Erythema multiforme in COVID-19 patients and following COVID-19 vaccination: manifestations, associations and outcomes

Dear Editor:

Erythema multiforme (EM) is a delayed-type hypersensitivity reaction linked to infectious agents in 90% of cases and medications or vaccination in less than 10% of cases. A 19-year-old male presented with a 48-h history of an itchy rash. Examination revealed erythematous papules and plaques with central dusky erythema and crusting on the bilateral upper extremities. There was no involvement of the palms, soles or oral mucosa. He had no fever, cough or medications. Prednisone 20 mg and cetirizine 10 mg daily were started. After 3 days, he developed fever, shortness of breath and dry cough; and a SARS-CoV-2 test was positive. He was started on remdesivir and dexamethasone. After 5 days, the rash started to improve, and after 2 weeks, it completely resolved.

EM in patients with COVID-19 has been reported in 23 publications (Fig. 1), including 36 cases with 19 males (53%). Four articles reported EM after COVID-19 vaccination (Fig. 1). The details of these manuscripts are summarized in Table 1. Among patients with EM and COVID-19, 16.7% (6/36) patients were less than 18-year-old, 19.4% (7/36) patients were 18–40 years old and 63.9% (23/36) patients were more than 40 years old. Eleven patients (30.6%) took no medications before EM; however, 25 patients (69.4%) reported exposure to medications before. Drugs to which patients were exposed before EM were HCQ in 20 cases (55.5%), azithromycin in 14 cases (38.9%) with 13 of them receiving HCQ in addition to azithromycin and lopinavir/ritonavir in 12 patients (33.3%), all in combination with HCQ. EM occurred before any classic COVID-19 symptoms in 23/36 (63.9%) patients, only in 5/36 patients (13.9%), four of them under 23 years. Three patients (8.3%) presented with EM and COVID-19 symptoms simultaneously. However, in most of the patients (78%), EM started after COVID-19 symptoms. Four patients (11.1%) had only mucosal involvement, five patients (13.9%) had mucosal and skin involvement, but most of the patients (27 patients,

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75%) had only skin lesions. Thirty-five of 36 patients survived, and only a 72-year-old woman died. Interestingly, her skin lesions were the first manifestation of infection. Therefore, we believe EM is not associated with worse outcomes. EM following vaccination is rare, with eight reported cases: three after Moderna (37.5%), four after Pfizer (50%) and one after CoronaVac (12.5%) (Table 1). In another study, three of 414 cases of dermatological presentations were EM after the first dose of the Moderna vaccine. This rarity makes it hard to establish a causal link. Infection with SARS-CoV-2 may have a role in the pathogenesis of EM. The underlying mechanism is not clear. EM may result from the interaction with the virus itself, antiviral immune response and medications. EM can rarely be the presenting sign of COVID-19, and EM is not associated with worse outcomes. Further studies are needed to elucidate the exact relationship between infection, medications and erythema multiforme in the setting of COVID-19.

Conflict of Interest
Not declared.

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Data Availability Statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### Table 1: Reported cases of EM in patients with COVID-19 and related to vaccination

