# Pesticide-Associated Pemphigus Vulgaris

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*We present a 40-year-old man with occupation-induced pemphigus vulgaris (PV). He developed PV within days of a one-time heavy exposure to fumes of burning glyphosate, a broad-spectrum nonselective pesticide. This exposure suggests acute cutaneous contact as a stimulus in the development of his pemphigus. While the patient initially required mycophenolate mofetil and prednisone therapy, he has since eliminated contact with pesticides and has been successfully tapered off systemic medication. We discuss the case and review concepts of inducible PV by pesticides and physical cutaneous injury.*

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## Case Report

A 40-year-old man presented to our clinic with a 2-month history of recurrent blisters on his trunk and extremities. The blisters appeared within days of a one-time heavy exposure to fumes of burning glyphosate, a broad-spectrum pesticide. He was seen in an emergency department 2 days after the fume exposure, with flaccid bullae noted on his chest, back, abdomen, and extremities (Figures 1 and 2). Treatment with short-term minocycline hydrochloride for possible bullous impetigo did not provide relief, and on presentation to our clinic, he remained afflicted with recurrent blisters on his extremities. Punch biopsy specimens were obtained for both hematoxylin and eosin staining (Figure 3) and direct immunofluorescence. Microscopically, a cell-poor bulla with suprabasal acantholysis was noted, which differed from the expected histology of bullous impetigo, essentially a subcorneal bulla replete with neutrophils. Direct immunofluorescence revealed IgG deposition in the intercellular regions of the epidermis in a chicken-wire pattern. Clinically and histologically, the diagnosis was pemphigus vulgaris (PV). Description of occupation revealed a 3-year history of farmwork harvesting corn. One of the patient's tasks on the farm included spraying fields with a 41% glyphosate isopropylamine salt pesticide. Disposal of the pesticide drums was accomplished by burning them in an open field. During the most recent drum-burning episode, the patient was directly exposed to the fumes and reported immediate skin irritation. His first blistering lesions presented within days of this exposure to the burning drums, prompting his initial visit to the emergency department.

## Comment

Pemphigus vulgaris is a blistering dermatosis characterized by short-lived bullae that quickly rupture and progress to crusted erosions.[1] The bullae are caused by acantholysis resulting from autoantibodies directed against desmogleins (ie, epidermal adhesion molecules).[2] The etiology of PV has been considered multifactorial and the pathophysiology autoimmune because of the presence of the antidesmoglein antibodies. As part of a multifactorial etiology, the phenotype of pemphigus often results from environmental triggers acting on a certain genetic predisposition.[3] The idea of exogenous agents inducing pemphigus was first introduced by Degos et al[4] with their report of penicillamine-induced pemphigus in 1969. Environmental agents, some more commonly associated with the development of bullous dermatoses than others, have been summarized.[5] The more commonly implicated triggers include medications, physical agents, infectious agents, and pesticides.[6] Physical agents purported to induce pemphigus include UV radiation, burn injury, and ionizing radiation. Numerous other exogenous factors have been reported to affect the onset or course of bullous dermatoses, including hormones[6]; stress[7]; vaccination[8]; topical medications[9]; thiurams[10]; and the allium group of plants, including onion and garlic.[11,12]

Pesticides are chemicals that kill pests and include herbicides, insecticides, fungicides, and rodenticides.[13] Glyphosate is a broad-spectrum, water-soluble,

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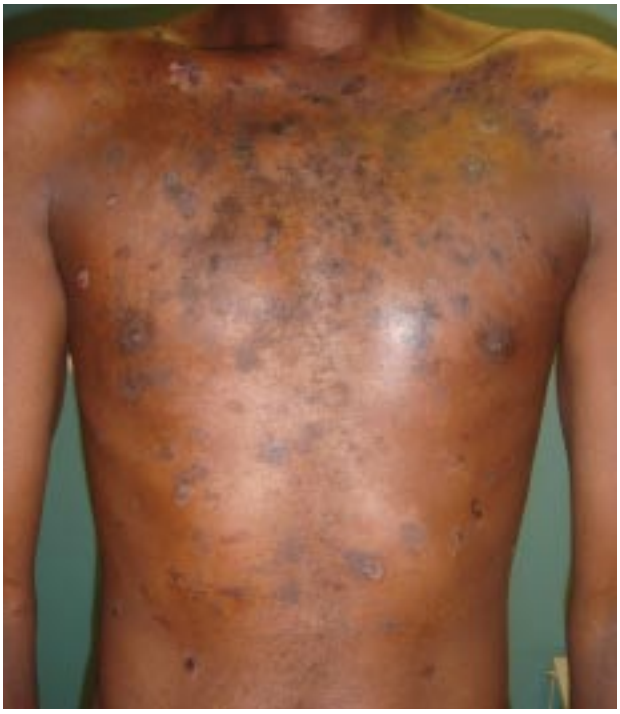

