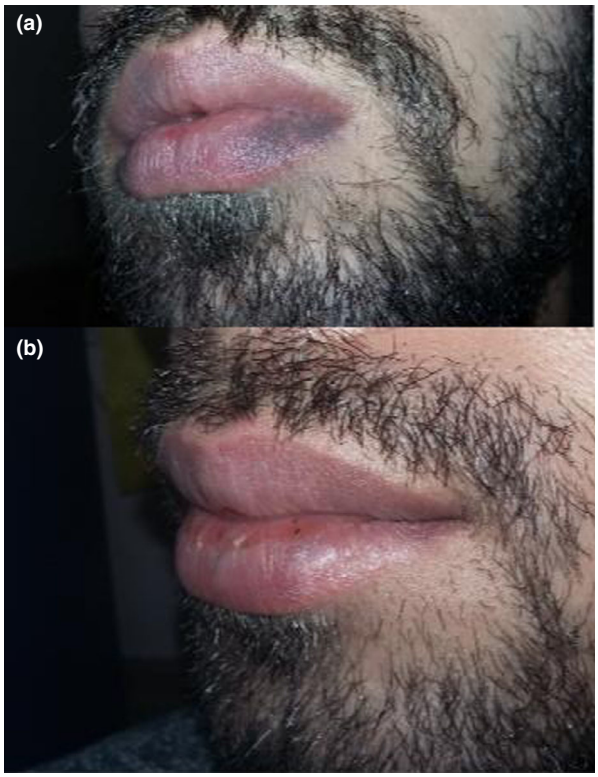

Figure 1 (a,b) Patient's lip (a) before and (b) after cryotherapy.

Treatment options for drug-induced pigmentation are very limited. Stopping the causative drug, applying topical steroids and whitening agents, and waiting for spontaneous recovery are options.[4] If lesions persist in such cases, laser therapy is probably recommended as the most effective method.[5] Topical bleaching agents have poor efficacy in the treatment of pigmentation arising from fixed drug eruptions. Laser treatment is considered the most effective way to get rid of pigmentation, and was initially offered to our patient, but cost prevented its use. The mucosal tissues have advantages in healing compared with skin, as scar formation during wound healing rarely occurs on the oral mucosa.[6] Therefore, we suggested performing liquid nitrogen freezing of the lip lesion, which resulted in almost complete disappearance of the lesion in 1 month, leaving only a very slight negligible shading; no scar formation was reported.

We have not come across a publication on cryotherapy of drug-induced pigmentation on skin, including lips. Only a few articles have been reported regarding the cryotherapy of gingival pigmentation.[2] Our patient gave excellent response to liquid nitrogen freezing with a single application. In conclusion, cryotherapy can be considered as a simple, inexpensive and safe option in the treatment of benign discoloration on the lips, including those due to medication.

H. Aktaş,[1] O. E. Yılmaz[2] and G. Ertuğrul[1]
[1]*Department of Dermatology, Karabuk Training and Research Hospital, Karabuk, Turkey and* [2]*Department of Plastic and Reconstructive Surgery, İzmir Medical Park Hospital, İzmir, Turkey*
E-mail: aktashabib@hotmail.com
Conflict of interest: the authors declare that they have no conflicts of interest.
Accepted for publication 1 April 2021

References

1 Farah CS, Koelmeyer N, Kaney A, Simanovic B. Nitrous oxide cryotherapy for the management of benign lesions of the oral cavity. *J Oral Pathol Med* 2019; **48**: 611–18.
2 Uyar B, Akgun E. Treatment of gingival hyperpigmentation with open spray cryotherapy. *Turkderm* 2013; **47**: 50–3.
3 Araujo MR, Jomaa S, Mobile RZ *et al*. Sclerotherapy and cryotherapy in the management of oral vascular lesions: a series of 10 cases. *Gen Dent* 2016; **64**: 25–9.
4 Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. *Am J Clin Dermatol* 2001; **2**: 253–62.
5 Moore M, Mishra V, Friedmann DP, Goldman MP. Minocycline-induced postsclerotherapy pigmentation successfully treated with a picosecond Alexandrite laser. *Dermatol Surg* 2016; **42**: 133–4.
6 Wong JW, Gallant-Behm C, Wiebe C *et al*. Wound healing in oral mucosa results in reduced scar formation as compared with skin: evidence from the red Duroc pig model and humans. *Wound Repair Regen* 2009; **17**: 717–29.

