

Pemphigus Foliaceus with Epidermal Detachment: Adverse Events from Patch Testing

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Uncommon adverse reactions to patch testing have been reported, but few cases have shown patch testing to be a potential contraindication. We report a patient with known pemphigus foliaceus who had significant epidermal detachment of normal skin during the removal of patch-testing tape.

Case Report

A 66-year-old man presented with a 3-month history of a crusting eruption that abruptly spread in a cephalocaudal manner (Fig 1). Histologic examination of two biopsy specimens from lesions on the patient's back revealed focal acantholysis in the granular and superficial spinous zone of the epidermis. Direct immunofluorescence illustrated immunoglobulin G(+) and C3(+) staining on the cell surface of keratinocytes. The results of both histologic and immunofluorescence analyses supported the diagnosis of pemphigus foliaceus. Appropriate laboratory studies were performed, and the patient was started on azathioprine and prednisone. After 2 months of treatment, his pemphigus was improved by 90 to 95%. However, a significant periorbital crusting eruption persisted despite continual stable doses of azathioprine (150 mg per day) and prednisone (10 mg per day) (Fig 2). At this time, contact dermatitis was suspected. The patient was instructed to discontinue any topical antibiotics and was referred for patch testing.

On evaluation in the contact dermatitis clinic, the patient's history revealed an array of topical preparations applied over a 6-month period for his periorbital dermatitis, including white petrolatum, pimecrolimus, desonide, bacitracin, mupirocin, and ocular lubricant eye ointment. However, avoidance of topical antibiotics had not improved his eruption. Patch testing was performed with a standard series fashioned after the Mayo Clinic Contact Dermatitis Group standard allergen tray. Finn Chambers

(Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway) and Beiersdorf Cover-Roll (Beiersdorf AG, Hamburg, Germany) were used. In addition, we prescribed levofloxacin on the basis of prior culture results taken from the periorbital eruption that grew coagulase-negative *Staphylococcus epidermidis*, *Corynebacterium* spp, *Moraxella catarrhalis*, and *Proteus penneri*. On day 3, when his patches were removed, the patient had striking yet asymptomatic epidermal sloughing in the areas where the tape had been placed (Fig 3). On day 5, his patch-test readings were negative for all allergens tested, and his eyes had significantly improved with the levofloxacin. His treatment consisted of application of wet dressings with diluted acetic acid to remove yellow exudate from around his eyes, application of white petroleum jelly and Telfa wound dressings (Tyco Healthcare/Kendall, Mansfield, MA) to his back, and continuation of his stable doses of azathioprine and prednisone for his pemphigus. The sites of epidermal detachment healed. Because of the improvement after oral antibiotics were administered and because of negative patch-test results, the periorbital involvement was felt to be due to the bacterial infection rather than a topical allergen.

Discussion

We present this case to (1) alert clinicians to potential complications when patch-testing patients with pemphigus and other immunobullous disorders and (2) review documented adverse events or complications subsequent to patch testing.

Potential Complications in Pemphigus Patients

Our case involves a 66-year-old man with known pemphigus foliaceus who experienced epidermal detachment

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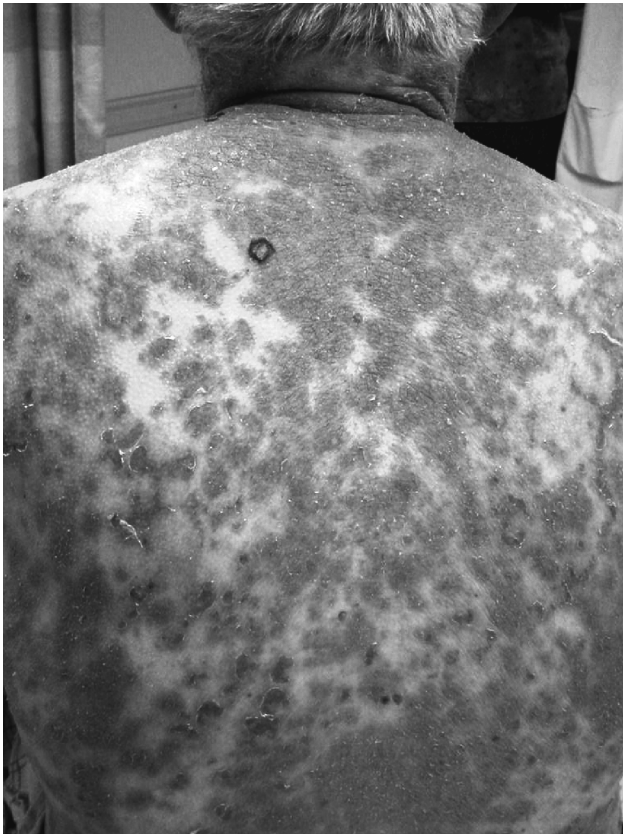


