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Case Report

New onset bullous pemphigoid after covid-19 inactivated virus vaccination: A case report

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Abstract Bullous pemphigoid (BP) is an autoimmune bullous disease caused by circulating immunoglobulins G (IgG) against hemidesmosome antigens commonly found in elderly patients. Pemphigoid cases have been reported in association with vaccination. Cases of subepidermal blistering eruptions including BP had also been reported after COVID-19 vaccination. Here we report a case of an elderly woman who developed BP after receiving SARS-CoV-2 inactivated virus vaccine. She was presented to our hospital with a pruritic blistering eruption which started 10 days after her second dose of SARS-CoV-2 inactivated virus vaccine. She had a history of pruritic redness skin lesions on her arms and legs that appeared seven days after her first dose of vaccine. Histopathology and direct immunofluorescence examination were suggesting BP. Symptoms were improved after oral and topical corticosteroid treatment. The timeline of vaccination and appearance of blistering skin lesions suggesting possible association between BP and COVID-19 vaccination. We should be aware that the onset or flare-up of BP can occur after vaccination in the elderly.

Key words
Bullous pemphigoid; Covid-19 vaccination; Inactivated virus; SARS-CoV-2.

Introduction

Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disease typically affects the elderly. BP is characterized by appearance of tense blisters and the presense of circulating immunoglobulins G (IgG) against hemidesmosome antigens, the BP antigen 180 (BP180 or BPAg2) or the BP antigen 230 (BP230 or BPAg1) or both.[1] The presence of BP autoantibodies leads to complement activation, mast cells degranulation, recruitment of eosinophils, neutrophils and release of proteolytic enzymes resulting in damage of dermal-epidermal junction and subepidermal blistering.[2] Several trigger factors have been reported for the occurence or exacerbation of the disease such as drugs, physical factors, vaccines, viral infections, transplantations, and others.[3]

Pemphigoid cases have been reported in association with various vaccination.[4] During COVID-19 pandemic, several vaccines have been developed to give protections against the virus. There are several types of vaccine available, the mRNA (manufactured by Moderna and BioNTech/ Pfizer), inactivated virus (Sinovac, Sinopharm), viral vector (Oxford/ AstraZeneca, Gamaleya, Janssen/ Johnson&Johnson, CanSino), and protein subunit (Novavax).[5] In the meantime, cases of subepidermal blistering eruptions had also been reported after the mRNA vaccine of COVID-19.[6,7] Here we report a case of an elderly woman who developed BP after receiving the second dose of inactivated virus vaccine of COVID-19

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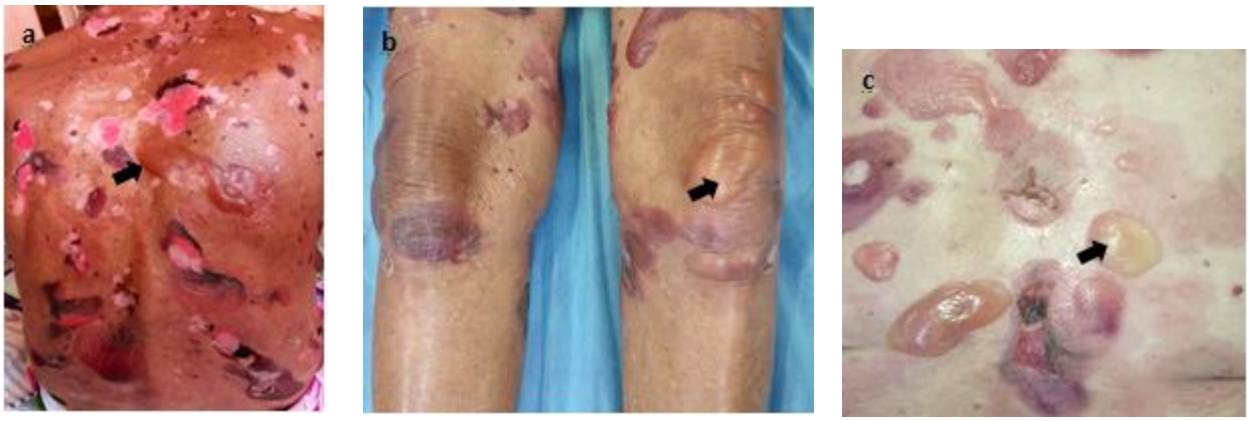

Figure 1 (a-c) Multiple tense bullae (black arrow) on erythematous patches over patient's back, legs, and chest.

Figure 1 (d) Buccal erosions (black arrow) and coated tongue.

which was the only available vaccine in Indonesia at the time of this case.

Case report

An 88-years-old, otherwise healthy woman was presented to our Dermatologic Department with pruritic blistering eruption for three months which started after her second dose of SARS-CoV-2 inactivated virus vaccine (Sinovac). She had a history of pruritic skin redness on her arms and legs that appeared seven days after her first dose of vaccine and resolved after medication. Ten days after her second dose of vaccine, which was administrated one month after the first dose, the same pruritic skin redness appeared on her arms and legs. On the redness patch, some tense blisters appeared. The blisters continued to increase in number, became generalized and highly pruritic for the next three months. Some of the blisters had ruptured into painful erosions. There were several blisters in her oral mucosa causing difficulty in swallowing dan reduced nutrition intake. No other systemic symptoms was found. At presentation, the patient had multiple tense bullae on erythematous patches, and some had ruptured into erosions over her face, neck, chest, abdomen, back, both arms, hands, legs, and feet. **(Figure 1a-c)** On her oral mucosa, there were some erosions and erythematous lesions **(Figure 1d)**.

