# Pemphigus Vulgaris Induced by Electrical Injury

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GOAL

To understand pemphigus vulgaris (PV) to better treat patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the histology of PV.
2. Discuss the effects of cutaneous electrical injury.
3. Explain the pathogenesis of PV following electrical injury.

CME Test on page 175.

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*Pemphigus refers to a group of autoimmune blistering diseases that affect the skin and mucous membranes. Pemphigus may be induced following exposure to various exogenous agents, including thermal burns, drugs, infectious agents, and neoplasms, as well as UV, ionizing, and x-ray irradiation. We report a case of a 28-year-old man with pemphigus vulgaris (PV) induced by a severe electrical injury. Approximately one month after the electrical injury, he began to develop recurrent painful oral ulcers; one year later, he began to develop cutaneous bullae. Results of a histopathologic examination and immunofluorescence studies were diagnostic of PV. The primary mechanisms of high-voltage electrical injury involve electroporation, electroconformational protein denaturation, and both joule and dielectric heating. Cutaneous electrical injury ultimately results in the destruction of cells with release of their cellular constituents. Through these mechanisms, desmoglein 3 (Dsg3) may be released and become available to the*

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*immune system, which potentially leads to an autoantibody response and the subsequent development of PV.*

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Pemphigus refers to a group of autoimmune blistering diseases that affect the skin and the mucous membranes. Pemphigus vulgaris (PV) is characterized histologically by suprabasal intraepidermal blisters secondary to acantholysis and immunopathologically by the finding of in vivo bound and circulating immunoglobulin G (IgG) directed against the keratinocyte cell surface. The primary antigen in PV is desmoglein 3 (Dsg3), a component of keratinocyte desmosomes. The anti-Dsg3 antibodies are pathogenic: they combine with Dsg3 found in cutaneous and mucosal epithelium, which interferes with desmosome function and leads to acantholysis of the epithelial cell layers and clinically apparent cutaneous and mucosal blisters.[1]

Pemphigus may be induced following exposure to various exogenous agents. This heterogeneous group includes physical agents such as thermal burns and UV, ionizing, and x-ray irradiation[2,3]; drugs such as penicillamine, pyritinol, captopril, and rifampicin; and infectious agents such as arbovirus and herpes simplex viruses.[2] The clinical course is variable, ranging from rapid resolution following removal of the inciting agent to persistence of disease.[2]

## CASE REPORT

In September 1995, a 28-year-old man received a severe electrical shock injury when he came within 2 to 3 feet of an electrical line and an electrical arc formed that exposed him to 7620 V of electricity. The arc resulted in an entrance wound on the man's right dorsal hand with an exit wound on the left lateral foot. Initially, he was noted to have "first-degree and second-degree burns" to these areas. In addition to the cutaneous injuries, results of laboratory tests indicated underlying muscle damage, with an elevated serum creatine kinase level of 480 U/L. The following month, he underwent a skin graft to repair the burned area on the left foot.

Approximately one month after the electrical injury, the patient developed a painful hemorrhagic blister on the roof of his mouth. Subsequently, he developed recurrent painful oral ulcers and initially was diagnosed with aphthous stomatitis. In May 1996, he underwent endoscopy and was noted to have esophageal ulcers and esophagitis.

In November 1996, the patient developed bullae on the left forearm. In conjunction with the ulcerations on the buccal mucosa, he clinically was diagnosed with PV. Results of a skin biopsy demonstrated acantholysis and suprabasal bullae formation. Results of direct immunofluorescence studies revealed that IgG antibodies and complement component 3 were deposited in an intracellular pattern throughout the epidermis; and results of indirect immunofluorescence studies demonstrated a high titer of anti-Dsg3 antibodies at 1:640. Results of an HLA typing revealed the patient's HLA type to be HLA-DR10, HLA-DR14(6), and HLA-DR52.

In December 1996, the patient was started on oral prednisone 60 mg/d and halobetasol propionate 0.05% ointment applied several times a day to both the oral and cutaneous lesions. In January 1997, oral azathioprine was started at 100 mg/d as a steroid-sparing agent and subsequently was increased to 150 mg/d in March 1997. In October 1997, he was started on intramuscular gold 50 mg/wk with the intent of ultimately discontinuing the azathioprine. The patient has since had the prednisone tapered and the azathioprine discontinued, and his PV is well controlled with oral prednisone 20 mg/d, intramuscular gold 50 mg/wk, and topical halobetasol propionate ointment intermittently.

## COMMENT

### Overview of Cutaneous Electrical Injury

The epidermis contributes 95% to 99% of the resistance to direct current passage. At low voltages, the epidermis is a highly insulating barrier; however, with voltages greater than approximately 150 V, the epidermis experiences structural breakdown. The cell layers undergo rapid boiling, which results in charring and vaporization of the epidermis. After an electrical current crosses the skin, the current spreads rapidly through internal tissues and results in widespread injury, much of which is internal and may not be apparent clinically.[4]

The primary mechanisms of high voltage electrical injury involve electroporation, electroconformational protein denaturation, and both joule and dielectric heating.[4,5] Other contributors to tissue damage include cell swelling and rupture, cell fusion, cell fission, lipid peroxidation, and shock or acoustic wave disruption of supramolecular structures and tissues.[5] These mechanisms ultimately result in the destruction of cells due to the release of their cellular constituents.

