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# Bullous pemphigoid triggered by swine flu vaccination: case report and review of vaccine triggered pemphigoid

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## Abstract

**Background:** Bullous pemphigoid (BP) is an acquired autoimmune blistering disease mainly affecting the elderly. Recent reports have shown an association with pre-existing neurodegenerative diseases. Triggers including diseases, medications and vaccination have been reported although in most patients no clear trigger is identified.

**Main observations:** We report a case of atypical bullous pemphigoid which was strongly suspected to have been triggered by the swine flu vaccination. This is the first reported case of pemphigoid triggered by this vaccine.

**Conclusions:** The use of the swine flu vaccine is likely to increase in the future and it is important that clinicians are aware of the potential adverse effect of swine flu vaccination induced bullous pemphigoid. (*J Dermatol Case Rep*. 2011; 5(4): 74-76)

## Introduction

Bullous pemphigoid is an autoimmune subepithelial blistering disease characterised by tense blisters and positive immunofluoresence with linear IgG and C3 at the basement membrane.[1-3] An association with neurodegenerative diseases has been demonstrated but the precise triggers for the disease remain unclear.[2] Previous reports have suggested that vaccination can be a trigger for pemphigoid and this report describes the first known case of swine flu triggered bullous pemphigoid.

## Case Report

An 81-year-old man presented with a 2-week history of a widespread erythematous rash and blistering at the site of a vaccination. Fourteen days prior to the onset of the rash he had received a swine flu vaccination from his family doctor administered into the left upper arm (Pandemrix, GlaxoSmithKline). He was previously well with a past history of psoriasis, controlled by coal tar and emollients, and diet controlled diabetes. The rash had begun at the injection site and had been associated with small localised blisters. The rash then spread from the left upper arm to the abdomen, back and upper thighs. Skin tenderness and itching were reported. Due to the severity of the rash the patient was admitted for investigation. Over the subsequent 7 days he began to develop blisters within the areas of skin affected by the rash. Physical examination on admission revealed a dark erythematous, slightly urticated eruption on the trunk and thighs. Affected areas on the thighs, forearms and lower back were annular and targetoid in places. Blisters, which were initially found at the left arm only then appeared more widely over the following one week (Fig. 1). Mucous membranes were not involved. The appearances led to an initial suspicion of bullous erythema multiforme. Subsequent investigations did not support this and were entirely consistent with bullous pemphgoid. Both direct and indirect immunofluoresence were positive with linear IgG and C3. Indirect immunofluorescence on salt split skin demonstrated IgG staining to the roof of the blister. A biopsy for histology, taken at admission from an area of urticated erythema showed spongiosis with numerous eosinophils

