

SKIN MANIFESTATIONS ASSOCIATED WITH ANTI-SARS-CoV2 VACCINATION: A CASE SERIES

OANA TIUCĂ*, **, ROXANA ILCUŞ*, RALUCA BULIGĂ*, LIUBA GARAGA*, ALEXANDRA PAŢA*,
RALUCA NICULESCU***, ****, ROBERT TIUCĂ****, *****, MIRCEA AMBROS*,
OVIDIU S. COTOI***, ****), SILVIU-HORIA MORARIU*, **

Summary

Introduction: Vaccination is the main method used to prevent severe forms and reduce COVID-19 associated mortality. Of great interest are the skin reactions possibly associated with vaccination.

Clinical cases: By analyzing data from patients' charts who were evaluated between May 2021 and January 2022, we intend to present a case series of cutaneous manifestations possibly associated with anti-SARS-CoV2 vaccination.

Conclusions: The reactions associated with SARS-CoV-2 vaccination are currently a matter of interest. The direct causal relationship between various vaccines and skin response is still unclear. A proper recognition of possible skin manifestations associated with vaccination would allow a better assessment of risk groups and, as such, the development of more effective therapeutic strategies.

Keywords: COVID-19, vaccine, pityriasis rubra pilaris.

Received: 23.02.2022

Accepted: 11.03.2022

Introduction

Vaccination represents the main method used to decrease the severity of cases and the mortality associated with COVID-19 pandemic. Currently, in the European Union (EU) five vaccines are approved. They are developed on different action mechanisms: messenger RNA (mRNA, Pfizer-BioNTech and Moderna), viral vector (AstraZeneca and Johnson & Johnson), respectively recombinant proteins (Novavax) [1]. With their use on a large scale for the immunization of the population, a special attention was given to the identification of a potential link between their administration and post-vaccination reactions. Nowadays, cutaneous manifestations associated with the use of vaccines is of great interest. However, the exact

causal relationship between the administration of different vaccines and the appearance of cutaneous lesions is difficult to establish. Therefore, a better characterization and understanding of such cutaneous findings proves to be useful for the daily practice.

Clinical cases

By analyzing data from patients' charts who were evaluated between May 2021 and January 2022, we intend to present a case series of cutaneous manifestations possibly associated with anti-SARS-CoV2 vaccination.

Clinical case 1. Patient PA, a 37-year-old female patient from the urban area, without any significant medical history, presented on the

* Dermatovenerology Clinic, SCJ Mureş.

** UMFST „G.E. Palade” Târgu-Mureş, Discipline of Dermatology.

*** Pathological Anatomy Service, SCJ Mureş.

**** UMFST „G.E. Palade” Târgu-Mureş, Discipline of Pathophysiology.

***** Endocrinology Department, SCJ Mureş.

***** UMFST „G.E. Palade” Târgu-Mureş, Discipline of Endocrinology.

outer part of the right arm with a well-defined erythematous and edematous plaque which appeared one day after the administration of the second dose of BNT163b2 (Pfizer-BioNTech). The lesion measured approximately 5x4cm in size (Fig.1), was accompanied by local pain and fever (38.2°C) and extended over the course of the next two days. Based on the anamnesis and skin examination, the diagnosis of cutaneous reaction at the vaccination site is established. Treatment with acetaminophen 500 mg once a day, methylprednisolone aceponate (Advantan) cream twice a day and thermal water sprayings was started. Patients' evolution was favorable, with complete remission in 5 days (Fig.2)

Clinical case 2. Patient MM, a 48-year-old female patient from the urban area, suffering from epilepsy controlled with Levetiracetam treatment, presented to the emergency unit 9 days after the second dose of BNT163b2 vaccine (Pfizer-BioNTech) with a rash consisting of well-defined nodules and erythematous-edematous plaques. The lesions were tender and painful, and were located on sun exposed areas, on the neckline, scalp, and forehead (Fig.3, Fig.4, Fig.5). No mucosal lesions were identified. The patient also presented two fever episodes, the last one on

the day of admission (38.4°C). The patient denies the use of any other drugs and taking other vaccines. Laboratory tests revealed an inflammatory syndrome (ESR 20 mm/h, NV: 0-12 mm/h; PCR 12.57, NV: 0-5 mg/L) and leukocytosis with neutrophilia (15740/mm³ leukocytes, 83.3% neutrophils). No infectious sources have been identified. Considering the aspect and the evolution of the lesions, the suspicion of anti-SARS-CoV2 vaccination associated Sweet syndrome has been raised. Systemic treatment with hydrocortisone hemisuccinate 100 mg/day, ceftriaxone 1g 2x1/day, levocetirizine 5 mg 2x1/day and topical treatment with methylprednisolone aceponate emulsion twice a day was started. The evolution was favorable, with complete remission of the associated symptoms and quasi-complete of the cutaneous lesions within 5 days.