Ribonucleic acid COVID-19 vaccine-associated cutaneous adverse drug events: a case series of two patients

doi: 10.1111/ced.14673

Dear Editor,

Vaccines are biological preparations that enable their recipients to acquire immunity to a specific infectious disease. All vaccines can be associated with cutaneous adverse drug events (ADEs). The new ribonucleic acid (RNA) vaccine type developed by Pfizer-BioNTech was first tested in humans in COVID-19 prevention trials in 2020. This vaccine utilizes lipid nanoparticles, which act as a vector for the embedded mRNA. In a phase III clinical trial, it was found that local reactions at the injection site are the commonest side effect (84.7%), with other adverse reactions including fatigue, headache, muscle ache, chills, joint pain and fever.[1] A recent report described a case of recurrent morbilliform rash that developed 48 h following administration of the Pfizer-BioNTech COVID-19 vaccine on two

Table 1 Clinical characteristics, investigation results and management for both patients.

	Patient 1	Patient 2
Age, years	60	75
Sex	Female	Female
Ethnicity	White British	White British
Comorbidities	Hypothyroidism	Hypertension
Dose of Pfizer vaccine	First dose	First dose
Vaccine batch number	ER1741	EL0141
Time to onset of rash following vaccine administration, days	14	2
Duration of skin rash	Rash improved significantly by day 17 (Fig. 1b)	Fully resolved by day 10 (Fig. 2c)
COVID-19 PCR	Negative	Not performed
Key investigation results	Negative ANA, ANCA and complement. Normal plasma viscosity and serum electrophoresis. Normal white cell count differentials. Urine microscopy showed red cells 2×10^6/L.[a] Normal urine albumin/creatinine ratio	Negative ANA, ANCA and complement. Normal plasma viscosity and serum electrophoresis. Normal white cell count differentials. Urine microscopy not performed. Normal urine albumin/creatinine ratio
Skin biopsy histology and immunofluorescence	Histology: epidermis showed focal parakeratosis, hyperkeratosis and spongiosis; dermis showed superficial perivascular lymphohistiocytic infiltrate and scattered eosinophils; no definite blood vessel wall fibrinoid necrosis, fibrin thrombi or nuclear dust seen. Negative direct immunofluorescence study	Not performed as the rash had fully resolved by the time the patient first presented to the dermatology team
Treatment given	7-day course of oral prednisolone 30 mg once daily; topical clobetasol 17-propionate 0.05375% w/w (Dermovate) ointment; Cetraban cream as emollient; chlorphenamine 5 mg once daily at night	5-day course of oral prednisolone 40 mg once daily

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody. [a]Red blood cell value of ≤ 25 is not considered significant.

Figure 1 (a,b) A 60-year-old woman with a widespread symmetrical erythematous and purpuric rash predominantly affecting her legs: (a) rash at day 5 as she was commenced on treatment and (b) resolving rash is at day 17.

