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Herpes Zoster Post-Vaccine Mimicking "COVID Arm" in an Old Femall

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Abstract

Cutaneous adverse effects related to SARS-CoV-2 vaccines are still a challenging issue. "COVID arm" is a manifestation of delayed hypersensitivity reaction appearing after the SARS-CoV-2 vaccination as reddish, warm, pruritic, indurated, or swollen areas in the limb of the vaccine site. These skin alterations may be associated with systemic symptoms and have been observed after the first or second dose of COVID-19 vaccines. The aim is describe a 76-year-old woman who had "COVID arm simile" lesions caused by herpes virus in the left upper limb 4 weeks after the AstraZeneca vaccine first dose. The reaction, with 30 days duration, needed treatment and was considered severe. However, the patient received the second dose of the same vaccine uneventfully. Case reports of intercurrences during mass vaccinations are advantageous for health care workers and patients.

Keywords: COVID Arm, Herpes Zoster, Immunocompetent, SARS-CoV-2, Vaccine

1. Introduction

The following described clinical and epidemiologic features of the immediate and delayed cutaneous reactions associated with coronavirus disease 2019 (COVID-19) vaccination and "COVID arm" aim to enhance the interest in dermatological manifestations of this challenging pandemic context.

Manifestations of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or COVID-19 are associated with cytokine storm and systemic inflammatory response, and the mass vaccination constitutes the paramount measure of the public health system.[1-21] Neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), platelet/lymphocyte ratio (PLR), derived NLR (DNLR), and systemic immune-inflammatory index (SII) are prognostic tools.[1]

Immediate and late adverse reactions related to COVID-19 vaccines are often mild to moderate, but severe cases and herpes zoster (HZ) can occur and need to be monitored.[2-27] Moderna mRNA-1273 and Pfizer-BioNTech SARS-CoV-2 vaccines use lipid nanoparticle encapsulated mRNA to provide immunity by encoding for the spike protein necessary for viral entry, while the AstraZeneca and the Janssen Johnson and Johnson (J and J) vaccines use an adenovirus as a viral vector to provide the immunity.[13,21] "COVID arm" is a novel entity associated with this infection as well as with vaccines, and manifestations can be mimicked by episode of HZ.[3-10,12,13,17-19] Skin changes have been described 4–11 days after the first dose of mRNA-1273 vaccines and are considered delayed reactions which appeared near the injection site.[4] Some patients had similar reactions after the second dose, with duration of 2–11 days. Classical HZ skin rash and post-herpetic neuralgia (PHN) have also increased along with COVID-19 pandemic and may develop following an adenovirus-vectored vaccination.[3,5,8,18] Both immunocompromised

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and elderly people are more susceptible to HZ as well as to COVID-19, phenomenon that can increase the diagnostic challenges; and in this setting, acyclovir is often utilized within 24–72 h of rash onset and during 7–21 days.[3,5,18] Cutaneous abnormalities may be solid or lesions containing liquid and are often associated with general manifestations including fever, headache, and arthralgia.[4-14,16-19] Patients frequently undergo topical treatment with ice, antihistamines, glucocorticoids, and lidocaine; while paracetamol, nonsteroidal anti-inflammatory drugs, nortriptyline, amitriptyline, gabapentin, pregabalin, and opioids can be utilized to treat HZ or PHN.[4-14,16-19]

The main objective is to describe elderly woman with early and late local and systemic manifestations after the first and the second doses of the AstraZeneca vaccination. The "COVID arm" is here emphasized to enhance the interest in this very challenging entity, in addition to an overview about the HZ reactivation after vaccination against COVID-19.

2. Case Report

A 76-year-old woman, who has controlled hypertension and hypothyroidism, underwent complete administration of the AstraZeneca vaccine against SARS-CoV-2. She had neither history of varicella-zoster virus (VZV) infection nor HZ episode during the life. The first dose was on the left arm (February 26, 2021) and caused immediate pain at the site of injection followed by 48 h of feverishness, headache, and polyarthralgia in hand fingers that were alleviated by the use of paracetamol 3 times daily. Approximately a month later, appeared skin changes (pruritus, rash, edema, erythematous plaques, and crops of vesicles, which gradually involved the upper left extremity. The classical HZ lesions coexisted with intense neuropathic pain, persisting for 30 days, and need use of famciclovir (500 mg daily, for 7 days), topical betamethasone, antihistamine, meloxicam, and paracetamol plus codeine. The lesions evolved to complete resolution and absence of scarring with treatment (Figure 1).