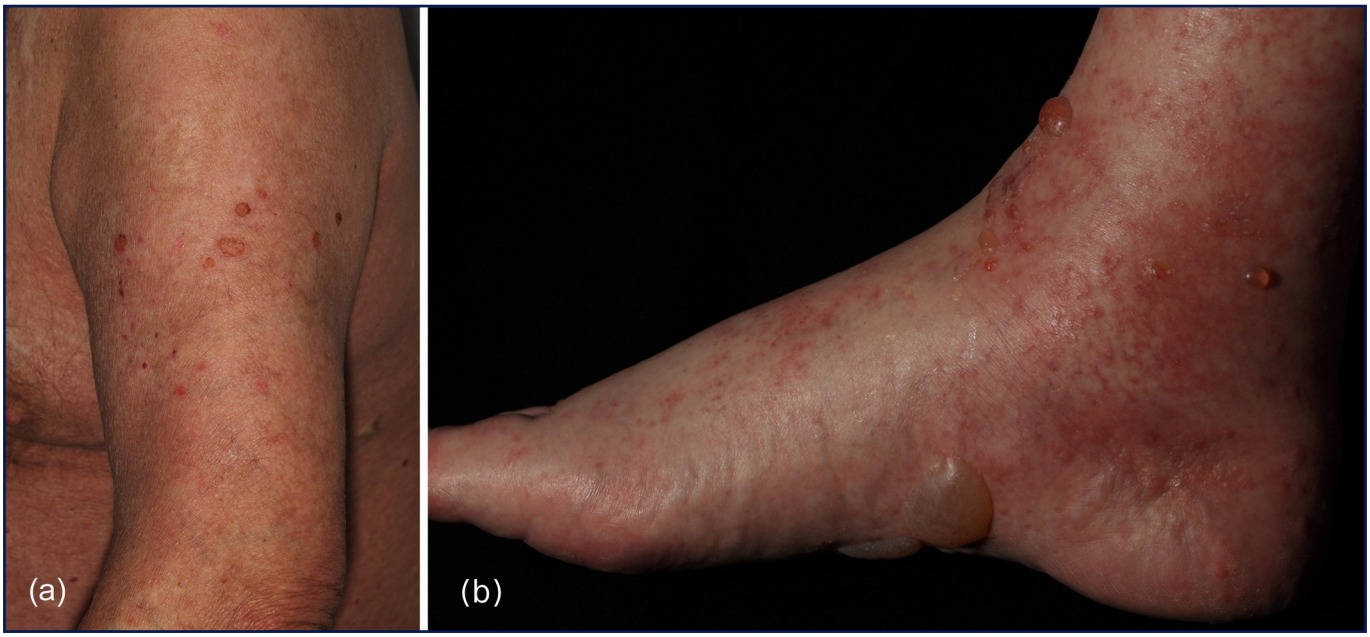


**Figure 1**
*The urticated eruption with blistering began at the vaccine injection site at the left arm deltoid area (a). Later on in the course of the disease, blistering occurred at widespread locations including on the feet (b).*

consistent with pre bullous pemphigoid (Fig. 2). There were no dyskeratotic cells or other signs to suggest erythema multiforme.

Treatment with oral prednisolone 40 mg daily and topical dermovate was commenced with a good response. The admission was complicated by an episode of lower respiratory tract infection requiring antibiotics and supportive therapy. The patient was blister free at discharge on day 18 and treatment was gradually reduced over the following months in outpatient clinic with no new lesions developing over this time. The patient has not received any further swine flu or seasonal flu vaccinations.

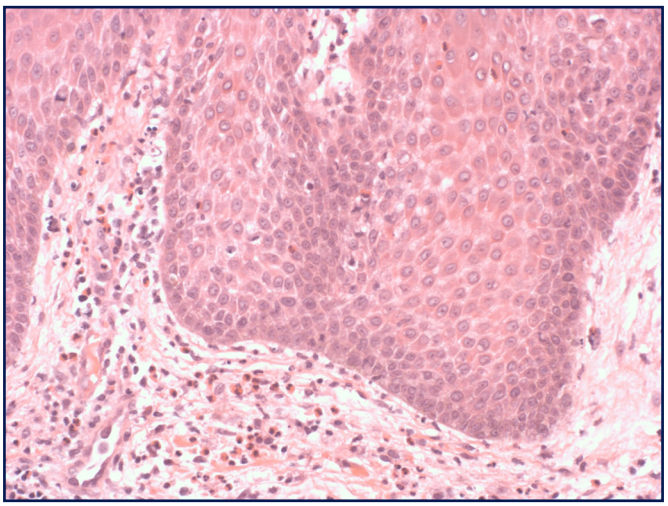

**Figure 2**
*A section (200) from biopsy taken at admission from an area of urticated erythema. Spongiosis with numerous eosinophils is seen consistent with pre bullous pemphigoid. No dyskeratotic cells or other signs to suggest erythema multiforme are noted in the section.*

