inpatients for 17 months the prevalence of 0.56% is thought to accurately reflect the clinical situation.

We also reveal that maculopapular lesions are common (75.0%) in Japan. The most common COVID-19-related skin rash was reported to be pseudo-chilblain lesions (40.9%) and 97% of these cases were from Europe or the USA.[4] The differences in cutaneous patterns may owe to a genetic/racial predisposition. The minor allele frequency of the *IFIH1* gene which is common in Caucasians increases the production of type-1 interferons that can induce microangiopathy.[5] The patient age and the observation period might also explain the low frequency of pseudo-chilblains. The median age of pseudo-chilblains is reported to be 16.6–27.2 years and approximately 80% of cases were noticed at more than 2 weeks after onset whereas the figures for our study are median age of pseudo-chilblains of 68 years and mean duration of hospitalization of 14.0 days.[4,6,7]

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Conflicts of interest

None declared.

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None.

Data availability statement

The data that support the findings of this study are available upon request from the corresponding author, Y.F.

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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 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,

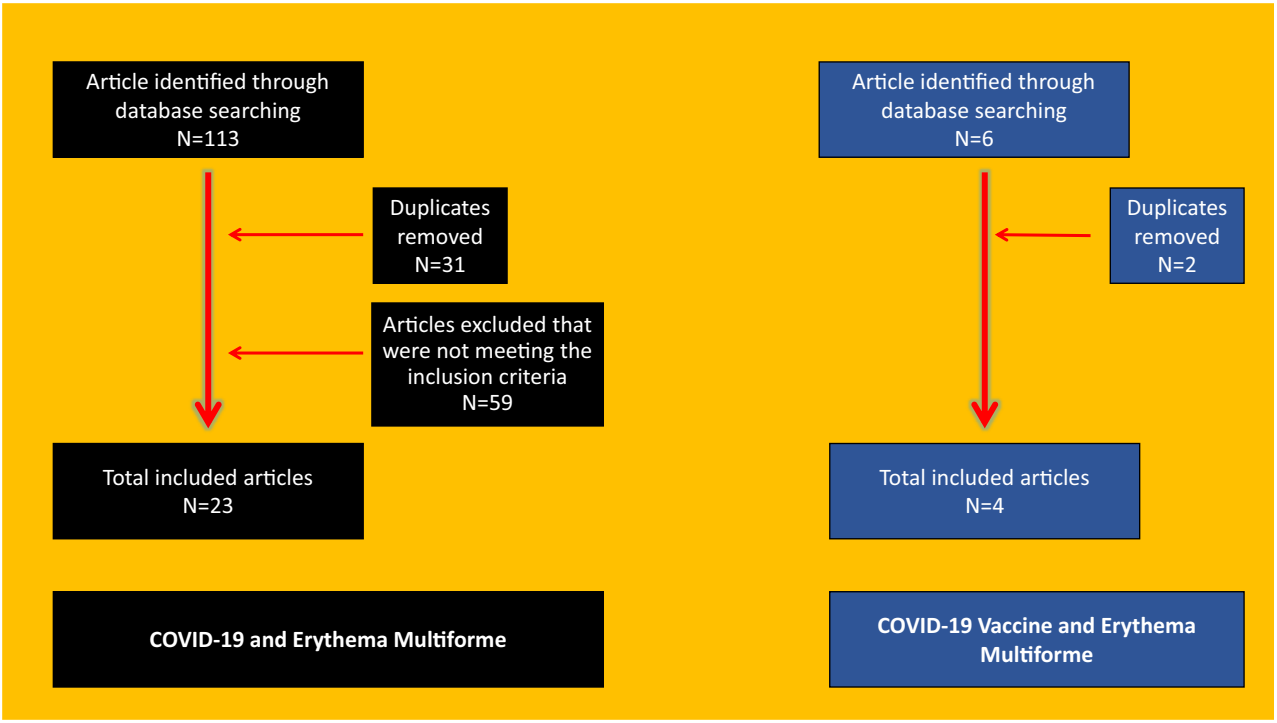

Figure 1 Literature search and article selection for the cases of Erythema multiforme in COVID-19 patients.

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.[1] 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.[2] This rarity makes it hard to establish a causal link. Infection with SARS-CoV-2 may have a role in the pathogenesis of EM.[3] The underlying mechanism is not clear.[4] 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

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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

EM related to the COVID-19 infection							
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	

Table 1 *Continued*

EM related to the COVID-19 infection							
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	23Y 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	55Y 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	6Y 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	72Y 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	46Y M	Azithromycin and HCQ and specific IgE was positive for ampicillin and amoxicillin	48 h after finishing the course of HCQ, therapy, he 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	None	Presented with EM and fever, cough and breathlessness.	Face and limbs	Blood culture was sterile.	Intravenous methyl prednisolone and intravenous immunoglobulin G along with antibiotics.	[18]
1 of 3	63Y F	Lopinavir/ritonavir, HCQ, azithromycin	19 days after COVID-19 symptoms.	Mucosal involvement on Palate	None	None	[19]
2 of 3	58Y F	Lopinavir/ritonavir, HCQ, azithromycin, tocilizumab, corticosteroids	24 days after COVID-19 symptoms.		None	None	
3 of 3	69Y M	Lopinavir/ritonavir, HCQ, azithromycin	19 days after COVID-19 symptoms.		None	None	
1	57Y 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	13Y 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*

EM related to the COVID-19 infection							
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, cetirizine, intravenous immunoglobulin, zinc gluconate, albumin and vitamin D, and meropenem were administered during the treatment course.	[24]
1 of 4	64Y 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	79Y 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	74Y 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 of 4	47Y M	HCQ, Lopinavir/Ritonavir, IFN-β, ceftriaxone, tocilizumab, azithromycin	Time from hospital admission to EM onset was 24 days.	Generalized targetoid lesions	None	Methylprednisolone	
4	Age: 60 (40–78) 2 of 4 were F	All of 4 patients had new drugs interference	>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 cetirizine, 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 Work-up Result or Recent Medication Use**	**Treatment for EM**	
1	75Y 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.	Topical corticosteroids and oral antihistamines	[27]

Table 1 *Continued*

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 Work-up Result or Recent Medication Use**	**Treatment for EM**	
1	58Y F	BNT162b2 (Pfizer–BioNTech)	Within 12 h of receiving the first BNT162b2 vaccine. A similar eruption occurred 24 h after receiving the second BNT162b2 vaccine.	Palms and soles bilaterally.	Her medical history included rheumatoid arthritis and a multinodular thyroid goitre.	Topical clobetasol	[28]
3	MD	Moderna first dose	MD	MD	MD	MD	[29]
3	MD	BNT162b2 (Pfizer/BioNTech)	MD	MD	MD	MD	[30]

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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Transient inflammation in surgical scars following Covid-19 mRNA vaccination

Editor

Since December 2020, extensive vaccination campaigns have been introduced in Europe, using novel messenger ribonucleic acid (mRNA) anti-severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) vaccines. A wide range of adverse cutaneous events have been reported since the advent of vaccination programmes,[1,2] 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).[3,4]

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

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 stiches 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