The unique changes on physical examination were the skin lesions. Except for elevated high-sensitivity CRP (reference value [RV]: <1.0) 3.96 mg/L, routine tests were unremarkable.

However, the level of COVID-19 neutralizing antibody (plaque reduction neutralization test) was 95%; while of IgG and IgM against VZV was 3638.0 (RV: <135.0) and 0.43 (RV: <0.90) mIU/mL, respectively. Therefore, the diagnosis conclusion was "COVID arm-like" due to vaccine-related HZ. After the second dose on the right arm (May 20, 2021), there was no reaction. The patient is asymptomatic performing normal activities.

3. Discussion

COVID-19 vaccination involves mRNA, adenoviral vectored, inactivated virus, adjuvanted spike glycoprotein, and neutralizing antibody response after immunization.[16] The patient had Oxford University/AstraZeneca vaccine with chimpanzee adenovirus-vectored platform (ChAdOx1/AZD1222) that encodes the spike glycoprotein of SARS-CoV-2, and induces humoral responses characterized by anti-spike glycoprotein IgG NABs, IFNγ T-cell responses in the majority of cases after the first dose of vaccine.[15,19] ChAdOx1 nCoV-19 seems well-tolerated in older adults, with similar immunogenicity in all age groups after a boost dose, and injection-site pain and tenderness are most common local adverse reactions and more often occur in the first 48 h of vaccination.[16,19] The spike glycoprotein binds to ACE2 receptors on target cells during the viral entry.[16] In most of cases, the reactions to the COVID-19 vaccination resolve within 3–4 days.[11] Frequent reported events are pain, swelling, and redness at the site of injection, in addition to feverish, fatigue,

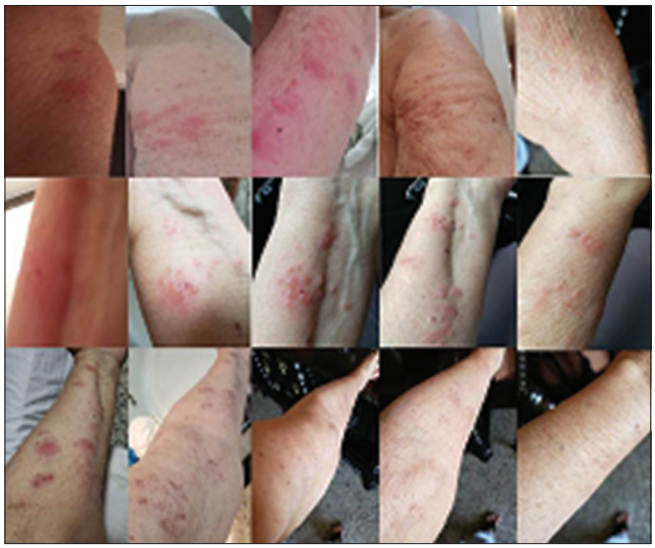

Figure 1: The evolution of herpes zoster lesions mimicking a "COVID arm" manifestation, after the AstraZeneca/Oxford COVID-19 (ChAdOx1 S [recombinant]) first dose vaccination in a 76-year-old woman.

