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New Onset Pemphigus Foliaceus Following m-RNA COVID-19 Vaccine: A New and Rare Trigger

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Abstract

Pemphigus is a group of autoimmune blistering disorder characterized by intra-epithelial blisters in the skin and/or mucosa. Pemphigus foliaceus (PF) is one of the less common variants. Only a limited cases of onset or flare of pemphigus after receiving vaccination against Covid-19, have been reported in the literature so far. The diagnosis is made via direct or indirect immunofluorescence and histopathologic investigations complemented by serum IgG antibodies in the setting of appropriate clinical presentation. There is no consensus on treatment guidelines due to limited literature but Rituximab (RTX) and/or intravenous immunoglobulins are considered the treatment of choice. We are reporting a case of PF with symptoms onset 2 weeks after receiving m-RNA Covid vaccine. The patient had a good response to RTX and methylprednisolone.

Keywords: Pemphigus; Pemphigus foliaceus; Covid-19 mRNA vaccine; Vaccine-induced pemphigus foliaceus

Introduction

Pemphigus is derived from the Greek word “pemphix” referring to blister or bubble [1], and it includes life-threatening blistering disorders. Pemphigus was first described by Stephen Dickson in 1788, when he observed a patient with a blister on her tongue [2]. Pemphigus represents a group of autoimmune entities that are characterized by intra-epithelial blisters in the skin and/or mucosa [3]. Pemphigus has several variants including pemphigus vulgaris (PV) which is the most common variant, pemphigus foliaceus (PF), paraneoplastic pemphigus, and IgA pemphigus [4]. Endemic pemphigus foliaceus (EPF) or Fogo Selvagem, and pemphigus erythematosus are less common variants of PF while pemphigus vegetans (PVeg) is a variant of PV.

A limited number of cases of PF after receiving mRNA vaccine against the Corona virus disease 2019 (COVID-19) are available in the literature. We found less than half a dozen cases upon reviewing literature. Hence, not much is known about the clinical course and its management. We report a case of new onset PF after receiving m-RNA vaccine against COVID-19 virus (Moderna), which is an extremely rare occurrence.

Case Presentation

A 36-year-old patient with hypertension and history of gastric bypass, seen for a painful pruritic rash mainly in the scalp area while she was on vacation. It spread to her chest, breasts and to the back over the next few days. The rash appeared in the sun-exposed areas where she had developed sunburn. She recalls using sunblock cream on a regular basis. Topical mupirocin was prescribed by the primary care physician but the rash progressed to become blisters. Oral Prednisone was prescribed along with oral Bactrim for 5 days as there was a concern for infection, resulting in transient improvement in symptoms. The patient's symptoms worsened; hence, additional course of antibiotics (14 days of Bactrim) was initiated, and dermatology referral was placed. Numerous erosions, scabbed areas, and some vesicles were noticed on upper, mid, lower back, chest, inframammary, and lower abdomen and scaling plaques on the scalp (Figure 1A-D). Nikolsky sign was noticed in some lesions. No obvious trigger was identified after taking extensive history for new exposures and reviewing the medication list, except for receiving m-RNA vaccine against COVID-19 two weeks prior to the trip.