Clinical case 3. Patient HM, a 57-year-old male patient from the urban area, with grade 1 obesity developed 135 days after the administration of the second dose of BNT163b2 vaccine (Pfizer-BioNTech) a tender ecchymosis, measuring 8x4 cm and located on the right abdominal flank (Fig. 6). Patient's history is positive for atopic rhinitis and dermatitis,



Figures 1 and 2. Local reaction on vaccination site: before and after treatment.



Figure 3. Erythematous-edematous nodules and plaques located on the neckline, anterior and posterior trunk and near the hair.



Figure 4. Erythematous-edematous nodules and plaques located on the neckline, anterior and posterior trunk and near the hair.

without other episodes of bleeding or bruising. The patient denies any history of major trauma and has not used anticoagulant or antiplatelet therapy prior to the appearance of the cutaneous lesions. No laboratory tests were performed, due to patient's refusal. Topical treatment with chondroitin polysulfate cream (Hirudoid) once a day was started, with favorable evolution and complete remission of the lesion in 14 days. The 10-month follow-up showed no other manifestations, except for a mild and persistent pain on the vaccination site for several months and unexplained episodes of headache which responded to nonsteroidal anti-inflammatory drugs. Due to the localisation of the lesions the differential diagnosis was performed with Cullen's sign and periumbilical atraumatic ecchymoses encountered in aortic rupture and pancreatitis.

Clinical case 4. Patient MS, a 67-year-old male patient from the rural area, developed 2 months after the administration of the second dose of BNT163b2 vaccine (Pfizer-BioNTech) purpuric lesions, of irregular shape, measuring a maximum diameter of 4 cm and located on the upper limbs (Fig.7). The patient denies any history of trauma or administration of steroids.



Figure 5. Erythematous-edematous nodules and plaques located on the neckline, anterior and posterior trunk and near the hair.

Platelet number was normal ($303000 / \text{mm}^3$), as well as the value of coagulation indices (INR = 1.03, PT = 11.2 seconds). Based on the clinical aspect, the diagnosis of purpura likely induced by anti-SARS-CoV-2 vaccination was established. A complete resolution of cutaneous lesions was



Figure 6. Ecchymosis located on the right abdominal flank.



Figure 7. Purpuric lesions located on the left upper limb.

noted in approximately one month without any kind of local and systemic treatment.

Clinical case 5. Patient HR, a 78-year-old female patient from the rural area, developed one week after the second dose of BNT163b2 vaccine (Pfizer-BioNTech) a pruritic rash consisting of

papules, plaques and plaquards with a tendency towards confluence and desquamation with fine, easily removable furfuraceous scales, located on the anterior and posterior trunk, abdomen, upper and lower limbs and on the scalp (Fig. 8, Fig. 9). The lesions presented a cranio-caudal evolution.



Figure 8. Erythematous papules, plaques and plaquards located on the trunk, abdomen and upper limbs. Cutaneous desquamation.



Figure 9. Erythematous papules, plaques and plaquards located on the trunk, abdomen and upper limbs. Cutaneous desquamation.



Figure 10. Round, well-defined erythematous plaque located at the injection site.

In the deltoid region, at the site of vaccination, a well-defined round shape erythematous plaque is identified (Fig.10). The patient denies taking any drugs in the last two weeks. Laboratory tests indicate an inflammatory syndrome (PCR 24.54 mg/dl) and eosinophilia (8.5%) and do not identify other infectious factors. Dermoscopy examination reveals diffuse erythema, sometimes orange in color, small-sized areas of apparently normally looking skin, white keratotic follicular plugs, dilated dotted and reticular vessels, and white scales with a diffuse disposition. (Fig. 11, Fig. 12). The patient was started on systemic treatment with intravenous methylprednisone 125 mg/day, levocetirizine 5 mg 2x1/day and topical treatment with hydrocortisone ointment twice a day, with favorable evolution and resolution of the lesions in about 30 days. Skin biopsy was performed from the right deltoid erythematous plaque and from a hyperkeratotic follicular papule. Histopathological examination confirmed the diagnosis of pityriasis rubra pilar (PRP) (Fig.13, Fig.14), most likely induced by anti-SARS-CoV-2 vaccination.