**Figure 1.** Trunk with scattered flaccid bullae and vesicles in various stages of evolution.

nonselective systemic herbicide. It is one of the most widely used pesticides by volume, with 13 to 20 million acres treated with 18.7 million pounds of glyphosate annually.[14] Its most common uses include hay pastures, soybean farms, and cornfields. Most toxicity reports from occupational exposures to glyphosate describe mild eye or skin irritation only.[14]

There is a growing amount of literature reporting the association between pesticides and pemphigus. In one epidemiologic study comparing patients with PV to controls via a physician-administered questionnaire, patients with PV showed a significantly increased rate of exposure to both pesticides ($P<.005$) and gardening materials ($P<.0001$).[15] A similar questionnaire-structured epidemiologic study of 200 Iranian patients with pemphigus also showed an increased rate of pesticide exposure compared with controls.[16] Individual case reports have documented the onset or change in clinical course of pemphigus following exposure to various pesticides, including chlorpyrifos,[17] diazinon,[18] dihydrodiphenyltrichlorethane,[19] and phosphamide.[20]

The etiology of pesticide-induced pemphigus is unknown. Numerous mechanisms for chemically induced autoimmunity have been proposed.[21] Most mechanisms center around the chemical's ability to manipulate antigens, either by creating haptens or by exposing normally sequestered and protected self-antigens to the immune system. The chemical's influence on the immune system itself also has been implicated, causing either widespread inappropriate activation or suppression of inhibitory pathways (eg, suppressor T-cell malfunction). Another mechanism, possibly most germane to the reported case herein, is contact pemphigus.[22] Brenner et al[22] used the sensitization pathophysiology of contact dermatitis to describe the sequence of events seen in contact pemphigus. In this model, the skin is sensitized (induction phase) via chronic low-level exposure to an exogenous substance, which is sometimes followed by an irregularly heavy exposure, leading to some fundamental change in biologic behavior (elicitation phase) that can occur in hours to days. At the time of the elicitation phase, clinically apparent disease is produced—pemphigus.[22] The course of the disease may then be influenced by future exposure to the sensitizing chemical, similar to contact dermatitis.

Our patient had long-term (3 years) exposure to the sensitizing glyphosate pesticide. However, it was not until he was exposed to fumes of burning