| Sample size for case reports or case series | Age (years) and sex | Medication type for COVID-19 | Latency of EM after positive COVID-test (days) | Involved areas | Infectious work-up result other than positive COVID-19 test | Treatment for EM | Reference |
|-------------------------------------------|---------------------|------------------------------|-----------------------------------------------|----------------|-------------------------------------------------------------|-----------------|----------|
| 1 of 4                                    | 63Y F               | Lopinavir/ritonavir, HCQ, azithromycin, ceftriaxone, corticosteroids | 16 days after COVID-19 symptoms | In all patients, skin lesions begun as erythematous papules in upper trunk. | Not performed | Systemic corticosteroids | [5]      |
| 2 of 4                                    | 77Y F               | Lopinavir/ritonavir, HCQ, azithromycin, corticosteroids | 16 days after COVID-19 symptoms | Negative for HIV, EBV, CMV, VZV, HSV, M. pneumoniae, syphilis | Systemic corticosteroids |                |          |
| 3 of 4                                    | 58Y F               | Lopinavir/ritonavir, HCQ, azithromycin, ceftriaxone, corticosteroids | 24 days after COVID-19 symptoms | Not performed | Systemic corticosteroids |                |          |
| 4 of 4                                    | 58Y F               | Lopinavir/ritonavir, HCQ, azithromycin | 19 days after COVID-19 symptoms | Negative EVB for HIV, EBV, CMV, VZV, HSV, M. pneumoniae, syphilis. HSV PCR found in vesicle swab | Systemic corticosteroids |                |          |
| 1                                         | 11Y F               | None                         | Presented with EM | Elbows, knees, thighs, arms, forearms, legs, ankles, dorsal feet, dorsal hands | MD | None | [6]      |
| 1 of 2                                    | 17Y M               | Vitamin C                     | 15 days after COVID-19 symptoms | Palms | A negative syphilitic serology | None | [7]      |
| 2 of 2                                    | 29Y M               | HCQ and azithromycin          | 12 days after COVID-19 symptoms | Palms | A negative syphilitic serology | None |          |
| 1                                         | 95Y F               | HCQ                          | COVID-19 infection and EM developed simultaneously | Trunk and extremities | Serological study on parvovirus B19 infection showed negative IgM and positive IgG. | Topical corticosteroids | [8]      |
| 1                                         | 22Y F               | Metronidazole, ceftriaxone, meropenem, ribavirin and HCQ | COVID-19 infection and EM developed simultaneously | Oral and face | None | Oral valaciclovir | [9]      |
| 1                                         | 25Y F               | None                         | EM appeared on the day 2 of the disease course | Both palms | None | None | [10]     |
| 1                                         | 37Y F               | HCQ, azithromycin and oseltamivir | 10 days after COVID-19 symptoms | Ventral/dorsal sides of hands, elbows, lips and oral mucosa | HSV, EBV, CMV, HbsAg, Anti HCV and Mycoplasma antibodies were within normal limits. | Oral methylprednisolone | [11]     |
| 1 of 2                                    | 82Y M               | HCQ, ceftriaxone and ertapenem | 30 days after COVID-19 symptoms | Generalized involvement of trunk and limbs | None | Prednisone | [12]     |
| 2 of 2                                    | 48Y M               | HCQ, ritonavir, lopinavir, ceftriaxone and azithromycin | 3 weeks after COVID-19 symptoms | Generalized involvement of trunk and limbs | None | Prednisone |          |
| Sample size for case reports or case series | Age (years) | Sex | Medication type for COVID-19 | Latency of EM after positive COVID-test (days) | Involved areas | Infectious work-up result other than positive COVID-19 test | Treatment for EM | Reference |
|-----------------------------------------|------------|-----|-----------------------------|-----------------------------------------------|----------------|---------------------------------------------------------------|-----------------|----------|
| 1                                       | 23 Y M     | M   | None                        | Presented with multiple painful mouth ulcers with no respiratory symptoms | Mouth, arms/legs, penis | Both CMV IgM and anti-EBV IgM were negative. | Intravenous fluids and analgesia | [13]     |
| 1                                       | 55 Y F     | F   | HCQ                         | 12 days after COVID-19 treatment              | trunk and upper limbs, without mucosal involvement | HSV and Mycoplasma pneumoniae were negative. | Treatment with HCQ was discontinued. | [14]     |
| 1                                       | 6 Y M      | M   | None                        | Presented with cheilitis, conjunctivitis and skin lesions. Respiratory function was normal. | Cheilitis, extremities, conjunctivitis. | Mycoplasma pneumoniae and HSV were negative. | None | [15]     |
| 1                                       | 72 Y F     | F   | Paracetamol                 | EM as the first manifestation of the infection, 10 days before the onset of any respiratory symptoms. | Trunk and upper and lower limbs | None | Methylprednisolone i.v. | [16]     |
| 1                                       | 46 Y M     | M   | Azithromycin and HCQ and specific IgE was positive for amoxicillin and ampicillin | 48 h after finishing the course of HCQ, the patient developed EM | Face and palms, then generalized | IgM for CMV, HSV 1/2 and mycoplasma were all negative. | Prednisone and oral antihistamines | [17]     |
| 1                                       | 57-day-old F | F | None                        | Presented with EM and fever, cough and breathlessness. | Face and limbs | Blood culture was sterile. | Intraavenous methyl prednisolone and intravenous immunoglobulin G along with antibiotics. | [18]     |
| 1 of 3                                   | 63 Y F     | F   | Lopinavir/ritonavir, HCQ, azithromycin | 19 days after COVID-19 symptoms. | Mucoosal involvement on Palate | None | None | [19]     |
| 2 of 3                                   | 58 Y F     | F   | Lopinavir/ritonavir, HCQ, azithromycin, tocilizumab, corticosteroids | 24 days after COVID-19 symptoms. | None | None | None | |
| 3 of 3                                   | 69 Y M     | M   | Lopinavir/ritonavir, HCQ, azithromycin | 19 days after COVID-19 symptoms. | None | None | None | |
| 1                                       | 57 Y M     | M   | None                        | 5 days after COVID-19 symptoms. | Mouth, glans penis and conjunctiva | HIV antibodies were negative, CMV and EBV serologies only found IgG, and mycoplasma pneumoniae was negative. | None | [20]     |
| 1                                       | 13 Y M     | M   | Paracetamol                 | 7 days after COVID-19 symptoms. | Left shoulder and conjunctiva | A full sepsis work-up Was negative. Mycoplasma pneumoniae, EBV, HSV 1 and 2, adenovirus and parvovirus B19 were negative. | None | [21]     |
### Table 1 Continued