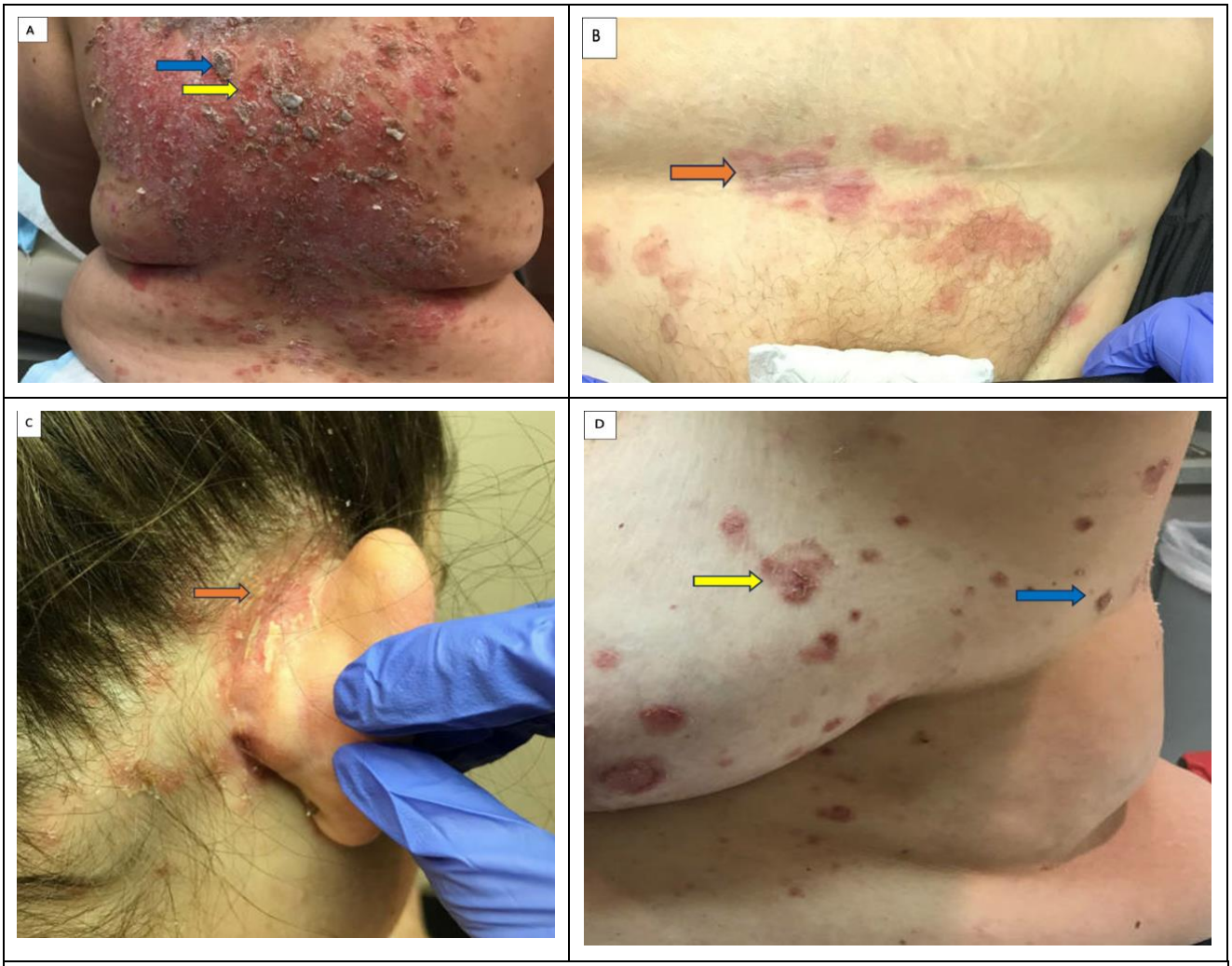

Figure 1(A): Back; **(B):** Pubis; **(C):** Right ear; **(D):** Left breast.

Extensive erythematous lesions with erosions (yellow arrows), scabs (blue arrows), and vesicles noticed on different areas of the body. The orange arrows show pruritic flaky lesions that were seen on different parts including the ear, pubis and below the breasts.

Punch biopsy of the skin lesion and perilesional area was taken. The skin lesion biopsy showed intraepidermal vesicular dermatitis with intraepidermal suprabasal blister suspicious for pemphigus vulgaris versus foliaceus. Perilesional biopsy also suggested pemphigus (Figure 2A and B). Direct immunofluorescence showed elevated Desmoglein (DSG) 1 antibody, and DSG 3 was just above normal threshold. The clinical presentation and laboratory and histopathology findings all pointed towards the diagnosis PF. Pemphigus specialist was taken on board, and patient was started on Rituximab and pulse steroids (methylprednisolone), resulting in significant improvement in patient's symptoms.