headache, and myalgia.[11,16] Diverse cutaneous changes are described in patients affected by COVID-19, including chicken-pox-like lesions, erythema multiforme, livedo reticularis, maculopapular eruption, morbilliform rash, pityriasis rosea, urticaria, COVID toe, and "COVID arm."[4-14,16-19] "COVID arm" and delayed large hypersensitivity reactions refer to swollen, indurated, erythematous, itchy, or painful rash appearing several days to weeks after SARS-CoV-2 vaccination.[13] Some patients with clinically suspected or diagnosed HZ may present unsuspected or confirmed concomitant COVID-19, without knowledge about any antecedent contact.[8] This phenomenon is related to lowered counts of lymphocytes, monocytes, and eosinophils, and reduced B cells, CD4+ T cells, CD8+ T cells, and natural killer cells in COVID-19.[3,8,18] One should consider immunosenescence, a gradual decline of the immune system related to aging, which explains differences in the functionality and availability of T-cell and B-cell populations and in decreased immune responses, and 50% of HZ affecting people aged 80 years or more.[3,8,15,16,18]

Kaur *et al.* systematically reviewed the evidence on the safety data from the COVID-19 vaccine trials; and in the ChAdOx1 nCoV-19 (AZD1222) vaccine trial, there were 5489 participants in the test vaccine group and 5184 in the control group.[11] Three events were related to the test or control vaccines: Hemolytic anemia after 10 days of the control vaccine; transverse myelitis 14 days after booster dose of the experimental vaccine; and fever higher than 40°C occurring 14 days after vaccination. Worthy of note, there were four non-COVID-19 deaths, three in the control group, and one in the experimental vaccine group, but none of cases was considered related to the vaccines.[11] Mathioudakis *et al.* reported their online survey of epidemiological data, details on COVID-19 exposure, vaccination history, and incidence and severity of side effects.[14] They included the answers from over than 2000 recipients of COVID-19 vaccines and concluded that COVID-19 vaccines are often safe with limited severe adverse effects. Besides, previous COVID-19 illnesses led to a higher number of vaccination side effects, and mRNA vaccines caused milder, less frequent systemic side effects but more local reactions than viral vector-based vaccines; data needing validation by research.[14] Blumenthal *et al.* described 12 cases of late large local adverse reactions to Pfizer/BioNTech's BNT162b2 and Moderna, appearing 4–11 days after the first dose.[4] These lesions appeared after resolution of the initial local and systemic symptoms, and delayed-type or T-cell-mediated hypersensitivity was showed by the skin biopsy study. Three patients had recurrent reactions similar to those of initial dose, and three patients had recurrent reactions of a lower grade than those of the initial dose. The median onset of cutaneous symptoms after the second dose was earlier than observed in the first dose.[4] Zafar *et al.* reported two cases of disseminated itchy rash related to SARS-CoV-2 vaccination and were controlled by oral antihistamines and topical steroid creams.[21] The reactions appeared 11 days after the second dose of Pfizer vaccine in an 84-year-old man, and 2 days after the first dose of AstraZeneca vaccine in a 55-year-old woman. They emphasized that reactions of vaccinations are becoming more often described.[21] Català *et al.* reviewed 405 cutaneous reactions within 21 days after any dose of SARS-CoV-2 vaccination in Spain utilizing BNT162b2 (Pfizer-BioNTech, 40.2%), mRNA-1273 (Moderna, 36.3%), and AZD1222 (AstraZeneca, 23.5%); the mean patient age was 50.7 years and 80.2% were female.[6] Lesions included: "COVID arm" (32.1%); urticaria (14.6%); morbilliform (8.9%); papulovesicular (6.4%); pityriasis rosea-like (4.9%); purpuric (4%); VZV; and herpes simplex virus (HSV) reactivations (13.8%). "COVID arm" predominated in women (95.4%) and had the closest association with systemic symptoms (64.6%). The most common reactions of each vaccine were "COVID arm" (Moderna, 61.9%), VZV reactivation (Pfizer-BioNTech, 17.2%), and urticaria (AstraZeneca, 21.1%). The vast majority of reactions to Moderna vaccine occurred in women (90.5%), 21% of them were classified as severe or very severe and 81% required treatment.[6] The authors commented on the female immune system, which can be more reactive to SARS-CoV-2 proteins, and less susceptible to COVID-19 with higher reactions to vaccines. There were a large number of herpes reactivations (VZV and HSV, 13.8%). For VZV (n = 41, 10.1%), severity (36.6%) and the rate in healthy people <50 years (29.2%) were particularly striking.[6] Corrado *et al.* recently described the case study of erythema migrans-like rash as a very infrequent manifestation of "COVID arm" developing after the Moderna vaccination.[7] Fernandez-Nieto *et al.* reviewed data of 103 skin reactions to BNT162b2 mRNA COVID-19 vaccine in 4775 patients aged 19–72 years, 83.4% of females in Spain.[9] Delayed local reaction affected 103 (2.1%) patients 20–64 years, 88.3% of females, after the first dose (47.6%) or the second dose (52.4%), and