| Sample size for case reports or case series | Age (years) and sex | Medication type for COVID-19 | Latency of EM after positive COVID-test (days) | Involved areas | Infectious work-up result other than positive COVID-19 test | Treatment for EM | Reference |
|------------------------------------------|---------------------|------------------------------|-----------------------------------------------|----------------|-------------------------------------------------------------|----------------|-----------|
| 1                                        | 83Y F               | HCQ and azithromycin         | While receiving HCQ and azithromycin, an extensive skin rash developed. | Entire trunk with a transition to the shoulders and buttocks | None | Parenteral glucocorticosteroids | [22] |
| 1                                        | 20 Y F              | None                         | The rash started 4 days after cervical, axillary and inguinal lymphadenopathy. | Thighs | None | She did not receive any treatment. | [23] |
| 1                                        | 1 Y M               | Azithromycin                 | On the second day of illness, the febrile child developed skin rashes. | Soles, trunk and face | None | Ceftriaxone, HCQ, otezirine, intravenous immunoglobulin, zinc gluconate, albumin and vitamin D, and meropenem were administered during the treatment course. | [24] |
| 1 of 4                                   | 64 Y F              | HCQ, Lopinavir/Ritonavir, IFN-β, ceftriaxone | Time from hospital admission to EM onset was 14 days. | Generalized targetoid lesions, and facial oedema | None | Methylprednisolone | [25] |
| 2 of 4                                   | 79 Y M              | HCQ, Lopinavir/Ritonavir, IFN-β, ceftriaxone | Time from hospital admission to EM onset was 28 days. | Generalized targetoid lesions | None | Prednisone, oral | |
| 3 of 4                                   | 74 Y F              | HCQ, Lopinavir/Ritonavir, IFN-β, ceftriaxone | Time from hospital admission to EM onset was 23 days. | Generalized targetoid lesions, and facial oedema | None | Methylprednisolone | |
| 4                                        | Age: 60 (40–78)     | All of 4 patients had new drugs interference | Time from hospital admission to EM onset was 24 days. | Generalized targetoid lesions | None | Methylprednisolone | |
| 1                                        | 19 Y M              | None                         | >10 days after COVID-19 symptoms. | Targetoid lesions | None | None | [4] |
| 1                                        | 19Y M               | None                         | Presented with rash 5 days before COVID-19 symptoms. | Upper extremities | None | Prednisone, oral and otezirine, oral | [26] |

### EM related to the COVID-19 vaccine

| Sample size | Age (years) and sex | Type of vaccine | Latency of EM after COVID-vaccine (days) | Involved areas | Infectious Result or Recent Medication Use | Work-up for EM | Treatment for EM |
|-------------|---------------------|-----------------|----------------------------------------|----------------|--------------------------------------------|----------------|-----------------|
| 1           | 75 Y M              | CoronaVac, developed by Sinovac Life Sciences (Beijing, China) | 5 days after the second dose | Knees, face and trunk | He denied systemic symptoms, intake of new medications, and had no signs suggesting any infections. | None | Topical corticosteroids and oral antihistamines | [27] |
Table 1  Continued

|MEDICATIONAL HISTORY | TREATMENT FOR EM | WORK-UP OR MEDICATION USE | INVOLVED AREAS | INFECTIOUS WORK-UP | SAMPLE SIZE | AGE (YEARS) AND SEX | TYPE OF VACCINE | LATENCY OF EM AFTER COVID-vaccine (days) | RESULT OR RECENT MEDICATION USE |
|----------------------|-----------------|---------------------------|----------------|-------------------|--------------|--------------------|-----------------|-----------------------------------|-------------------------------|
| 1 58Y F              | BNT162b2 (Pfizer/BioNTech) | MD | Palms and soles bilaterally | Within 12 h of receiving the first BNT162b2 vaccine. A similar eruption occurred 24 h after receiving the second BNT162b2 vaccine. | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD | MD |