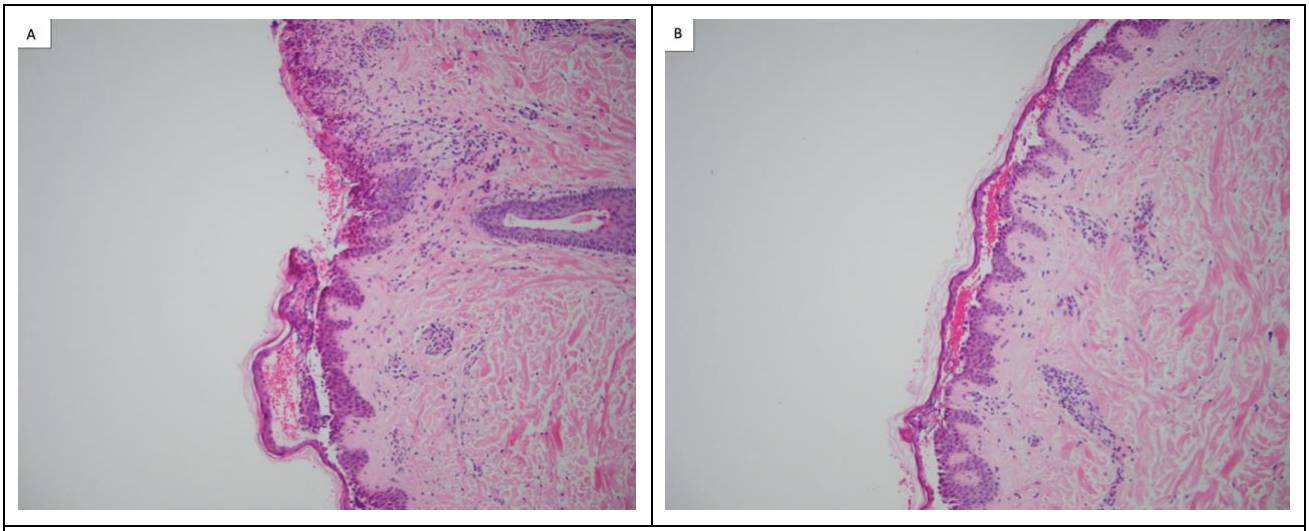

Figure 2(A and B): The intraepidermal acantholysis is suprabasilar and within the granular layer. In the subjacent dermis there is a superficial perivascular, predominantly lymphocytic inflammatory infiltrate with neutrophils and prominent eosinophils.

Discussion

A few cases of pemphigus have been reported in the literature after receiving vaccination against COVID-19 virus, mostly PV or its variants, and PF is less common occurrence. Corra et al reported 5 cases of pemphigus i.e., 3 cases of PV and 2 cases of PF [5], Calabria et al reported only 1 case among 35 cases of autoimmune blistering disease triggered by COVID-19 vaccination [6], and similarly, other case series of new onset pemphigus have either only 1 or no cases of PF. A prospective observational study reported earlier this year reported an overall risk of 1.2% (n=92) for cutaneous adverse reactions among 7505 patients who were vaccinated against COVID-19. Only a single case of PF was observed in the study [7], again suggesting that it is a very rare occurrence following COVID-19 vaccination. Viral infection and vaccines are believed to trigger spontaneous autoimmune bullous disorders (ABD) like PF and bullous pemphigoid (BP). Infections like herpes viruses, hepatitis B, and human immunodeficiency virus (HIV), and vaccinations against influenza, swine flu, tetanus toxoid, and herpes zoster have been implicated in infantile and adult BP and pemphigus [8-11]. There are recent reports of ABD flare after receiving COVID-19 vaccine [12].