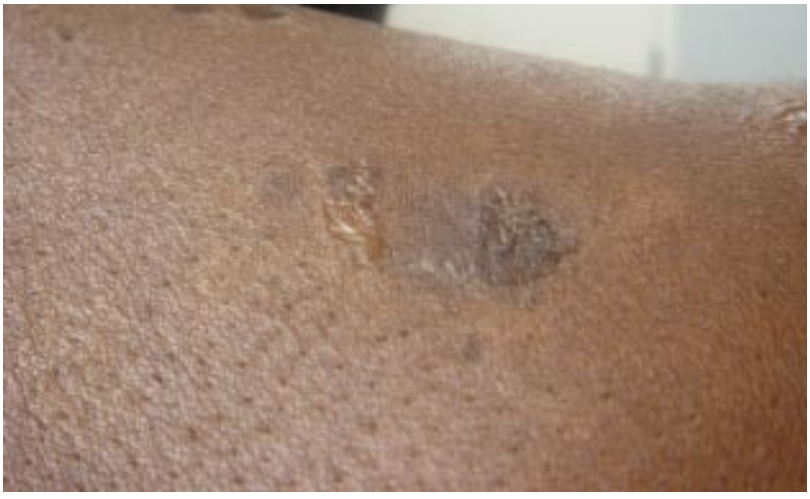

**Figure 2.** Right shoulder with flaccid bullae and healing erosions.

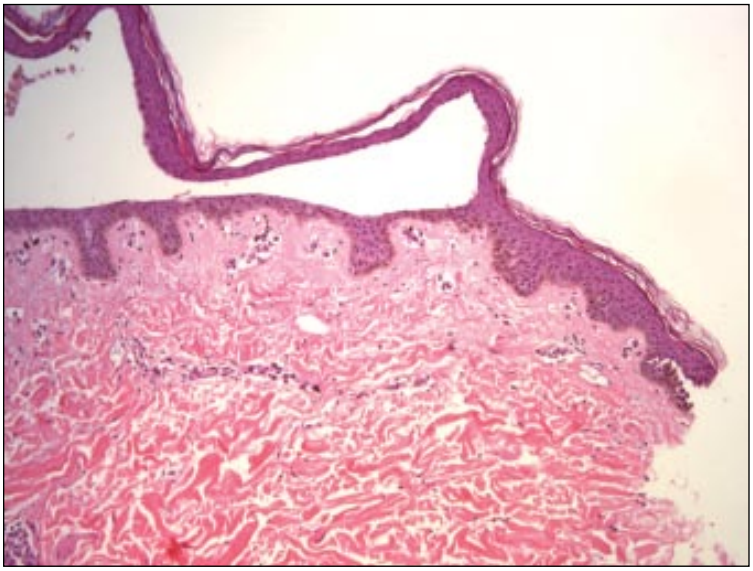

**Figure 3.** Punch biopsy specimen revealed a cell-poor suprabasal bulla (H&E, original magnification ×10). On the right side, there is suprabasal acantholysis, giving the typical tombstone appearance. The left side demonstrates the reepithelialized floor of the bulla.

pesticide that he developed his first blisters within days of contact. This sequence of events is consistent with contact pemphigus. Given a certain genetic predisposition, the patient's chronic low-level pesticide exposure could afford him the opportunity to form antidesmoglein antibodies. Because new antibody formation after the first exposure to an antigen typically takes at least one week,[23] he may have had some amount of autoantibody prior to the acute fume exposure, perhaps at low enough titers to preclude clinical disease.

Glyphosate decomposes on heating, producing toxic gases of nitrogen oxides and phosphorus oxides.[24] Phosphorus oxides, particularly phosphorus pentoxide and diphosphorus pentoxide, while still related to the parent compound, are severe topical and inhalational irritants.[25] It has been hypothesized that a contact irritant may alter the skin structure, exposing cryptic antigens and self-peptides to a prepared immune system,[26] which may amplify antibody production and induce clinically relevant pemphigus. Tan et al[27] proposed a similar model in their report of PV induced by electrical injury. They also noted that in physical cutaneous injury, production of proinflammatory cytokines may further instigate or perpetuate an autoimmune disease such as pemphigus.[27] In our case, the acute irritation could have been the stimulus necessary to push forward expression of the PV phenotype in a patient already exposed to chronic low levels of pesticides. If the T-cell arm was active, having been previously exposed to cryptic epidermal antigens, perhaps a large influx of epitope secondary to cutaneous injury could catalyze and/or perpetuate the antibody response necessary to produce clinically relevant disease. In broader terms, if PV is a disease that may be induced by one or more environmental factors interacting on endogenous (genetic) factors, the clinical expression of PV seems even more likely with additive effects of environmental triggers, in the form of contact sensitization and physical cutaneous injury.

Our patient initially required mycophenolate mofetil 500 mg twice daily and prednisone 10 mg daily. Since changing his occupation (nonagricultural work), with no subsequent exposures to pesticides or toxic cutaneous substances, we have been able to taper him off both medications. He now only requires superpotent topical steroids as needed for disease flares, which have continued to lessen both in severity and frequency.

## Conclusion

We report a patient with occupation-associated PV and review some salient features of inducible pemphigus by cutaneous trauma and pesticides. Environmental factors seem to play a role both in the onset and course of pemphigus. Minimizing exposure to these documented triggers, including pesticides, may benefit the course of disease and minimize the need for systemic immunomodulatory medications.

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