Figure 1. Photograph of the patient's back, showing a crusting eruption that abruptly spread in a cephalocaudal manner.

of clinically normal skin during the removal of adhesive tape used for patch testing. Pemphigus foliaceus (PF) is a chronic autoimmune vesiculobullous disease of the skin and is characterized by a loss of cohesion between epider-



Figure 2. Photograph of patient's face showing persistent periorbital crusting despite adequate control of his pemphigus and topical care.



Figure 3. Photograph of patient's back immediately after removal of patch tests on day 3, showing asymptomatic epidermal sloughing.

mal cells (acantholysis) in the upper parts of the epidermis. The acantholytic process is induced by immunoglobulin G (IgG) autoantibodies against desmoglein 1, a 160 kD glycoprotein of desmosomes (cell adhesion molecules) located primarily in the granular layer of the epidermis. Characteristic PF lesions are superficial scaly crusted erosions on an erythematous base; they normally appear first on the scalp and face in a seborrheic pattern and later involve the chest and back. In contrast to pemphigus vulgaris, PF does not usually involve the mucous membranes and is associated with less morbidity and lower mortality. Treatment involves topical corticosteroids and possibly immunosuppressants such as azathioprine, mycophenolate mofetil, dapsone, cyclophosphamide, and prednisone.

PF is likely a convergence of predisposing genetic factors (such as human leukocyte antigens) with environmental triggers. Several exogenous factors such as medications (most common), viral infections, malignancies, diet, emotional stress, and exposure to ultraviolet and ionizing radiation have been shown to activate or exacerbate pemphigus.¹ Similarly, in numerous cases, contact dermatitis (irritant or allergic) is reported to have aggravated or induced pemphigus by triggering intraepidermal acantholysis.²⁻⁴ In fact, "contact pemphigus" is now recognized by some as a subgroup of induced pemphigus.³⁻⁵ In 1998, Tsankov and colleagues described a 63-year-old woman who experienced contact pemphigus induced by the pesticide dihydrodiphenyltrichloroethane (DDT).⁴ Rudolph and colleagues described a patient who had Hailey-Hailey disease (benign familial chronic pemphigus) provoked by contact irritation from Colognette Zitrusfrisch refreshing tissue.⁶ Other substances shown to have caused contact pemphigus include various pesticides,³ 1,3-dichloropropene

(a soil fumigant),³ benzoin tincture,⁷ basochrom (basic chromium sulfate),³ and a triple antibiotic treatment containing polymyxin B sulfate, neomycin, and bacitracin.²

As discussed above, contact dermatitis has been implicated in the induction or exacerbation of pemphigus. The exact mechanism of this is unknown. However, the mechanism may be analogous to that of other inducers, such as penicillamine and captopril, whose chemical structure contains a thiol group (-SH) that may interact with the sulfhydryl group in desmoglein 1. This interaction has been hypothesized either to cause desmosomal adhesion dysfunction with acantholysis⁸ or to increase the antigenicity of the molecules, with subsequent autoantibody formation.⁹

Although it is prudent to counsel pemphigus patients to avoid excessive exposure to common allergens, contact dermatitis may not be easily characterized without patch testing. Recommendations concerning the benefits and risks associated with patch-testing pemphigus patients who have a suspected contact dermatitis are lacking in the literature. In 1996, Voza and colleagues described a 23-year-old patient who had contact pemphigus induced by a soil fumigant and who was patch-tested without complications.³ Rudolph and colleagues reported on a pemphigus patient who was patch-tested and who experienced an "unusual irritation reaction" characterized by erythema and purpura on day 3; however, the testing did not cause significant adverse events.⁶ In contrast, in 1992, Peppiat and colleagues described a patient with Hailey-Hailey disease (benign familial chronic pemphigus) who had "severe local blistering" during patch testing.¹⁰ In 2003, Guin reported the case of a woman with pemphigus foliaceus precipitated by an allergic contact dermatitis. The patient would have benefited from patch testing but did not undergo the testing because of the risk of adverse events.² In the report, Guin states that the "risk-benefit ratio should be considered before patch testing patients with active or recently active pemphigus."²

Unlike the patients in the cases reported by Peppiat and colleagues and by Guin, our patient had a persistent localized crusting around the eyes, without any other involvement of his skin. The risk-to-benefit ratio was considered and discussed with the patient and his family, and we felt it was reasonable to perform patch tests. On day 3 of testing, epidermal sloughing occurred as the tape was being removed. Biopsy and direct immunofluorescence of the affected skin to localize the epidermal split were not performed at this time. However, there was no pinpoint bleeding to imply superficial dermal involvement. In retrospect, we recognize that localization of the epidermal split would have enhanced this discussion. Furthermore,

the effect of the patient's low maintenance dose of oral prednisone on this event is secondary. The catabolic effects of systemic corticosteroids are primarily on the dermis, not on the epidermis.