Median age of the cases of pemphigus group is 60 years (interquartile range 50-76 years) [5,6]. The onset of symptoms from the administration of the vaccine ranged from 3 days to 4 weeks [6]. Immune cross-reactivity caused by molecular mimicry is suggested as the possible pathogenesis of autoimmune disorders following antiviral vaccination [13]. Another thought process is that mRNA vaccines seem to ramp up the immune system generally, since many other autoimmune diseases have been triggered by the vaccine as well as by the Covid-19 infection itself [14]. Histopathology, direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) microscopy are the mainstay of diagnostic workup, which is complemented by serologic detection of IgG autoantibodies against specific autoantigens [15]. Acantholysis as a consequence of suprabasilar loss of epidermal keratinocyte adhesion is noticed in PV. Acantholysis can be seen in hair follicles and the ducts of sebaceous glands. This acantholysis is more superficial, i.e., subcorneal at the level of stratum spinosum in PF [16]. The clinical presentation among different variants of pemphigus varies, depending on the autoantibody formation against intraepidermal proteins [16]. The IgG autoantibodies in PV are directed against a group of transmembrane adhesion proteins located in desmosomes. They are called Desmoglein (DSG), and the subtypes 1 and 3 are involved in mucocutaneous form and subtype 3 involved in mucous form, which leads to acantholysis in the suprabasal spinous layers [3].

PF usually starts as blisters and erosions in the seborrheic areas, such as the face, scalp, and chest, while painful erythematous erosions and plaques develop later on [4,16]. PV is characterized by painful mucosal erosions and flaccid blisters that easily rupture [17] and progression is from mouth to cutaneous manifestations [18]. Erosions appearing on the intertriginous, anogenital, and nasolabial areas is the characteristic of PVeg, and these erosions undergo repetitive cycles of incomplete healing to gradually become hypertrophic vegetating plaques. Mucous membrane and intense foul odor are common [19].

The first line therapies for PF include dapsone, corticosteroids, or RTX (RA protocol) according the updated 2020 guidelines by the European Academy of Dermatology and Venereology (EADV) [20]. In a very recent systemic review on biologic treatments for PF, 105 patients with included from 41 studies; 85 treated with rituximab (RTX), 8 with intravenous immunoglobulin (IVIG), and 12 received both. 48 (63.2%) patients had complete remission but 30 (39.5%) patients relapsed, the infection rate was 19.7%, and mortality rate was 3.9%. Similar clinical outcomes were reported for both rheumatoid arthritis (RA) and lymphoma (LP) protocols, although less relapse was seen with RA protocol. 5 patients (62.5%) achieved remission with IVIG that was sustained without side effects. But these patients were on IVIG at the time of reporting, hence a true relapse could not be reported. When RTX and IVIG are used in combination, the outcomes depend on the order in which they are used. No relapse or infection was seen when RTX was used was first followed by IVIG, and relapse was reported when RTX was used after IVIG [21]. The relapse rate is thought to be related to the duration of follow-up, as noticed in a French study of PV patient treated with RTX [22]. It is difficult to ascertain the etiology of new onset ABD, but one can assume the causative agent by excluding as many known etiologies as possible by taking a detailed history and reviewing patient's information. We understand and are aware of the hesitation surrounding vaccination against Covid-19 virus, we simply aim to add to the current literature on the possible adverse outcomes related vaccination Covid-19, and their management.

Conclusion

Administration of m-RNA vaccination against Covid-19 virus may be associated with new onset pemphigus. High index of suspicion and thorough history along with diagnostic investigation in the presence of appropriate clinical presentation is required to establish the diagnosis. Skin biopsy at the earliest, establishing with a dermatologist and initiation of treatment improve the outcome.

Author's Contributions

Wajiha Ali: Data collection, literature review and drafting the manuscript.

Kanza Ahmed: Case description, drafting the manuscript.

Lal Muhammad: Contributed to discussion, review and editing and referencing.

Genadij Sienkiewicz: Conception, review and editing of literature and case description.

Yasir Ahmed: Primary and corresponding author. Supervised the entire process, from conception to finalizing the draft. Literature search, review and editing and final draft for publication.

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