CMV, Cytomegalovirus; COVID-19, Coronavirus Disease 2019; EBV, Epstein-Barr virus; EM, Erythema multiforme; HCQ, Hydroxychloroquine; HSV, Herpes simplex virus; MD, Missing data.

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but to our knowledge, there have been no reports of inflammatory changes occurring on surgical scars or wounds. Very recently, inflammation occurring in Bacille Calmette-Guérin (BCG) scars following mRNA vaccination were observed, both on old scars as well as new ones, as part of a randomized trial evaluating whether BCG protects against Coronavirus disease 2019 (COVID-19).\(^{1,2}\)

We currently report the occurrence of inflammatory painful reactions, limited to the area of previous surgical procedures, in four otherwise healthy Caucasian patients (Table 1), 24–48 h after the first dose of the novel mRNA anti-SARS-CoV-2 Pfizer-BioNTech vaccine (BNT162b2). Two men and a woman had very recent scars, the excision having been performed 2–6 weeks before vaccination, while the other woman had surgery 6 months before vaccine injection. The intensity of the reaction varied from local erythematous swelling to bullous formation and purulent discharge, which were very painful even in the milder reactions (Fig. 1).

All patients had surgery to remove basal cell carcinomas, radically excised. Consulting the medical charts, the procedure required an internal absorbable vicryl suture in three patients, while in one patient, the reaction occurred before removal of the external suture (prolene). The site of vaccine injection was not affected with inflammatory changes, nor did the patients experience other general or bothersome symptoms. The inflammatory reaction on scars was treated with local mixed antibiotic-corticosteroid cream, resolving within 10–14 days, and left no sequelae. No further reactions occurred following the second dose of the vaccine. The cases were reported to the Italian Pharmacovigilance Authority.

Variable cutaneous reaction patterns have been associated with COVID-19 vaccination, including delayed type IV hypersensitivity reactions to dermal filler injections, inflammatory changes on previous radiation sites and old BCG scars re-activation.\(^{1,4}\) In our patients, the wound healing or remodelling phase of the surgical scars or the presence of residual suture materials might have stimulated some immunological mechanisms, similar to forms of hypersensitivity reactions. However, due to the self-healing, benign course of the reaction, no other invasive investigations were performed in our patients to clarify the pathogenesis. The observation is reported to the medical community to raise attention and collect further experiences or studies.

In conclusion, dermatologists are actively committed to supporting the Vaccine Adverse Event Reporting System (VAERS) and enhancing continuous safety monitoring.\(^{5}\) The risk of

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**Table 1** Patient data and medical history

| Patient sex and age | Surgical scar origin                      | Clinical manifestations                                                                 | Treatment                        | Course                        |
|---------------------|-------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------|-------------------------------|
| Man, 75 years       | Basal cell carcinoma excision on the nose 4 weeks before vaccination | 24 h after the injection, deep pain and progressive induration of the scars, erythema and crusting formations. | Mixed antibiotic-steroidal cream twice daily | Complete healing in 4 weeks   |
| Man, 65 years       | Basal cell carcinoma excision on the scalp 2 weeks before vaccination | 48 h after vaccine injection, severe pain and swelling of the wound, while suture was still in place. Removal of stitches was postponed for another week. | Mixed antibiotic-steroidal cream twice daily | Complete healing in 2 weeks   |
| Woman, 52 years     | Basal cell carcinoma excision on the upper abdomen 6 weeks before vaccination | 24 h after vaccination, erythema, swelling, followed by bullous formation. | Mixed antibiotic-steroidal cream twice daily | Complete healing in 4 weeks   |
| Woman, 40 years     | Basal cell carcinoma excision on her right shoulder 6 months before vaccination | 24 h after vaccination, sudden painful induration, swelling, followed by purulent discharge on a consolidated scar | Mixed antibiotic-steroidal cream twice daily | Complete healing in 6 weeks   |