Reumatismo, 2022; 74 (2): 88-92

Disseminated cutaneous herpes simplex infection after COVID-19 vaccination in a rheumatoid arthritis patient: a case report and review

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SUMMARY

Since COVID-19 vaccination started in December 2020, different side effects were reported. This case report describes the possibility of developing disseminated herpes simplex infection after COVID-19 vaccine in a patient with rheumatoid arthritis. In this case report, we describe a 63-year-old Iranian female. She was a known case of seronegative rheumatoid arthritis and presented with generalized papulo-pustular itchy and painful skin lesions which appeared about seven days after the second dose of Sinopharm BIBP COVID-19 vaccine (BIBP-CorV). A biopsy of the skin lesions revealed acantholysis, neutrophils, and enlarged keratinocytes with eosinophilic intra-nuclear inclusions. Findings were consistent with herpes simplex infection. She was successfully treated by acyclovir. Disseminated cutaneous herpes simplex infection may have been triggered by COVID-19 vaccination. Reactivation of herpes virus after COVID-19 vaccines was reported in both rheumatic patients and other individuals. Whether having an underlying autoimmune inflammatory disorder could be an additional risk factor is still unknown.

Key words: *COVID-19 vaccination, herpes simplex, rheumatologic disorder, autoimmune disorder.*

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), originated in Wuhan, (China) and has become an ongoing pandemic. Vaccination against COVID-19 has started in December 2020. The most common side effects of vaccination are pain at the injection site, fever, nausea, myalgia, and malaise (1). Reactivation of the herpes zoster virus (HZV) after COVID-19 vaccination has already been reported by previous articles. BNT162b2 mRNA and mRNA-1273 vaccines were linked to the reactivation of HZV (2-7). As far as we know, no previous article has reported disseminated herpes simplex infection after COVID-19 vaccination. Here we report a case of a 63-year-old woman who was a known case of seronegative rheumatoid arthritis, who developed disseminated cutaneous herpes simplex infection after Sinopharm BIBP COVID-19 vaccine.

The objective of this case report is to demonstrate the possible relation between the COVID-19 vaccine and increased risk of reactivation of the herpes virus in rheumatic patients.

CASE REPORT

The patient, a 63-year-old woman, was affected by seronegative rheumatoid arthritis. She presented to the emergency department of our hospital with generalized papulo-pustular skin rashes on November 27, 2021, in Kermanshah City, Iran. She claimed that her symptoms started about seven days after injection of the second dose of the COVID-19 vaccine. She had received a previous injection of Sinopharm BIBP COVID-19 vaccine (BIBP-CorV) two months earlier. She developed fever and oral ulcers after vaccination, which re-

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solved in two days. About five days later she developed itchy and painful erythematous papules and plaques that started from the buttocks and lower limbs and progressed into a generalized ulcerative rash within a few days. She was treated with anti-histamine and topical corticosteroids in an outpatient setting and no improvement was seen. Her past medical history included seronegative rheumatoid arthritis since 15 years. Arthritis symmetrically involved the small joints of the hands, elbows, knees, and ankles; it was non-erosive in previous radiographies. She had no extra-articular involvement, nor other comorbidities. The patient was treated with conventional disease-modifying anti-rheumatic drugs (cDMARDs) and oral prednisolone. Any attempt to reduce the medication dose resulted in a disease flare-up. There was the indication of a biologic DMARDs, but, due to financial problems, she refused this treatment. At admission, her drug history included prednisolone 7.5 mg daily, methotrexate 15 mg weekly, hydroxychloroquine 200 mg daily, leflunomide 10 mg every other day, alendronate sodium 70 mg weekly, and calcium-vitamin D supplement daily. She denied any flare-ups of the disese in the previous two years.

On general examination, her vital signs were stable and she was not febrile. Generalized erythematous papules, plaques, vesicles, and pustules were observed over the skin of the buttocks, trunk, and lower and upper extremities. She had an erythematous rash on her face, nose, and cheeks which included pustular and necrotic areas (Figure 1). The rest of the general examination including cardiovascular, abdominal, and musculoskeletal systems were within normal limits.

The laboratory tests results on the day of admission were as follows: hemoglobin of 11.2 mg/dL, mean corpuscular volume 97, white blood cell count $9.3x10^3/mm^3$ (differential count: neutrophils 95%, lymphocytes 5%), platelet count $263x10^3/mm^3$, and creatinine 1.5 mg/dL. The remaining investigations were within normal limits, including erythrocyte sedimentation rate and C-reactive protein. Gram smear, Tzanck smear, and skin histology were performed on the skin lesions and she was started on an empirical antimicrobial therapy with intravenous vancomycin, ceftazidime, and acyclovir. Systemic lupus erythematosus or overlap syndrome was suspected due to the skin lesions, but antinuclear antibodies, anti-ds DNA antibodies, ANCA, Anti Ro, Anti La, angiotensin-converting enzyme, C3, C4, and CH50 were all negative.