## Discussion

At a molecular level, BP is characterised by IgG autoantibodies targeting BP antigens. The two BP antigens are located in the hemidesmosome, an adhesion complex attaching epithelial cells to adjacent basement membrane. BPAg1 (230 Kda) is located intracellularly and BPAg2 (160-180 Kda) or type XV11 collagen, is a transmembrane protein.[4] It is proposed that bound IgG activates complement, recruiting immune mediators causing inflammation that disrupts dermal-epidermal protein binding. It has also been shown that IgG may act directly on the function of hemidesmosomes, causing blister formation.[5]

Whether certain individuals are genetically predisposed to pemphigoid remains unclear as do the triggers which determine why pemphgoid begins at a specific time. An association between BP and neurological diseases; namely Dementia, Multiple Sclerosis and Parkinson's Disease is increasingly recognised.[2,6] Neural crest is the origin of both skin and nervous system, helping to explain the finding of a neuronal isoform of the epithelial antigen (BPAg1) in a mouse model.[7] There are convincing temporal relationships between the onset for neurological disease and BP in various case reports and this relationship has been confirmed in a larger population based.[2] This suggests that pathological alterations in the nervous system, could lead to the neuronal isoform triggering an autoimmune reaction, involving cross-reactions with the epithelial isoform, and the development of pemphgoid. In other cases it is suggested that insults to the basement membrane, such as trauma, inflammation and UV light could enhance the antigenicity of BP antigens with the subsequent loss of immune tolerance.[8,9]

Although the pathological relationship remains obscure, it is possible that a similar immune response is responsible for BP following vaccination. The process of vaccination,

involving inflammation within the skin, could lead to disruption of the basement membrane architecture with subsequent generation of anti basement membrane specific antibodies.[10] It is unlikely that the vaccines themselves and the subsequent antibody response to the vaccine would explain the process as there are no similarities between the structure of the implicated vaccines and the relevant basement membrane proteins. One important question however is why reported cases of vaccine triggered pemphigoid are rare when vaccination is so widespread.[11] One suggestion is that vaccination may trigger a heightened autoimmune response, in patients with the relevant immunological predisposition or with subclinical BP. The presence of anti basement membrane antibodies has been reported in patients without clinical pemphigoid supporting the concept of sub clinical pemphigoid.[10-12]

There have been less than 20 previously reported cases of vaccine triggered bullous pemphigoid, the majority involving flu vaccination. Venning *et al* reported a 1 month latency period from the time of vaccination to the onset on the first lesion and suggested that this was an appropriate duration for the induction of anti-basement membrane antibodies.[9] Other reports have suggested a latency of between 1 day to 1 month before flu vaccine induced pemphigoid. Interestingly in the 4 cases of infantile BP shorter latency periods have been reported. Hafiji *et al*[13] reported a 3 month old boy who had received his first set of childhood vaccinations (diphtheria, pertussis, polio, Haemophilus influenza B and pneumococcus) 8 days prior to the onset of bullous pemphigoid. Baykal *et al*[8] reported a similar case in a 3.5 month old boy who developed blisters 24h after his first set of childhood vaccinations (diphtheria, pertussis, polio, tetanus). Histology and IF showed features of bullous pemphigoid although evidence of staph aureus infection was also detected.[8,13] In addition to vaccines, over 30 different systemic medications have been suggested to have a role in triggering pemphigoid.[14] A minority of the implicated drugs have been confirmed as genuine triggers by re-challenge.

This case is the first report of bullous pemphigoid triggered by swine flu vaccination. The patient refused to have further swine flu vaccinations, so it is not possible to obtain absolute confirmation by re-challenge. However, the clinical details and time course are highly suggestive and the case is consistent with previous reports of vaccine induced pemphigoid, some of which have included re-challenge. Psoriasis has been reported as being associated with pemphigoid and pre-existing psoriasis may have been relevant in this case. The unusual targetoid rash which preceded the blistering also distinguishes this case from most other typical presentations of pemphigoid. The accumulating evidence suggests that vaccination can be a rare trigger for bullous pemphigoid and that swine flu vaccine needs to be added to the list of vaccine triggers.

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