Her routine blood tests showed increased eosinophils, low lymphocytes, and hyponatremia. A biopsy taken from one of the arm lesions revealed spongiotic epidermis and subepidermal cleft contained lymphocytes. The dermis is edema with a superficial dermal inflammatory infiltrate consisting of eosinophils and lymphocytes. Direct immunofluorescence from perilesional skin showed a linear deposit of IgG and C3 on dermo-epidermal junction. All these findings supported the diagnosis of bullous pemphigoid.

The patient was prescribed oral methylprednisolone equivalent to prednisone 0.9 mg/kg/day, topical desoximetasone ointment twice daily, wound care, and oral care. The oral steroid was tapered off over two months in conjuction with topical treatment and she was

asymptomatic with no new blisters present, leaving only post-inflammatory hypopigmentation.

Discussion

The reported case is a presentation of BP, the most common form of autoimmune subepidermal blistering in the elderly. We acknowledge that the possible differential diagnosis of this disease is bullous pemphigoid-like epidermolysis bullosa acquisita (EBA). However considering the epidemiology of bullous disease in the elderly and the histological features of eosinophilic-predominate infiltrate, we take BP as the working diagnosis. Our patient showed mucosal involvement which is usually seen in relatively few cases of BP. Oral cavity is the most frequently involved mucous membrane. Mucosal lesions can appear before, after, or simultaneously with skin lesions. It is important to identify the presence of mucosal lesions since it can cause more suffering and require prompt treatment.[8]

Several cases of BP after various vaccination such as measles, varicella-zoster, influenza, hepatitis B, and human papillomavirus vaccines have been reported. Kasperkiewicz[4] in a systematic review reported 28 cases of autoimmune bullous disease (AIBD) after vaccination and 14 among them were diagnosed as BP. The manifestations of AIBD occurred between one day and three months after vaccination.[4] New cases or flare-ups of BP after COVID-19 vaccination have been reported. Tomayko *et al*.[6] reported 12 cases of new-onset subepidermal blistering eruptions including 8 cases of BP after receiving the first or second dose of SARS-CoV-2 mRNA vaccine (Moderna/Pfizer). Damiani *et al.*[7] reported three cases of BP flares after the SARS-CoV-2 mRNA vaccine (Moderna/Pfizer).

Immune-mediated disease arises from a variety of different sources: environmental, genetic, hormonal, and immune defects, which may be termed the "mosaic of autoimmunity".[9] Infectious agents are considered to be the most common triggers of autoimmunity. Vaccines that contain antigens from infectious agents might induce autoimmunity by similar mechanisms such as molecular mimicry, epitope spreading, and bystander activation.[9,10]

Molecular mimicry describes the structural similarity between self and non-self-epitopes, which trigger activation of cross-reactive B and/or T cells.[10,11] Epitope spreading is a secondary autoimmune response generated after a release of neo-self-antigens caused by inflammation.[10] These new antigens may derive from the incorporation of cell membrane fragments into the envelope of the virus. A virus may insert, expose, modify, or release hidden antigens.[9] Bystander activation is a heterologous activation of non-antigen-specific lymphocytes. This activation is mediated by indirect signals that favor an inflammatory milieu such as ligands of co-signaling receptors, cytokines, chemokines, pathogen-associated molecular patterns, and extracellular vesicles with microbial particles.[10]

The occurence of BP after COVID-19 vaccination raises a question of whether this vaccine might play a role in the initiation of the disease. However, since pemphigoid is common in the elderly, the possibility of coincidence can not be excluded.[6] The latency period ranges from one day to one month after vaccination. The exact mechanism by which a vaccine induced BP is not well understood since there is no known similarities between the vaccine structure and the basement membrane antigen.[12] It is proposed that vaccination might unmask the

individuals who had underlying subclinical BP or immunology predisposition.

The presence of anti-basement membrane antibodies in patients without clinical pemphigoid has been reported which further supports the presence of subclinical pemphigoid.[13] In those with the rapid development of bullae, transient immune activation induced the existing subclinical autoreactivity, while those with delayed manifestation developed a new cutaneous response.[6] Adult pemphigoid cases after vaccination were mainly reported in the elderly. Aging-related immunosenescence may cause a failure of self-tolerance and increase the risk of autoimmune disease.[14]

SARS-CoV-2 vaccine manufactured by Sinovac is an inactivated viral vaccine containing aluminum hydroxide adjuvant. The SARS-CoV-2 strain CN2 was extracted from bronchoalveolar lavage of a patient in Wuhan, cultured in Vero cells, harvested, inactivated, and absorbed into aluminum hydroxide.[15] Various adjuvants are added to a vaccine to increase the immune response to specific antigens and are hypothesized to have a role in the development of autoimmune disease. However, a causal relationship between adjuvants and autoimmune disease is difficult to prove.[16]

In our patient, BP developed after ten days of second dose vaccine administration. She had a history of the erythematous patch after the first dose which might be the non-bullous phase of BP or manifestation of other cutaneous diseases. In approximately 20% of BP patients, nonspecific skin lesions without skin blistering is the only sign at the time of diagnosis.[1] This was followed by an eruption of pruritic skin blistering after the second dose of vaccine. Our patient's symptoms were improved after oral and topical corticosteroid treatment for two months. Previous report of new-onset BP and flare of previous BP after first dose or second dose of inactivated SARS-CoV-2 vaccine has been published.[17] The timeline of vaccine administration and skin lesions appearance supports a possible relationship between SARS-CoV-2 inactivated virus vaccine and BP. Currently, the data on association of BP and COVID-19 vaccine is lacking, therefore, further studies are required to confirm this possibility.

Conclusion

In conclusion, we reported an elderly BP case that developed after a second dose of SARS-CoV-2 inactivated virus vaccine suggesting a possible association. We should be aware that the onset or flare-up of BP can occur after vaccination in the elderly.

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