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CASE REPORT

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# Pemphigus foliaceous following vaccinations

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## ABSTRACT

Pemphigus is a rare autoimmune bullous disease, with pemphigus vulgaris (PV) and pemphigus foliaceous (PF) being its most common forms. This report presents a case of PF triggered by vaccinations. A previously healthy 38-year-old Caucasian man developed skin lesions six months after receiving vaccinations for hepatitis A, rabies, cholera, typhoid fever, and yellow fever before travelling to Sudan. Examination revealed pruritic erosions, crusts, and flaccid blisters primarily on the trunk and limbs. Histopathology was nonspecific, but direct immunofluorescence showed intercellular IgG, C3c, and C1q deposits. Elevated autoantibodies against desmoglein 1 (DSG1) confirmed the PF diagnosis. The patient responded well to oral prednisone and topical treatments, with complete resolution of symptoms within six months. The aetiology of pemphigus remains unclear, but vaccines can nonspecifically activate the immune system, potentially triggering pemphigus in predisposed individuals. This case highlights the need to consider pemphigus as a potential adverse effect of vaccination.

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**Keywords:** pemphigus foliaceous, vaccinations

## INTRODUCTION

Pemphigus is known as a rare autoimmune bullous disease that can be fatal if left untreated. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the most common forms of pemphigus. In contrast to PF, almost all patients with PV will develop oral lesions at some stage of the disease. This research presents the case of a patient who developed PF after a series of vaccinations. There were just a few reports of patients who developed pemphigus following vaccinations (Tab. 1) [1–9] and several cases of pemphigus exacerbation after vaccinations described in the literature [10, 11], before the coronavirus disease 2019 (COVID-19) pandemic. Most new scientific papers on the development of PV or PF after vaccination, describe the occurrence of these dermatoses after immunization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Tab. 1) [12–37]. This global pandemic and the mass vaccinations against COVID-19 that have taken place in recent years, have increased the demand for research on the relationship between autoimmune bullous diseases and specific immunization.

## CASE REPORT

A previously healthy 38-year-old Caucasian man was admitted to the department with skin lesions lasting half a year. About one month before the first symptoms had occurred, the patient had taken a series of vaccinations before his journey to Sudan [against hepatitis A, rabies (3 doses), cholera (2 doses), typhoid fever, and yellow fever].

The physical examination revealed numerous itching erosions, crusts, hyper- and hypopigmentation mainly on the trunk and limbs, and single thin-walled flaccid blisters filled with clear fluid that easily ruptured (Fig. 1). The hair, nails and mucous membranes were not affected.

The histopathological examination of the skin biopsy showed that the surrounding epidermis exhibited a slightly loosened structure in the deeper layers without evident acantholysis. The stroma showed a fairly intense perivascular lymphocytic infiltrate with occasional eosinophils. Direct immunofluorescence (DIF) of a perilesional skin biopsy revealed intercellular space deposition of IgG, C3c, and a granular pattern of C1q in the walls of superficial vessels. Enzyme-linked

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**Table 1.** Pemphigus following vaccinations — literature review