32.7% had recurrence of lesions following the second dose. The lesions had variable duration: <8 h (22.3%), between 8 and 24 h (26.2%), between 48 and 72 h (36.9%), and more than 72 h (13.6%). The authors commented on delayed injection-site reactions with similar features to SARS-CoV-2 infection, including the "COVID arm," and are not clear if they are due to a hypersensitivity reaction to the spike protein or other component of the vaccine.[9] Johnston *et al*. described 16 patients aged 25–89 years, and 81% of females, with the "COVID arm" reaction 2–12 days after the first Moderna vaccination; 68.75% had similar lesions on the second dose, and biopsy data showed a delayed hypersensitivity.[10] The changes near the injection site were pruritic, painful, and edematous pink plaques; different from anaphylaxis and urticaria that are immediate hypersensitivity reactions. "COVID arm" is not a contraindication to subsequent vaccination; although may occur again after the second dose, this manifestation is self-limited and not associated with serious vaccine adverse effects.[10] Kempf *et al*. reported findings of three patients aged 81–89 years, 66.7% of females, who had "COVID arm" 6–7 days after the first dose of the Moderna mRNA vaccine.[12] They commented that this immunological reaction is also a complication of COVID-19. And emphasized that the histomorphological findings of the delayed-type localized cutaneous hypersensitivity reaction to SARS-CoV-2 mRNA vaccines would be consistent with a pattern of immune reaction.[12] Lindgren *et al*. described three females aged 33–60 years with "COVID arm" after utilization of Moderna and Pfizer vaccines, and two cases were mistaken for cellulitis.[13] Nevertheless, the major differential clues were present including pruritus, occurrence approximately a week after the vaccinations, lack of progressive symptoms, rapid response to topical steroids, and/or spontaneous resolution occurring over 4–5 days.[13] Vaccines contain lipids that cause delayed hypersensitivity; in the polyethylene glycol (PEG2000) form in the Moderna and Pfizer, and Polysorbate 80 in the Janssen J and J. Authors suggest the second dose injection in the other arm aiming to reduce reactions.[13] Ramos *et al*. described 12 patients (91.7% women) aged 27–73 years with local reactions 5–11 days after the mRNA COVID-19 vaccine, which persisted for 3–8 days.[17] There was pain with or without redness and swelling in the first 2 days after vaccination that resolved before the onset of the very delayed injection site reactions.[17] The reactions followed the Moderna first dose (11) and the Pfizer second dose (1). As those who had reactions to the first dose received their second dose without recurrence, humoral or cellular immune response to the first dose could moderate further reaction.[17] Wei *et al*. reported four 54- to 74-year-old females with "COVID arm" after 7–10 days of the Moderna first dose, with gradual improvement from 2 to 7 days.[20] The cutaneous changes (edema, rash, macules, papules, and plaques), with a warm sensation and pruritus, measured up to 15 cm in diameter. Two treatments were topical (clobetasol propionate and mometasone furoate) and oral (diphenhydramine hydrochloride, cetirizine, and loratadine), while the other two needed no intervention.[20] The authors commented on the possible role of polyethylene glycol or other proprietary non-active ingredients of Pfizer and Moderna vaccines in the genesis of skin lesions.[20]

The herein reported patient had intense early systemic symptoms after the first dose of vaccine followed by accentuated manifestations of HZ evolving from the local of injection. She had neither antecedent of clinical diagnosis of varicella nor any previous episode of HZ. This first flare up of HZ can be related with systemic phenomena triggered by vaccination; moreover, in the convalescent phase of her HZ, the evaluation of inflammatory parameters revealed NLR: 2.57, DNLR: 0.90, PLR: 101.05, LMR: 4.33, and an elevated SII: 690.61.[1,22-27]

