CASE REPORT

Varicella-zoster virus reactivation following covid-19 vaccination: A Tunisian case series

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ABSTRACT

Reactivation of Varicella-Zoster Virus (VZV) most commonly manifests as shingles. A few months after the start of the COVID-19 vaccination campaign cases of shingles were reported.

OBJECTIVE: We aimed to report cases of VZV reactivation reported after COVID-19 vaccination to the Tunisian National Centre of Pharmacovigilance (NCPV).

METHODS: This is a retrospective study of VZV reactivation cases reported to the NCPV after COVID-19 vaccination from March 2021 to May 2022.

RESULTS: We included 20 patients with shingles. The sex ratio (M/F) was 0.8. The median age was 68.5 years. Nine patients were over 70 years of age. The administered vaccines were an mRNA vaccine for 15 patients. The onset delay ranged from one to 30 days (mean 4.5 days). All patients recovered within a few days and no severe cases have been reported. Two patients received the second dose; One patient did not experience a recurrence of the symptomatology. The other patient, had aggravation of symptomatology and occurrence of facial paralysis; noting that the initial symptomatology did not entirely disappear when the patient received the second dose. The patient was diagnosed with Ramsay Hunt Syndrome.

CONCLUSION: Our study draws attention to the chronological association between the SARS-CoV-2 vaccine and VZV reactivation, which should be investigated.

Key Words: *Varicella zoster virus infection; COVID-19 vaccines; Herpes Zoster; Drug-related side effects and adverse reactions; Hunt's syndrome*

INTRODUCTION

Varicella-Zoster Virus VZV is a DNA virus belonging to the herpes virus family, responsible for two clinical conditions. The primary infection generates varicella (chickenpox). Secondary infection also known as reactivation of latent VZV induces shingle [1].

Recently, following the massive administration of COVID-19 vaccines to a large population, several adverse events following immunization AEFI have been observed that were not initially mentioned in the safety data sheet of these vaccines or detected in clinical trials before its marketing [2]. Post-marketing, sporadic case reports, and a series of VZV reactivations have been reported [3].

In this study, we aimed to present and analyze the characteristics of VZV reactivation cases after COVID-19 vaccination.

CASE PRESENTATION

We conducted a retrospective descriptive study of VZV reactivation cases reported in 2021 to the National Center of Pharmacovigilance following COVID-19 vaccination. Data were collected from the database of the department of collection and analysis of adverse drug reactions.

RESULTS

We included 20 patients presented with shingles (one of whom had Ramsay Hunt Syndrome RHS). The sex ratio (M/F) was 0.8. The median age was 68.5 years (ranging between 22 years and 80 years). Nine patients had a minimum age of 70 years. The administered vaccines were an mRNA vaccine for 15 patients, a viral vector vaccine for four patients, and an inactivated vaccine for one patient. Symptomatology occurred after the first dose of an mRNA vaccine in 10 patients, and in two patients after the second dose of the viral vector vaccines. The symptoms delay ranged from one day to 30 days (mean of 4.5 days). Four patients had a medical history of diabetes. No concomitant use of immunosuppressants was reported for all patients. All patients recovered within a few days and no severe cases were reported.

An 80-year-old patient with a medical history of colorectal neoplasia received an inactivated vaccine and got the second dose without recurrence of the event. Another patient presented facial paralysis with aggravation of the initial symptomatology (vesicular rash of the left auricle one week after receiving his first dose) three days after receiving the second dose of mRNA vaccine; noting that the initial symptomatology was not entirely disappeared when the patient received the second dose. This patient was diagnosed with Ramsay Hunt Syndrome.

DISCUSSION

VZV reactivation cases were reported by Psichogiou et al. after hepatitis A, inactivated influenza, and rabies with Japanese encephalitis vaccines and yellow fever [4]. Despite the precise basis remains unsolved, immunomodulation and alloreactivity induced respectively by live attenuated vaccines and inactivated vaccines may be answerable mechanisms for the reactivation of VZV [4].

In a literature review, Iwanaga et al. noticed that VZV reactivation following the COVID-19 vaccines has been reported all over the world and with different vaccine types a few months after COVID-19 commercialization [5].