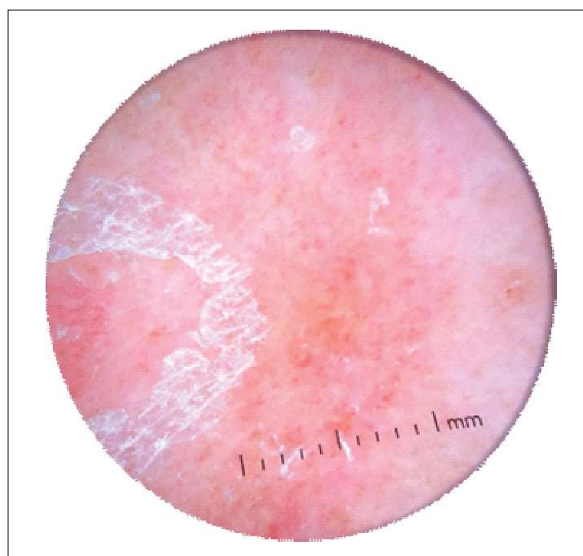


Figure 11. Diffuse orange erythema, follicular keratotic plugs, keratotic ring, dilated dotted and reticular vessels, white scales.



Figure 12. Yellowish-white keratotic follicular plugs, erythematous halo with dotted vessels.

Clinical case 6. Patient MD, a 16-year-old male patient from the urban area, with mild follicular kiperkeratosis history (Fig.15) develops ten days after the administration of the second dose of BNT163b2 vaccine (Pfizer-BioNTech) an atopic eczema (AD) located on the left arm. The skin rash presented as an erythematous-

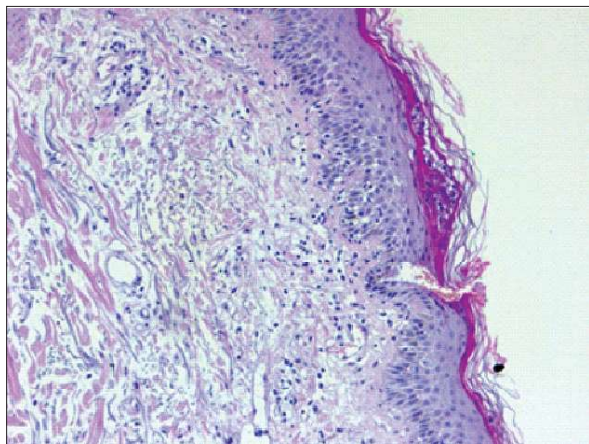


Figure 13. Histopathological examination.

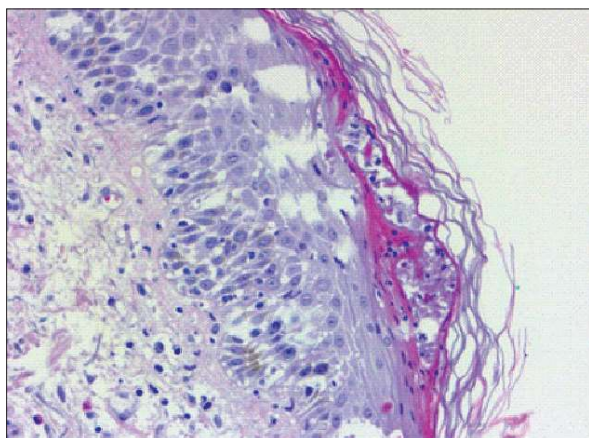


Figure 14. Histopathological examination.

squamous plaquard, measuring 14x8 cm, with ill-defined margins and intense itch (Fig.16, Fig.17). Local treatment with methylprednisolone aceponate cream (Advantan) two applications a day for 5 days, hydrating cleansing gel (Cerave Hydrating Cleanser) and moisturizer (Cerave balm) was started on the patient. The lesions and the itch resolved until the two-weeks check-up.