*Electroporation*—Membrane electroporation is the electrically driven formation of aqueous pores in lipid bilayer membranes.[6] These pores are formed randomly in the membrane within milliseconds of exposure to a sufficient electric field. Electroporation increases the permeability of membranes,

which allows the passage of ions and molecules as large as DNA. Electropores may seal spontaneously over a few milliseconds or a few hours; alternatively, electropores may remain open and eventually lead to cell death.[4,7,8] Cellular rupture probably results from the fusion of many pores.[6]

*Electroconformational Protein Denaturation*—As the temperature rises, both the molecular momentum transfer between colliding molecules and the frequency of intermolecular collisions increase. When sufficient momentum is transmitted to folded proteins, the bonds maintaining the protein conformation break, which results in molecular denaturation.[4]

*Joule and Dielectric Heating*—The passage of current through a resistive material leads to heating. Joule heating refers to the heat rise from ionic current, whereas dielectric heating refers to the heat rise from rotating molecular dipoles, such as water, in a high-frequency alternating current electric field. Both of these mechanisms contribute to the thermal component of electrical injuries.[4] The threshold for tissue injury is approximately 42°C: exposure to temperatures beyond this threshold results in macromolecular degeneration, hydration and lysis of cell membranes, and other alterations in cellular metabolism that produce cellular necrosis.[9] Furthermore, tissue cooling mainly is accomplished through blood perfusion[9]; thus, after an electrical injury, the subcutaneous tissue may remain at pathologically high temperatures for 8 to 10 minutes or more, which contributes to further thermal damage.[4]

## Pathogenesis of PV Induced After Electrical Injury

Normally, Dsg3 is not released into the blood or lymph in sufficient amounts to elicit an immune response; however, the aforementioned mechanisms of electrical injury may result in cellular rupture or necrosis. Following these processes, Dsg3 may be released and become available to the immune system, which could potentially lead to an autoantibody response toward Dsg3 and the subsequent development of PV. This is supported by the documentation of autoantibodies, including pemphiguslike autoantibodies, appearing in patients following thermal burns,[10-12] as well as by several case reports of pemphigus following thermal burns.[13-17] A potential mechanism for the induction of PV following electrical injury is shown in the Figure.

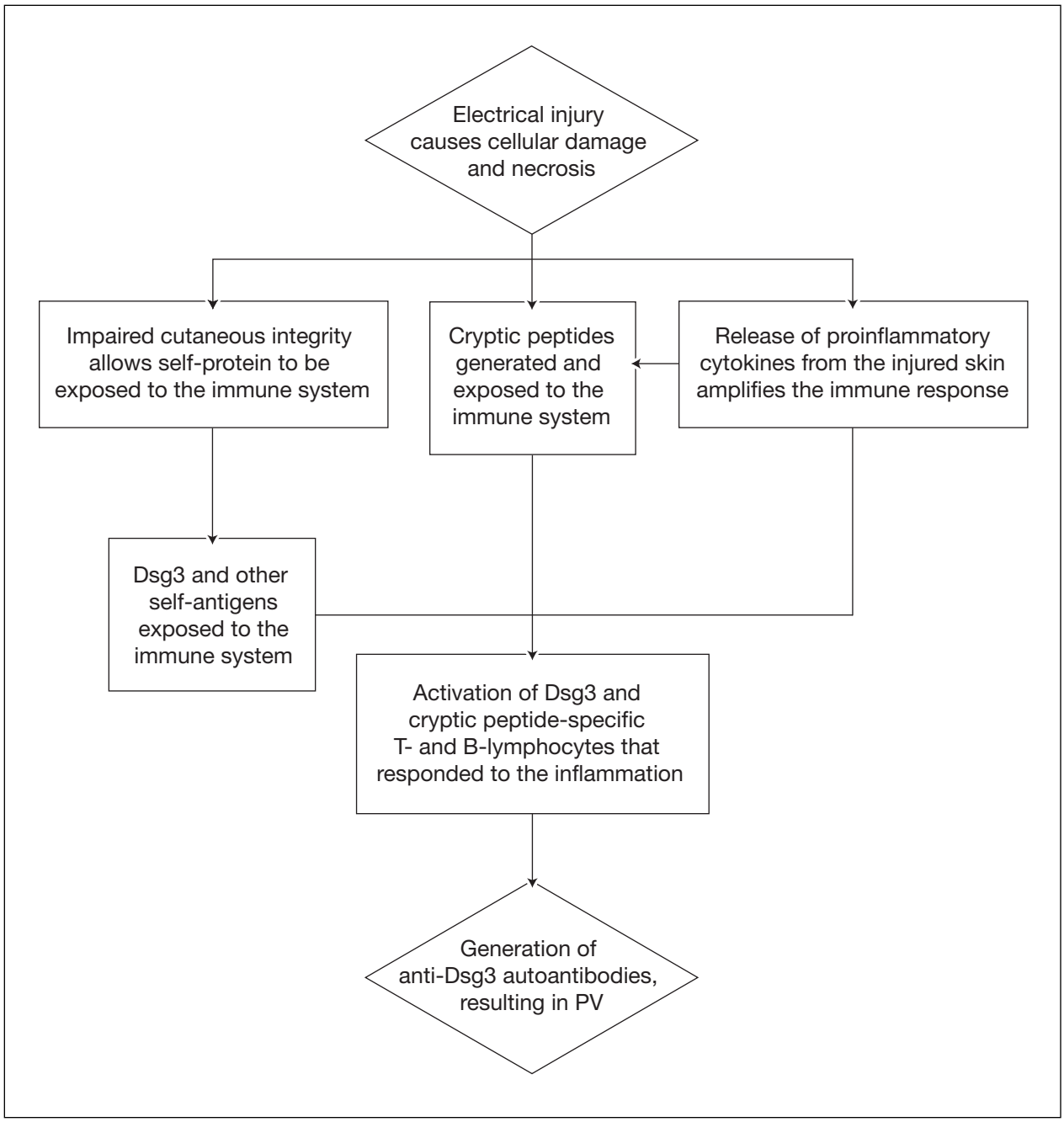
*Generation of an Immune Response to Self-Antigens*—T-cell tolerance depends on the presentation of self-proteins to T cells. Normally, tolerance is established to self-antigens that, under normal conditions, are generated in sufficient amounts to be recognized by T cells undergoing deletion in the thymus or anergy in the periphery. Thus, there are a large number of self-antigens that are cryptic because they either are not generated at all or are generated at subthreshold levels for T-cell deletion or anergy. T cells specific for these cryptic epitopes are present in the normal repertoire and may become activated and generate an autoimmune response if the epitopes are presented at higher concentrations.[18]