Arora *et al*. reported a patient presenting characteristic HZ lesions distributed on the right knee and anterior thigh after receiving the first dose of the inactivated vaccine COVAXIN.[22] Besides typical skin changes, the histopathological findings were consistent with HZ diagnosis. The patient was successfully treated with valacyclovir and topical fusidic acid, and there was no neuralgia. He underwent the second dose of the same vaccine without any adverse effect.[22] The authors commented that vaccine-induced T-cell dysregulation can reactivate the VZV.[22] Furer *et al*. comparatively evaluated the safety of BNT162b2 mRNA vaccination in 491 patients with some autoimmune inflammatory rheumatic disease (AIIRD) and 99 controls.[23] Six patients with AIIRD and none of controls developed the first episode of HZ in their lives shortly after the first dose in five cases and the second dose in one case. The majority of cases were mild and there was no manifestation of PHN. Five patients underwent antiviral treatment with improvement and received the second dose of vaccination without no adverse effect.[23] The authors emphasized the diagnosis

of HZ exclusively with base on clinical data, lacking histopathologic or molecular confirmation; and the possible under reporting of HZ episodes. Hence, further vigilance and safety monitoring of COVID-19 vaccination side effects is needed.[23] Katsikas Triantafyllidis *et al.* reviewed 12 reports of 91 patients with HZ after COVID-19 vaccination, and the antecedent VZV infection or vaccination against VZV occurred in 15%.[24] The majority of patients (58.2%) presented HZ symptoms after the first dose of vaccination. The main sites of HZ were the breast (9.9%), the back (8.8%), and T4 dermatome (13.2%); 25.3% used valacyclovir monotherapy while 13.2% also utilized fusidic acid or acyclovir.[24] The authors highlighted the increased awareness of clinicians to the early recognition of HZ for better management of cases and prophylaxis with valacyclovir for high-risk individuals.[24] Psichogiou *et al.* described seven patients with HZ after the first or second dose of Pfizer-BNT162b2 vaccine; all them reported varicella in infancy but none had antecedent of HZ.[25] The authors stressed the current low awareness to correlate HZ and COVID-19 vaccination; besides, they commented a transient prophylaxis by valacyclovir before vaccination for those patients at higher risk for reactivation of VZV following vaccination for SARS-CoV-2.[25] Tessas and Kluger described ipsilateral HZ after the first dose of BNT162b2 mRNA vaccine and was successfully controlled by valacyclovir, although with post-zoster neuropathic pain.[26] The patient presented mild varicella during the childhood, but none previous episode of HZ. As other cases of HZ after vaccines against COVID-19, the second dose had no side effect.[26] van Dam *et al.* reported two adults developing HZ after the Pfizer-BioNTech COVID-19 mRNA vaccine, and transient lymphocytopenia due to vaccination would be the main factor.[27] One patient had chickenpox 4 times in childhood and adolescence but never had HZ; without treatment, the lesions improved in 2 weeks, and there was no HZ relapse in the second dose. The other patient had chickenpox once in childhood, and never had HZ. Two weeks after the first dose of vaccine, he had HZ in right leg, and PCR test on vesical fluid confirmed the VZV. He underwent valacyclovir for 10 days and improved; the second dose was unremarkable.[27] The authors called attention about older or immunocompromised patients who should have further evaluations about adverse possible relationships between the COVID-19 and HZ.[27]

4. Conclusion

"COVID arm" is a rare adverse effect of the first or second doses of the vaccines and can be mistaken by the clinical manifestations of HZ, including neuralgia, as occurred in this case. These immediate or delayed reactions do not contraindicate a second dose of vaccines. Besides, even in the absence of suggestive symptoms of COVID-19, the presence of typical HZ lesions should be considered as a possible clue for a subclinical SARS-CoV-2 infection.

5. Informed Consent

Informed consent has been obtained from the patient for publishing.

6. Conflicts of Interest

No conflicts of interest are declared.

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