| References | Patient age/sex | Vaccine against (type) | Diagnosed |
|---|---|---|---|
| Bellaney et al. 1996 [1] | 46 y/female | Typhoid (Typhim Vi) | Pemphigus vulgaris |
| Mignogna et al. 2000 [2] | Not know | Influenza (n/a) | Pemphigus vulgaris |
| Cozzani et al. 2002 [3] | 11 y/female | Tetanus, diphtheria | Pemphigus |
| Muellenhoff et al. 2004 [4] | 41 y/male | Anthrax (Anthrax vaccine adsorbed) | Pemphigus vulgaris |
| Berkun et al. 2005 [5] | 43 y/male | Hepatitis B (Engerix B) | Pemphigus vulgaris |
| Yalçin et al. 2007 [6] | 43 y/female | Rabies | Pemphigus vulgaris |
| Albavera et al. 2012 [7] | 54 y/female | Influenza | Pemphigus vulgaris |
| Hviid et al. 2017 [8] | Not know/female | Human papilloma virus | Pemphigus vulgaris |
| Sharma et al. 2020 [9] | 5 y/female | Diphtheria | Pemphigus vulgaris |
| Solimani et al. 2021 [12] | 40 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| Thongprasom et al. 2021 [13] | 38 y/female | SARS-CoV-2 (AstraZeneca) | Pemphigus vulgaris |
| Lua et al. 2021 [14] | 83 y/male | SARS-CoV-2 (Comirnaty) | Pemphigus foliaceus |
| Hatami et al. 2021 [15] | 34 y/male | SARS-CoV-2 (AstraZeneca) | Pemphigus vulgaris |
| Knechtl et al. 2021 [16] | 89 y/male | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| Koutlas et al. 2021 [17] | 60 y/male | SARS-CoV-2 (Moderna) | Pemphigus vulgaris |
| Akoglu 2022 [18] | 69 y/female | SARS-CoV-2 (CoronaVac) | Pemphigus vulgaris |
| Calabria et al. 2022 [19] | 60 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| Saffarian et al. 2022 [20] | 76 y/female | SARS-CoV-2 (Sinopharm/BBIBP-CorV) | Pemphigus vulgaris |
| Yıldırıcı et al. 2022 [21] | 65 y/male | SARS-CoV-2 (Comirnaty) | Pemphigus foliaceus |
| Falcinelli et al. 2022 [22] | 63 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus foliaceus |
| Gui et al. 2022 [23] | 25 y/male | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| | 67 y/female | SARS-CoV-2 (Moderna) | Pemphigus foliaceus |
| Hali et al. [24] | 50 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus foliaceus |
| | 58 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| Corrá et al. 2022 [25] | 61 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| | 80 y/male | SARS-CoV-2 (Comirnaty) | Pemphigus foliaceus |
| | 66 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus foliaceus |
| | 73 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| | 63 y/female | SARS-CoV-2 (AstraZeneca) | Pemphigus vulgaris |
| Aryanian et al. 2022 [26] | 43 y/male | SARS-CoV-2 (AstraZeneca) | Pemphigus vulgaris |
| Singh et al. 2022 [27] | 44 y/male | SARS-CoV-2 (AstraZeneca) | Pemphigus vulgaris |
| Pourani et al. 202 [28] | 75 y/male | SARS-CoV-2 (Sinopharm/BBIBP-CorV) | Pemphigus foliaceus |
| Reis et al. 2022 [29] | 35 y/female | SARS-CoV-2 (Comirnaty) | Pemphigus foliaceus |
| Rouatbi et al. 2022 [30] | 70 y/male | SARS-CoV-2 (Comirnaty) | Pemphigus foliaceus |
| | 48 y/male | SARS-CoV-2 (AstraZeneca) | Pemphigus foliaceus |
| Agharbi et al. 2022 [31] | 72 y/male | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| Shakoei et al. 2022 [32] | 28 y/female | SARS-CoV-2 (Sinopharm/BBIBP-CorV) | Pemphigus vulgaris |
| | 30 y/female | SARS-CoV-2 (Sinopharm/BBIBP-CorV) | Pemphigus vulgaris |
| Alami et al. 2022 [33] | 44 y/male | SARS-CoV-2 (Sinopharm/BBIBP-CorV) | Pemphigus foliaceus |
| Norimatsu et al. 2023 [34] | 86 y/male | SARS-CoV-2 (Comirnaty) | Pemphigus vulgaris |
| Almasi-Nasrabadi et al. 2023 [35] | 62 y/female | SARS-CoV-2 (AstraZeneca) | Pemphigus foliaceus |
| Nguyen Nhat Pham et al. 2023 [36] | 53 y/female | SARS-CoV-2 (AstraZeneca) | Pemphigus foliaceus |
| | 30 y/female | SARS-CoV-2 (Moderna) | Pemphigus foliaceus |
| Kadylak et al. 2024 (present article) | 38 y/male | Hepatitis A (Avaxim 160U), rabies (Verorab), cholera (Dukoral), typhoid fever (Typhim Vi), yellow fever (Stamaril) | Pemphigus foliaceus |