*Excessive Release of Self-Antigens*—Extensive thermal and electroporation damage to cell membranes, especially in desmosome-rich tissue such as skin and mucosal epithelium, may lead to extensive cell death and to the massive release of Dsg3 and other desmosomal/cell membrane antigens. Even if such antigens were unaltered (conformationally unchanged) by the electrical injury, excessive amounts available to antigen-presenting cells could predominate in the antigen-processing pathway and activate any specific T cells that are not anergic to this self-protein.[18] These activated T cells could trigger the activation of B cells with the potential to differentiate into anti-Dsg3 IgG antibody-secreting plasma cells, which result in PV.

*Generation of Cryptic Peptides*—Thermal degeneration and electroconformational denaturation of desmosomes and other cell membrane antigens may lead to the formation of cryptic peptides. These altered defective proteins may enter the antigen-processing pathway and be detected by cryptic peptide-specific T cells and B cells. Cryptic peptide-reactive lymphocytes may be present in the normal T-cell repertoire because cryptic peptides are not available during T cell and B cell development to provoke deletion or inactivation of these cells.[18] If the cryptic peptides were similar to Dsg3, antibodies may be formed that may cross-react with native Dsg3, which results in PV.

*Inflammation Potentiating the Immune Response*—Cutaneous trauma can activate the regulatory components of the immune system that are needed to activate and perpetuate an immune response. The skin is a significant source of proinflammatory cytokines,[19] and injury to the skin can release these cytokines.[19-22] Additionally, these cytokines can cross the epidermal basement membrane and enter the lymphatic and systemic circulations.[22] For example, interleukins 1 and 6 released by skin injury have been implicated in the development of PV.[23] Thus, cytokines may help to potentiate the immune response leading to the development of PV.

*Enhanced Antigen Processing and Spread of Anti–Self-Responses*—After anti-Dsg3 antibodies are generated, enhanced self-antigen processing could occur as a result of antibody-mediated amplification




Proposed pathogenesis for electrical injury–induced pemphigus vulgaris (PV). Dsg3 indicates desmoglein 3.

of the anti–self-response. B cells are activated following antigen binding,[24] and further release of Dsg3 from the inflammatory process would provide more stimulus for B-cell activation. Enhanced antigen processing that occurs with inflammation and the generation and expansion of cryptic peptides could result in epitope spreading of the disease to other self-antigens.

*Temporal Considerations*—The mechanisms of generating self-antigen in amounts above T-cell activation thresholds could elicit the development of PV. The formation of antibodies after exposure to a new antigen would be expected to occur within 12 weeks.[25] Thus, it seems reasonable that the first clinical signs of PV that result from the presence of anti-Dsg3 antibodies and subsequent binding to desmosomes in skin and mucosal epithelium may occur within weeks following the electrical injury. During this time, all of the immune events leading to both foreign responses and anti–self-responses

occur, with the response manifested as clinical disease. Once established, the disease would generate sufficient antigens through continued cell membrane destruction.

## Conclusion

In conclusion, we report a case of the new onset of PV occurring after a significant electrical injury. The electrical injury caused significant tissue injury that resulted in the release of self-antigen (Dsg3), proinflammatory mediators, and possibly cryptic peptides. These stimuli presumably led to the generation of anti-Dsg3 autoantibodies, which resulted in the clinical manifestations of PV.

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