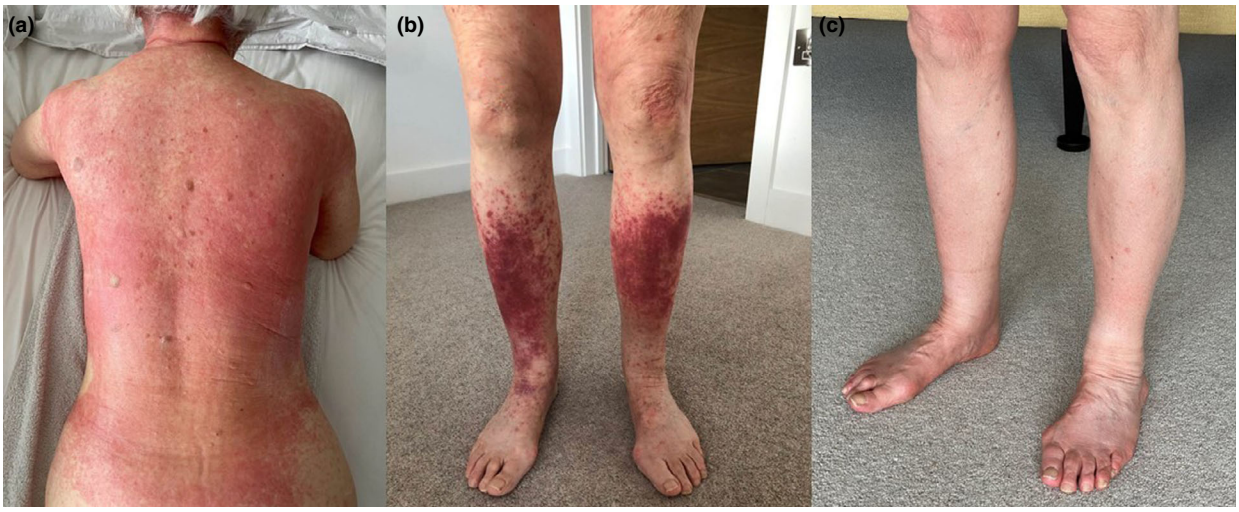

Figure 2 (a,b) A 75-year-old woman with (a) a confluent erythematous rash on trunk (b) and a symmetrical purpuric rash over the gaiter areas of her legs at day 3; (c) complete resolution of the rash at day 10.

separate occasions, 21 days apart.[2] We report two patients who presented with cutaneous ADEs following this vaccine.

In brief, both patients were systemically well with no COVID-19 or infection symptoms prior to their COVID-19 vaccinations and the onset of their skin rash. The patients' clinical characteristics, investigation results and management are presented in Table 1.

Patient 1 was a 60-year-old woman who developed a rash 2 weeks following vaccination. She presented to Dermatology 2 days later with a widespread symmetrical erythematous and purpuric eruption predominantly affecting her legs (Fig. 1a). Skin biopsies were obtained from the nonpurpuric rash and perilesional skin on her right thigh; histology showed eosinophils and the direct immunofluorescence microscopy result was negative. The rash gradually improved after 7 days of oral prednisolone and topical treatments (Fig. 1b).

Patient 2 was a 75-year-old woman, who developed a confluent erythematous rash on her torso (Fig. 2a) and a symmetrical purpuric rash over the gaiter areas of her legs (Fig. 2b), 2 days following vaccination. She had no history of lower limb chronic venous insufficiency. The primary care team commenced her on oral prednisolone for 5 days. A skin biopsy was not taken. The rash was fully resolved by day 10 (Fig. 2c). The patient did not experience any ADE following the second Pfizer-BioNTech COVID-19 vaccine.

We report two cases of post-RNA vaccination associated generalized rash with no systemic involvement. To date, the exact mechanism of vaccine-associated cutaneous ADEs remain poorly characterized.[3] It is possible that the whole class of RNA vaccines may share a similar cutaneous ADE profile to that of live and inactivated vaccines. Our patients' presentation of a purpuric rash on the legs raised the possibility of cutaneous small vessel vasculitis, although the clinical indications were not confirmed by skin biopsy. Vaccine-associated cutaneous vasculitis is a rare event. Bonetto *et al.* reported influenza vaccination as the vaccine type most likely to trigger vasculitis, particularly the cutaneous vasculitis subtype.[4] Our case series suggest that the mechanism of vaccine-associated cutaneous ADEs may not be dependent upon vaccine uptake by antigen-presenting cells, as is the case for live or inactivated vaccines. Understanding downstream transcriptomics-related events following drug administration (including vaccination) could potentially be useful in the identification of individuals at risk of experiencing ADEs.[5]

M. Lam,[1] M. Egail,[1] A. J. Bedlow[1] and S. Tso[1]
[1]*Jephson Dermatology Centre, South Warwickshire NHS Foundation Trust, Warwick, UK*
E-mail: simontso@doctors.org.uk
Conflict of interest: the authors declare that they have no conflicts of interest.
ML and ME contributed equally to this work and should be considered joint first authors.
Accepted for publication 1 April 2021

References

1 Polack FP, Thomas SJ, Kitchin N *et al.* Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; **383**: 2603–15.
2 Jedlowski PM, Jedlowski MF. Morbilliform rash after administration of Pfizer-BioNTech COVID-19 mRNA vaccine. *Dermatol Online J* 2021; **27**: 13030/qt4xs486zg.

3 Siegrist CA. Mechanisms underlying adverse reactions to vaccines. *J Comp Pathol* 2007; **137**: S46–50.
4 Bonetto C, Trotta F, Felicetti P *et al*. Vasculitis as an adverse event following immunization – systematic literature review. *Vaccine* 2016; **34**: 6641–51.
5 Kohonen P, Parkkinen JA, Willighagen EL *et al*. A transcriptomics data-driven gene space accurately predicts liver cytopathology and drug-induced liver injury. *Nat Commun* 2017; **8**: 15932.