The skin biopsy revealed intra-epidermal blisters containing acantholysis, inflammatory cells mainly neutrophils, and enlarged keratinocytes with eosinophilic intra-nuclear inclusions surrounded by a clear halo (Cowdry type A). Multinucleated keratinocytes with nuclear molding, focal epidermal necrosis, and neutrophilic vasculopathy were also seen. Findings were compatible with herpes simplex virus (HSV) infection (Figure 2). Therefore, antibiotics were discontinued and 400 mg

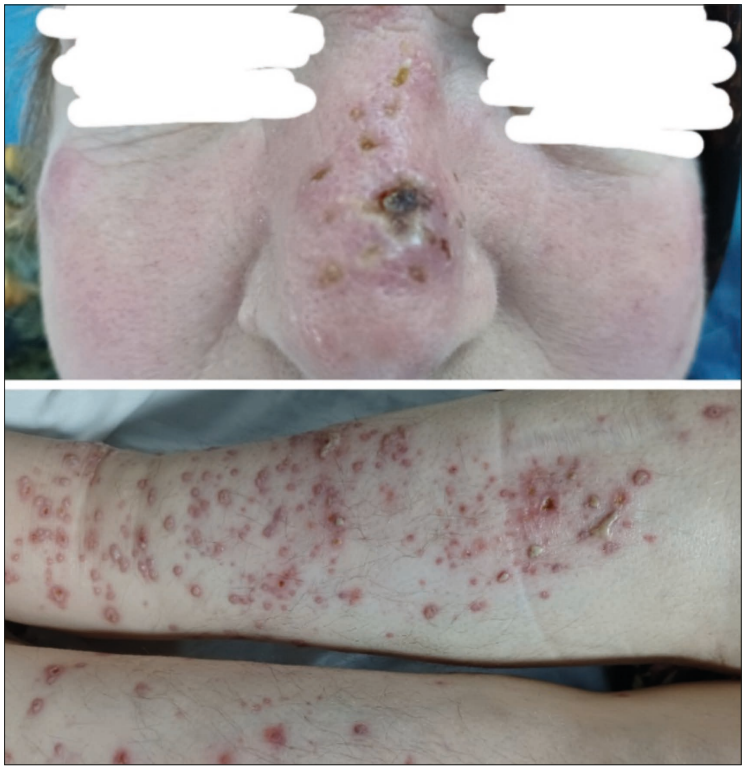

Figure 1 - Pictures of the patient's skin lesions by her permission. Top and bottom: erythematosus skin rash on the nose bridge and cheeks with ulcers, pustules and a necrotic area, papulo-pustular skin lesions on the lower limbs on the day of admission.

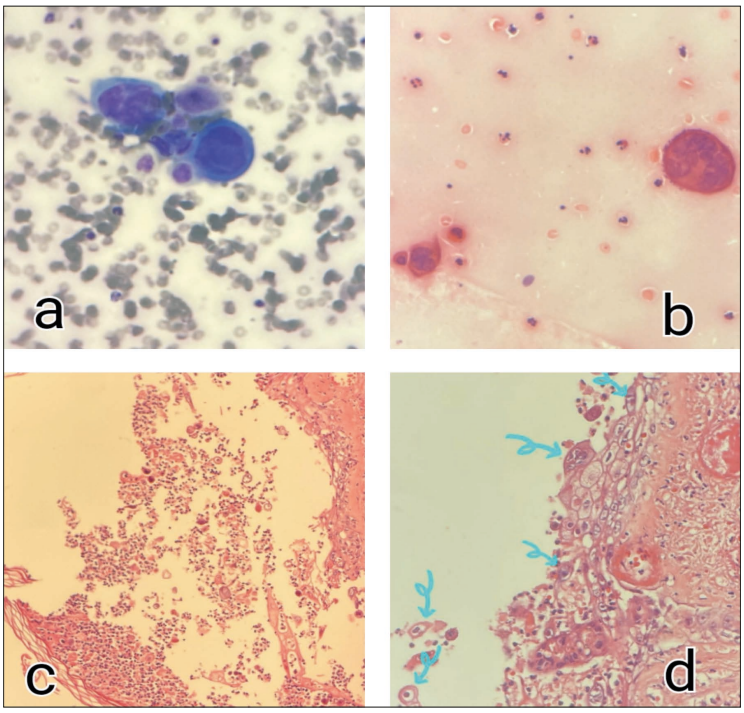

Figure 2 - Scanty cellular smear containing enlarged multinucleated cells with nuclear molding and inflammatory cells, mainly neutrophils, compatible with HSV infection (a: Giemsa staining & b: hematoxylin and eosin staining); c & d: Hematoxylin and eosin staining of skin biopsy showing intra-epidermal blisters containing acantholysis, inflammatory cells mainly neutrophils, and enlarged keratinocytes with eosinophilic intra-nuclear inclusions surrounded by a clear halo (Cowdry type A: blue arrows).

acyclovir was administered intravenously every eight hours for five days and changed to oral acyclovir with the same dosage for three weeks. Complete improvement of the lesions was observed after six weeks.