The VZV reactivation prevention relies on cell-mediated immunity. Decreasing cell-mediated immunity is associated with a decline in VZV-specific T cells, disrupting immune control and rising the risk of reactivation [6]. In addition, a decline in major class 1-histocompatibility complex results in the inhibition of interferon response serves as an antiviral, hence triggering the viral replication [1]. This immune system downregulation is affected by age as the major risk factor for 90% of cases of shingle [6]. In addition to the immunosenescence, trauma, malignancy, chronic kidney and liver disease, HIV infection, and immunosuppressive therapy predispose to the virus reactivation [1,6].

In our study, 45% of the patients were aged 70 years or older with a median age of 68.5 years which represents the main risk factor in our population. Only one patient had a medical history of malignancy

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(colorectal neoplasia). Thus, we should not sidestep that VZV can affect both immunocompromised as well as immunocompetent persons, even though it is much more likely in the latter group and the elderly, as was the case with our patients.

Furthermore, previous studies ascertained that increased psychological stress can trigger VZV reactivation. From the beginning of the pandemic, the increasing disease vulnerability, mortality rates, restrictions, and regulations applied to restrain the spread of SARS-CoV-2 infection have been a continued source of stress. COVID-19 vaccines could also be a stress factor, with all the discussions and controversies it has generated [4]. COVID-19 also could be a risk factor as it drops down cell-mediated immunity by inducing lymphopenia and lowering CD3+, CD4+, and CD8+ T cells [4].

Xu et al. reported that patients contaminated with SARS-CoV-2 have been reported to develop VZV reactivation naturally [7]. The potential mechanism of SARS-CoV-2-associated VZV reactivation could be a cytokine bombardment implicating the release of proinflammatory cytokines, such as interleukin-6, tumor necrosis factor-alpha, and interleukin-12 which affects CD4+ T cells function leads to excessive activation, and potential ensuing exhaustion of CD8+ T cells [8].

Reviewing the literature, Iwanaga et al. found that VZV reactivation following COVID-19 vaccination was more reported with mRNA vaccines than with other vaccine types. The risk was higher after the first dose than after the second dose with a median age of 58.9 years and a mean duration of 6.75 days [5]. Our results were similar to these findings. 75% of our patients have received an mRNA vaccine with 50% showing symptomatology after the second dose. The mean duration of symptoms onset was 4.5 days and our patient's median age was 68.5 years. This association between mRNA vaccines and VZV reactivation could be explained by the main use of mRNA vaccines comparatively to other vaccine types.

We reported only one patient, 80 years old who presented shingle after receiving his first dose of an inactivated vaccine. To our knowledge, VZV reactivation following inactivated COVID-19 vaccine has only been reported in turkey (four cases) and India (one case). Patients' ages ranged between 21 years and 94 years with a mean of 58.9 years. The reactivation seems more common after the first dose of inactivated vaccine than the second dose [5,9].

Herpes zoster Oticus or Ramsay Hunt Syndrome (RHS), is a late complication of VZV infection generating inflammation of the geniculate ganglion of cranial nerve VII. RHS is clinically diagnosed typically it's a triad of otalgia, ipsilateral facial paralysis, and limited skin rash with vesicles near the ear and auditory canal, as was the case for our patient. A rise in the incidence of long-term complications could be attributed to often missed or delayed diagnose [10].

Both VZV reactivation and facial paralysis were reported with virus vaccinations like hepatitis B and influenza vaccines [11]. Hence, it's not astonishing that cases of both conditions be reported about COVID-19 vaccination while the mechanism is still obscure.

After COVID-19 vaccine marketing, there were reported cases of facial paralysis following vaccination, with some cases attributed to the reactivation of VZV [12, 13]. The occurrence of the episodes immediately after the vaccine dose in many cases points to the role of the vaccine, even if a causality assessment cannot be proved. For our patient, the onset delay of RHS was three days after the first dose with a recurrence of the symptomatology one week after the second dose, which strongly suggests the role of the mRNA vaccine.

Herein, we would like to draw attention to an important assertion. While the diagnosis of RHS is clinical it may manifest without skin lesions, leading to differential diagnosis problems with unilateral facial paralysis [14]. Thus, without PCR or antibody detection, we could suggest that VZV reactivation induced by the vaccine may be the potential etiology behind this condition.

CONCLUSION

Vaccine-related VZV reactivation was reported worldwide most commonly with mRNA vaccine while RHS is an uncommon condition. Most reported cases had a favorable outcome with total regression within a few days.

Data are limited to support a causal link between COVID-19 vaccines and herpes virus reactivation. Therefore, further epidemiologic studies are needed to assess the vaccine's imputability.

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