COVID-19 and melanoma surgery in a dermo-oncology centre in Italy

doi: 10.1111/ced.14675

Dear Editor,

We have read with great interest the scientific literature regarding the diagnosis and treatment of skin cancer during the COVID-19 pandemic.[1–5] The resulting cancellation of routine dermatological visits could lead to the risk of neglecting cutaneous melanoma (CM), with potential consequences in terms of morbidity and mortality,[1,2] even though the specific impact of the pandemic on CM has yet to be estimated.

Several authors have proposed multidisciplinary protocols and guidelines for management, surgical decision-making, prioritization for systemic anticancer therapy and radiotherapy, and follow-up of patients with melanoma during the pandemic. However, there is still no unanimous consensus on the possibility of delaying therapeutic procedures, with guidelines differing, for example, between American and European associations.

In Italy, there was an immediate exponential increase in the number of COVID-19 infections from the end of January 2020, even though it was hypothesized that the 'dermatological Italian patient zero' may have been infected in November 2019.[3] The most stringent lockdown period, from 22 February to 3 May 2020, caused a dramatic reduction in the number of elective medical and surgical activities.[2]

We retrospectively analysed the number of histopathologically proven CMs at our Skin Cancer Unit in Bologna University, from January 2020 to December 2020. We considered only new cases of primary CM diagnosed by our Dermatopathology Laboratory and detected during routine clinical activity, excluding any radical surgeries on CMs that had been diagnosed elsewhere and also any metastatic cases. We compared the results with those from 2019.

In our hospital we were able to continue dermo-oncological surgery throughout the whole lockdown period. Our analysis showed that a total of 284 primary CMs were detected during the whole of 2020. This rate was similar to that of 2019, in which 278 primary CMs (using the same search criteria) had been diagnosed, and there was no significant difference in rates between the 2 years.

Conversely, other Italian authors reported a significant reduction in detection of CM during the COVID-19 pandemic, both in Northern[2] and Southern[4] Italy. In particular, at a third-level centre in Northern Italy, a 30% relative decrease in surgical activity and a significant 60% reduction in new diagnoses of CM were reported during the lockdown period.[2] In another dermo-oncology centre in a high-risk pandemic area of Northern Italy,[5] the global reduction in surgery performed for all skin cancers (including melanomas) ranged from 26% to 36% from 1 March to 30 April 2020, compared with the same period in the previous year, mostly because of patient cancellation.

Another interesting finding was that no complications arising from performing surgery were observed in the pandemic setting, as no new cases of COVID-19 infections were detected at our hospital in the 14 days after surgery. Our experience suggests that surgical activity could be continued in patients with CM, as similarly suggested by other authors.[5] We believe that the potential risk of neglecting CM should always be taken into account by clinicians, and we hope that our experience will reassure hospitals that such surgery can be performed safely.

E. Dika,[1,2] A. Barisani,[1,2] C. Baraldi,[1,2] F. Pepe,[1,2] A. Patrizi[1,2] and S. Vaccari[1,2]
[1]*Department of Dermatology, IRCCS Policlinico di Sant'Orsola, Bologna, Italy and* [2]*Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Alma Mater Studiorum University of Bologna, Italy*
E-mail: emi.dika3@unibo.it
Conflict of interest: the authors declare that they have no conflicts of interest.
Accepted for publication 7 April 2021

References

1 Gomolin T, Cline A, Handler MZ. The danger of neglecting melanoma during the COVID-19 pandemic. *J Dermatolog Treat* 2020; **31**: 444–5.
2 Barruscotti S, Giorgini C, Brazzelli V *et al*. A significant reduction in the diagnosis of melanoma during the COVID-19 lockdown in a third-level center in the Northern Italy. *Dermatol Ther* 2020; **33**: e14074.
3 Gianotti R, Barberis M, Fellegara G *et al*. COVID-19 related dermatosis in November 2019. Could this case be Italy's patient zero? *Br J Dermatol* 2021. https://doi.org/10.1111/bjd.19804.
4 Villani A, Fabbrocini G, Scalvenzi M. The reduction in the detection of melanoma during the coronavirus disease 2019 (COVID-19) pandemic in a melanoma center of South Italy. *J Dermatolog Treat* 2020. https://doi.org/10.1080/09546634.2020.1818674.
5 Ribero S, Caliendo V, Picciotto F *et al*. COVID-19 infection and dermatologic surgery: management in a dermo-oncology center in a high-risk pandemic area. *G Ital Dermatol Venereol* 2020; **155**: 684–5.