DISCUSSION AND CONCLUSIONS

Different herpes viruses including herpes simplex type 1 and 2 and herpes zoster (HZ) can infect humans. Aging and immunosuppression are well-recognized risk factors for the reactivation of herpes infections (2-7). We believe this article to be the first report of disseminated cutaneous herpes simplex infection following COVID-19 vaccination. The state of relative immunosuppression of the patient might have facilitated the disseminated form of HSV. Previous articles also reported reactivation of HZ and herpes simplex infection after COVID-19 vaccination (2-8). In most cases, the mRNA vaccines (BNT162b2 mRNA and mRNA-1273) were associated with HZ reactivation. Shah et al. described a case of HZ after the inactivated COVID-19 vaccine (Sinopharm), which was similar to our case. Also, reactivation of HZ was observed in individuals who received other inactivated vaccines such as hepatitis A, influenza, rabies, and Japanese encephalitis (5).

In addition, VZ infection could occur following COVID-19 infection. The explained mechanism is COVID-19 induced lymphopenia and alteration in T-cell function. The same mechanism could be explained for VZ reactivation after COVID-19 vaccines. Furer et al. (8) reported six cases and Maranini et al. (9) reported one case of HZ infection after COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD). Table I includes information on eight AIIRD patients who developed herpes infection after COVID-19 vaccination (the first seven patients are previously-reported cases, while the last one is the present case that developed disseminated herpes simplex infection). We compared the characteristics of these seven cases with our case. All the eight patients were women with a mean age of 49.8 years. Four patients had seropositive rheumatoid arthritis, one had seronegative arthritis, one had HLA-B27- related ankylosing spondylitis, one had undifferentiated connective tissue disorder (UCTD), and one had Sjögren's syndrome. Two patients were on JAK (Janus kinase) inhibitors, one on IL-6 (interleukin 6) inhibitor, one on the TNF-inhibitor adalimumab, and the rest of the patients were on conventional DMARDs. All the patients, except our case, received BNT162b2 mRNA, while our patient received Sinopharm BIBP (inactivated vaccine). The mean interval between vaccine injection and initiation of herpes infection was 7.6 days (minimum two days and maximum 14 days). Our patient was the only one who developed disseminated cutaneous skin lesions, while the other cases had skin involvement limited to

Table I - Reported cases of herpes virus reactivation after COVID-19 vaccination in rheumatic patients.

Cases	Age/ Sex	Type of AIIRD	Medication	Type of vaccine	Interval (days)	Location of skin lesions	Treatment	Time of resolution
1	44/F	Sjögren's syndrome	HCQ	BNT162b2 mRNA	3	L5	Nothing	3 weeks
2	56/F	Seropositive RA	Tofacitinib	BNT162b2 mRNA	4	V cranial nerve	Acyclovir	6 weeks
3	59/F	Seropositive RA	Upadacitinib, prednisolone 5 mg/daily	BNT162b2 mRNA	2	L1-L2	Valacyclovir	6 weeks
4	36/F	Seropositive RA	Mycophenolate mofetil, rituximab, prednisolone 7 mg/daily	BNT162b2 mRNA	10	T10	Acyclovir	6 weeks
5	38/F	Undifferentiated UCTD & APS	HCQ, aspirin	BNT162b2 mRNA	14	T4	Acyclovir	3 weeks
6	61/F	RA	Tocilizumab, prednisolone 5 mg/daily	BNT162b2 mRNA	14	T6	Valacyclovir	10 days
7 Maranini et al. (9)	41/F	Ankylosing spondylitis	Adalimumab	BNT162b2 mRNA	7	Right arm	Acyclovir	
8 (our case)	63/F	Seronegative RA	Prednisolone 7.5 mg daily, methotrexate, HCQ, leflunomide	Sinopharm BIBP	7	Disseminated cutaneous	Acyclovir	6 weeks

F, female; M, male; AIIRD, autoimmune inflammatory rheumatic diseases; HCQ, hydroxychloroquine; RA, rheumatoid arthritis; CTD, connective tissue disorder; APS, anti-phospholipid disorder; L, lumbar; T, thoracic.

a specific dermatome. All the patients except a 44-year-old woman with Sjögren's syndrome received anti-viral medication. The mean resolution time was 22 days (range 10 days-6 weeks).

Reactivation of HZ infections could occur after COVID-19 vaccination in AIIRD patients with both mRNA vaccines and inactivated vaccines, and reported the development of disseminated HS infection after COVID-19 vaccination in a rheumatic patient. Clinicians need to be aware of this possible consequence after the COVID-19 vaccination.

Informed consent

Informed written consent was obtained from the patient to publish her clinical data and images.

Conflict of interests

The authors declare that they have no conflicts of interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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