb the pandemic progression. The incidence of different cutaneous manifestations following vaccination, including the reactivation of herpes is on the rise in parallel with the rising vaccination count at least in predisposed groups of individuals. Several possible explanations have been proposed to delineate cause–effect relationship between VZV reactivation and COVID-19 even though further research is warranted. While it is prudent to remember that the case reports such as this are considered as the lowest grade of scientific evidence in the pyramid of clinical knowledge and decision-making, it is imperative to identify the patients at risk of developing reactivation of herpes prior to the vaccination and to educate, manage and to follow them up to minimize the vaccine-related hazardous outcomes.

Acknowledgements

The authors acknowledge Dr Nishanthan Subramaniam, Medical Officer in Anaesthesiology and Intensive care, Dr K. Jayasundara (Acting Consultant Paediatrician), the medical officers and the staff of surgical female ward in our institution for the support extended during management of the patient. The authors also want to acknowledge Professor Rajeeva De Silva, Consultant Immunologist at Medical Research Institute of Sri Lanka for arranging immunological studies.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iD

BM Munasinghe  <https://orcid.org/0000-0001-8373-4752>

References

- Gilden D, Mahalingam R, Nagel MA, et al. The neurobiology of varicella-zoster virus infection. *Neuropathol Appl Neurobiol* 2011; 37(5): 441–463.
- Crooke SN, Ovsyannikova IG, Poland GA, et al. Immunosenescence and human vaccine immune responses. *Immun Ageing* 2019; 16: 25.
- Marra F, Parhar K, Huang B, et al. Risk factors for herpes zoster infection: a meta-analysis. *Open Forum Infect Dis* 2020; 7(1): ofaa005.
- Walter R, Hartmann K, Fleisch F, et al. Reactivation of herpesvirus infections after vaccinations? *Lancet* 1999; 353(9155): 810.
- Bayas JM, González-Álvarez R and Guinovart C. Herpes zoster after yellow fever vaccination. *J Travel Med* 2007; 14(1): 65–66.
- Rothova A, de Groot JD and Mudrikova T. Reactivation of acute retinal necrosis after flu H1N1 vaccination. *Br J Ophthalmol* 2011; 95(2): 291.
- Gilden D, Cohrs RJ, Mahalingam R, et al. Neurological disease produced by varicella zoster virus reactivation without rash. *Curr Top Microbiol Immunol* 2010; 342: 243–253.
- Liesegang TJ. Herpes zoster ophthalmicus: natural history, risk factors, clinical presentation, and morbidity. *Ophthalmology* 2008; 115(Suppl. 2): S3–S12.
- Wollina U, Chiriac A, Kocic H, et al. Cutaneous and hypersensitivity reactions associated with COVID-19 vaccination – a narrative review. *Wien Med Wochenschr*. Epub ahead of print 23 August 2021. DOI: 10.1007/s10354-021-00876-0.
- WHO. Weekly operational update on COVID-19 – 4 October 2021, <https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19—4-october-2021> (2021, accessed 30 November 2021).
- World Health Organization. *WHO issues its first emergency use validation for a COVID-19 vaccine and emphasizes need for equitable global access*. Geneva: WHO, 2020.
- Centers for Disease Control and Prevention. Benefits of getting a COVID-19 vaccine, <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/vaccine-benefits.html> (2021, accessed 30 November 2021).
- Santovito LS and Pinna G. A case of reactivation of varicella-zoster virus after BNT162b2 vaccine second dose? *Inflamm Res* 2021; 70(9): 935–937.
- Aksu SB and Öztürk GZ. A rare case of shingles after COVID-19 vaccine: is it a possible adverse effect? *Clin Exp Vaccine Res* 2021; 10(2): 198–201.
- Eshleman E, Shahzad A and Cohrs RJ. Varicella zoster virus latency. *Future Virol* 2011; 6(3): 341–355.
- Insinga RP, Itzler RF, Pellissier JM, et al. The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med* 2005; 20(8): 748–753.
- Mehta SK, Cohrs RJ, Forghani B, et al. Stress-induced sub-clinical reactivation of varicella zoster virus in astronauts. *J Med Virol* 2004; 72(1): 174–179.
- Schmidt SA, Mor A, Schönheyder HC, et al. Herpes zoster as a marker of occult cancer: a systematic review and meta-analysis. *J Infect* 2017; 74(3): 215–235.
- Katsikas Triantafyllidis K, Giannos P, Mian IT, et al. Varicella zoster virus reactivation following COVID-19 vaccination: a systematic review of case reports. *Vaccines* 2021; 9(9): 1013.
- Palanivel JA. Herpes zoster after COVID-19 vaccination – can the vaccine reactivate latent zoster virus? *J Cosmet Dermatol* 2021; 20(11): 3376–3377.
- Arora P, Sardana K, Mathachan SR, et al. Herpes zoster after inactivated COVID-19 vaccine: a cutaneous adverse effect of the vaccine. *J Cosmet Dermatol* 2021; 20: 3389–3390.
- Psichogiou M, Samarkos M, Mikos N, et al. Reactivation of varicella zoster virus after vaccination for SARS-CoV-2. *Vaccines* 2021; 9(6): 572.
- Van Dam CS, Lede I, Schaar J, et al. Herpes zoster after COVID vaccination. *Int J Infect Dis* 2021; 111: 169–171.
- Furer V, Zisman D, Kibari A, et al. Herpes zoster following BNT162b2 mRNA covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. *Rheumatology* 2021; 60: SI90–SI95.
- Ramirez-Fort MK, Zeng J, Feily A, et al. Radiotherapy-induced reactivation of neurotrophic human herpes viruses: overview and management. *J Clin Virol* 2018; 98: 18–27.