Discussions

Since the approval of the first vaccine against SARS-CoV-2 (PfizerBioNTech) and later of the others, reports on post-vaccination cutaneous reactions have proved to be of particular significance for the practice of the dermatologist. Skin manifestations associated with anti-SARS-CoV-2 vaccination can be classified into de novo



Figure 15. Follicular keratosis.



Figure 16. Atopic eczema.

reactions and the aggravation of preexisting dermatoses. They range from delayed local reactions to pityriasis rosea Gilbert-like and even the reactivation of varicella-zoster virus [2]. The link between the rash and the administration of the vaccine may be supported by elements such as: chronological or topographical relationship



Figure 17. Atopic eczema.

with the administration of the vaccine, the absence of another associated triggering factor, or, in some cases, the recurrence of skin lesions following the administration of the booster doses.

Delayed cutaneous reaction, defined as an erythematous-edematous plaque at the injection site at least 2 days after vaccine administration, is most commonly encountered. Reactions after booster doses were milder compared to those after the first dose [2]. Maculo-papular and morbiliform rashes have been described especially after mRNA-based vaccines. Both mRNA and viral vector vaccines can induce different types of cutaneous vasculitis, especially starting with the second dose [3,4]. However, vascular damage has been more commonly described secondary to the administration of mRNA-based vaccines [5]. Thrombocytopenic immune purpura is an uncommon and severe adverse reaction of both mRNA and viral vector-based vaccines [6,7,8,9]. Therefore, any patient with skin lesions such as ecchymosis, purpura and with vaccination history should be investigated in this direction.

Sweet Syndrome, although rarely encountered, has been described in association with anti-SARS-CoV-2 vaccines, especially those developed on mRNA mechanism. Except for one case [10] in

which the patient also developed acute encephalitis and myoclonus secondary to the administration of the vaccine, the other cases up to now have favorably responded to treatment with steroids and antipyretics[11,12,13], such in the case of our patient.

Information regarding atopic manifestations secondary to SARS-CoV-2 vaccines are currently sparse. The mechanism of post-vaccination AD lesions is incompletely elucidated. Although the role of Th1 in the response to vaccines has been investigated, information on Th2 has not been published until now [14]. Furthermore, although eczematous reactions have been reported at a variable time after immunization, they are easily controllable by topical steroid therapy, and the establishment of a direct relationship between AD lesions and vaccine administration is a difficult one.

Vaccine-associated PRP reactions have been previously described in association with influenza or diphtheria vaccination [15-18]. Regarding the link between SARS-CoV-2 vaccination and the occurrence of PRP, the existing information is limited and mainly based on information gained from sporadic case reports. Thus, we can discuss about an uncommon reaction associated with vaccination. What is interesting about histopathologically confirmed cases and published as PRP until now is the fact that in some of them the patients presented with a typical orange rash associated with keratoderma, which were responsive to systemic retinoids [19,20,21], while in other cases, such as ours, the patients presented with eczematous, erythematous-papular lesions intertwined with spared skin and fine exfoliation that responded to topical and systemic steroid treatment [13, 22].

Conclusions

The reactions associated with SARS-CoV-2 vaccination are currently a matter of interest. The direct causal relationship between various vaccines and skin response is still unclear. A proper recognition of possible skin manifestations associated with vaccination would allow a better assessment of risk groups and, as such, the development of more effective therapeutic strategies.