Another variable to be considered with our patient was his persistent periorbital dermatitis with impetiginization. It has been shown that some dermatoses, like atopic dermatitis, can develop a generalized inflammatory T-cell activation and exacerbation through a bacterial superantigen effect, most notably from *Staphylococcus aureus*. For instance, *S. aureus* exfoliatin can cleave desmoglein 1. However, the bacteria cultured from our patient's periorbital area were bacteria that have not been associated with superantigens.

Therefore, we postulate that this patient had subclinical primary acantholysis from his pemphigus foliaceus owing to poor cell-to-cell adhesion, causing the epidermal sloughing during tape removal and unrelated to the allergens in the patches, the periorbital bacterial infection, or the low-dose oral prednisone. We thus advise clinicians to use caution when using adhesives on skin with inherent fragility (such as that seen in cases of pemphigus or pemphigoid) to avoid our pitfall and to avoid potentially inciting disease progression.

Review of Adverse Events Reported in Literature

The second goal of our case presentation is to briefly review various documented adverse events resulting from patch testing. We searched the literature to obtain further information regarding reported reactions associated with patch testing.

Common adverse reactions to patch testing include subjective complaints of itching on the back, fatigue, malaise, and light-headedness, and objective complaints of eczematous flare-ups.^{11,12} In 2000, Inerot and Moller performed a pilot questionnaire study to examine the subjective complaints as well as widespread skin reactions associated with patch testing.¹² Their results showed that the total incidence of side effects during patch testing was 5%. Eczematous flare-ups and transient fever were the most common side effects. Other complaints during testing included itching on the back and at the site of dermatitis, rash, headache, dizziness, sweating, fatigue, vomiting, and abdominal pain.¹² Inerot and Moller also reported that the number of skin reactions and subjective complaints was greater on the day the patch tests were applied than on the day of reading.

An additional common adverse reaction to patch testing is excited skin syndrome (ESS). Also known as "angry back," ESS is a hyperirritability of the skin during patch

testing and is characterized by “multiple positive test results, associated with one or more strongly positive tests, which are not all reproduced when the patient is tested afterward.”¹³ In a study to determine the frequency of ESS among patients patch-tested for suspected allergic contact dermatitis, Duarte and colleagues found that ESS recurred in 6.2% of patients when they were retested.¹³ In an earlier study, Duarte and colleagues found that 2.2% of patients who were patch-tested developed ESS and that there was a loss rate of 63.5% when the patients were retested.¹⁴ They also discovered that patients who developed ESS had contact dermatitis for a longer time than did patients who did not develop ESS and that positioning the allergens closer together on the patient’s back can lead to a higher incidence of ESS and thereby increase the number of false-positive readings.¹³ When the allergens tested were placed closer together, the patient may have had a greater number of positive readings owing to the true positive reactions inducing and intensifying inflammatory reactions in surrounding areas.¹³

Adverse reactions that are more serious but rare have also been reported. In 2000, Perfetti and colleagues reported the case of a woman who experienced an anaphylactoid reaction following patch testing with ammonium persulfate.¹⁵ Two cases of patients’ developing erythema multiforme secondary to patch testing are also documented.^{16,17} Other adverse reactions reported include necrotizing cellulitis,¹⁸ generalized pustular reactions,¹⁹ and superficial epidermal necrosis due to a patch-test skin marker containing fuchsin-silver nitrate.²⁰

In conclusion, several common and rare adverse side effects are associated with patch testing. Our case report demonstrates the importance of recognizing the role of contact dermatitis in the induction or exacerbation of pemphigus and shows that epidermal detachment from adhesives is a potential complication of patch-testing patients who have pemphigus. Because of the possibility of adverse events, we advise clinicians to use caution when patch-testing patients who have pemphigus, other autoimmune skin disorders, or skin conditions involving epidermal detachment, and we propose that immunobullous diseases are possible contraindications to patch testing.

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