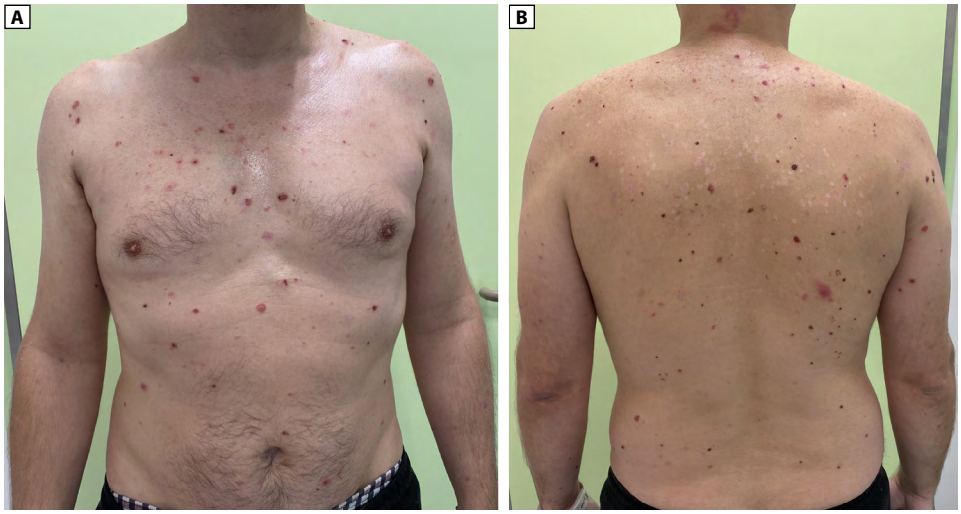


**Figure 1A, B.** Flaccid blistering, scabbing erosions, hyper- and hypopigmentation on the patient's trunk

immunosorbent assay detected circulating pemphigus autoantibodies against desmoglein 1 (DSG 1). PF was diagnosed based on clinical presentation, DIF and serological findings. Oral prednisone at 0.5 mg/kg/day and topical supportive treatment (clobetasol propionate, emollients) were introduced with good clinical response. Six months after onset skin was completely clear and asymptomatic.

## DISCUSSION

The exact aetiology and pathogenesis of pemphigus are still unknown. Several exogenous factors may trigger pemphigus initiation in susceptible individuals or be exacerbated in affected patients (*e.g.* cancer, infection and drugs) [10]. Vaccines as well as drugs, can cause a non-specific activation of the immune system and *de novo* induce or trigger an already existing but latent pemphigus in a predisposed population [5, 37]. An induced pemphigus may resolve after drug withdrawal [38]. Three groups of chemical structures in vaccines/drugs can trigger, exacerbate or induce pemphigus flare-ups: 1) thiol group (*e.g.* captopril, penicillamine); 2) phenol drugs (*e.g.* aspirin, levodopa, heroin); 3) non-thiol, nonphenol drugs (*e.g.* nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, calcium channel blockers) [39]. In the presented case the composition of all vaccines was checked and none of them contained thiol and phenol groups.

There are several possible hypotheses explaining blistering after vaccination: 1) genetically predisposed individuals may develop a hyperimmune reaction, which may result in the development of autoantibodies to DSG antigen [4]; 2) vaccines can directly affect DSG 1 and/or 3, adhesion molecules on keratinocytes or modify their structure [6]; 3) vaccination causes an increase of concentration of pro-inflammatory cytokines and proteolytic enzymes, which may affect the skin and mucous membranes [9]. There have also been reports of PV following the use of exogenous interferon and interleukin therapy [4]; 4) nonspecific activation of the innate immune system can also trigger autoimmunity by promoting the activation or expansion of autoreactive T cells [6]; 5) the immunization components may themselves act as foreign antigens, leading to cross-reactivity of antibodies directed against both the foreign antigen and the DSG [1]; 6) multiple antigenic stimulations activate the IgG4 synthesis pathway, which could be trigger factor of pemphigus [37].

## CONCLUSIONS

In conclusion, the authors believe that vaccinations were associated with PF in the described case. Unfortunately, it is not possible to determine exactly which one could have caused the disease. Although the occurrence is exceedingly uncommon, pemphigus can result from vaccination. It remains an undesirable consequence that clinicians should consider, particularly in predisposed individuals.

## Article information and declarations

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### *Author contributions*

Conceptualization — DK; methodology — DK; formal analysis — DK; investigation — DK; resources — DK; data curation — DK; writing: original draft preparation — DK, JS; writing: review and editing — DK, JS, WB-R, RJN and MS-W; visualization — DK; supervision — WB-R, RJN. and MS-W; project administration — DK. All authors have read and agreed to the published version of the manuscript.

## Conflict of interest

The authors declare no conflicts of interest.

## Ethics statement

Case report, consent of the bioethics committee is not required.

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## Supplementary material

None.

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