Bibliography

1. https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-19-vaccines-europeans_en
2. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. *J Am Acad Dermatol* 2021;85(1): 46–55
3. Mücke, V.T., Knop, V., Mücke, M.M. et al. First description of immune complex vasculitis after COVID-19 vaccination with BNT162b2: a case report. *BMC Infect Dis* 21, 958 (2021).
4. Dicks AB, Gray BH. Images in Vascular Medicine: Leukocytoclastic vasculitis after COVID-19 vaccine booster. *Vascular Medicine*. November 2021. doi:10.1177/1358863X211055507
5. Bellinato F, Maurelli M, Gisondi P, et al. Cutaneous Adverse Reactions Associated with SARS-CoV-2 Vaccines. *J Clin Med*. 2021;10(22):5344. Published 2021 Nov 16. doi:10.3390/jcm10225344
6. David P, Dotan A, Mahroum N, et al. Immune Thrombocytopenic Purpura (ITP) Triggered by COVID-19 Infection and Vaccination. *Isr Med Assoc J*. 2021;23(6):378–380.
7. Malayala SV, Mohan G, Vasireddy D, et al. Purpuric Rash and Thrombocytopenia After the mRNA-1273 (Moderna) COVID-19 Vaccine. *Cureus*. 2021;13(3):e14099. Published 2021 Mar 25. doi:10.7759/cureus.14099
8. Lee EJ, Cines DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol*. 2021;96(5):534–537. doi:10.1002/ajh.26132
9. Candelli M, Rossi E, Valletta F, et al. Immune thrombocytopenic purpura after SARS-CoV-2 vaccine. *Br J Haematol*. 2021;194(3):547–549. doi:10.1111/bjh.17508
10. Torrealba-Acosta, G.; Martin, J.C.; Huttenbach, Y., et al. Acute encephalitis, myoclonus and Sweet syndrome after mRNA-1273 vaccine. *BMJ Case Rep*. 2021, 14, e243173.
11. Darrigade AS, Théophile H, Sanchez-Pena P, et al. Sweet syndrome induced by SARS-CoV-2 Pfizer-BioNTech mRNA vaccine. *Allergy*. 2021;76(10):3194–3196. doi:10.1111/all.14981
12. Kinariwalla N, London AO, Soliman YS, et al. A case of generalized Sweet syndrome with vasculitis triggered by recent COVID-19 vaccination. *JAAD Case Rep*. 2022;19:64–67. doi:10.1016/j.jdc.2021.11.010
13. Sechi A, Pierobon E, Pezzolo E, et al. Abrupt onset of Sweet syndrome, pityriasis rubra pilaris, pityriasis lichenoides et varioliformis acuta and erythema multiforme: unravelling a possible common trigger, the COVID-19 vaccine. *Clin Exp Dermatol*. 2022;47(2):437–440. doi:10.1111/ced.14970
14. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T(H)1 T cell responses. *Nature* 2020; 586: 594–599
15. Naciri Bennani B, Cheikh Rouhou H, Waton J et al. Pityriasis rubra pilaris after vaccination. *Ann Dermatol Venereol* 2011; 138: 753–756.
16. Mohamed M, Belhadjali H, Hammedi F, et al. Pityriasis rubra pilaris occurring after vaccination with diphtheria-pertussis-tetanus and oral poliovirus vaccines. *Indian J Dermatol Venereol Leprol* 2015; 81: 618–620.
17. Musette P, Senet P, Verola ODL. A case of pityriasis rubra pilaris induced by DTPolio Vaccination. *Ann Dermatol Venereol* 1997; 124: S226.
18. Bitbol-Duneton V, Mikita M, Lebas D, et al. Pityriasis rubra pilaris triggered by Tetragrip vaccine. *Ann Dermatol Venereol* 2006; 133: S280–S281
19. Lladó I, Butrón B, Sampedro-Ruiz R, et al. Pityriasis rubra pilaris after Vaxzevria® COVID-19 vaccine. *J Eur Acad Dermatol Venereol*. 2021;35(12):e833–e835. doi:10.1111/jdv.17542
20. Hunjan MK, Roberts C, Karim S, et al. Pityriasis rubra pilaris-like eruption following administration of the BNT163b2 (Pfizer-BioNTech) mRNA COVID-19 vaccine. *Clin Exp Dermatol*. 2022;47(1):188–190. doi:10.1111/ced.14878
21. Criado PR, Ianhez M, Rocha PS, et al. Pityriasis rubra pilaris (type I) following ChAdOx1 COVID-19 vaccine: A report of two cases with successful treatment with oral isotretinoin [published online ahead of print, 2022 Mar 12]. *J Eur Acad Dermatol Venereol*. 2022;10.1111/jdv.18055. doi:10.1111/jdv.18055
22. Sahni, M.K.; Roy, K.; Asati, D.P., et al. An old entity, a new trigger: Post COVID-19 vaccine Pityriasis rubra pilaris. *Int. J. Risk Saf. Med*. 2021, 1–4, preprint.

Conflict of interest
NONE DECLARED

Correspondance address: Roxana Ilcuş
Dermatovenerology Clinic, SCJ Mureş.
e-mail roximed2005@yahoo.com.