Pemphigus Foliaceus: A Case Report and Short Review

Amor Khachemoune, MD, CWS; Kjetil Kristoffer Guldbakke, MD; Eric Ehrsam, MD

GOAL

To understand pemphigus foliaceus (PF) to better manage patients with the condition

OBJECTIVES

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

1. Distinguish between the various forms of pemphigus.
2. Recognize the clinical manifestations of PF.
3. Describe the treatment options for PF.

CME Test on page 104.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: July 2006.

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Drs. Khachemoune, Guldbakke, and Ehrsam report no conflict of interest. The authors discuss off-label use of azathioprine, corticosteroids, cyclophosphamide, cyclosporine, dapsone, extracorporeal photochemotherapy, gold, hydroxychloroquine, intravenous immunoglobulin, methotrexate, mycophenolate mofetil, niacinamide, plasmapheresis, rituximab, and tetracycline. Dr. Fisher reports no conflict of interest.

Pemphigus foliaceus (PF) is a rare autoimmune blistering disease presenting in endemic and sporadic forms. The typical presentation is recurrent shallow erosions in a seborrheic distribution. We present a case of a 58-year-old woman with PF who was successfully treated with a combination of oral corticosteroids and dapsone. We also provide a concise review of the literature and discuss the etiology, clinical features, diagnosis, and management of PF.

Cutis. 2006;78:105-110.

Accepted for publication January 6, 2006.

Dr. Khachemoune is Assistant Professor, Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York. Dr. Guldbakke currently is serving in the military in Norway. Dr. Ehrsam is in private practice, Le Cateau, France.

Reprints: Amor Khachemoune, MD, CWS, Ronald O. Perelman Department of Dermatology, New York University School of Medicine, 530 First Ave, Suite 7R, New York, NY 10016 (e-mail: amorkh@pol.net).

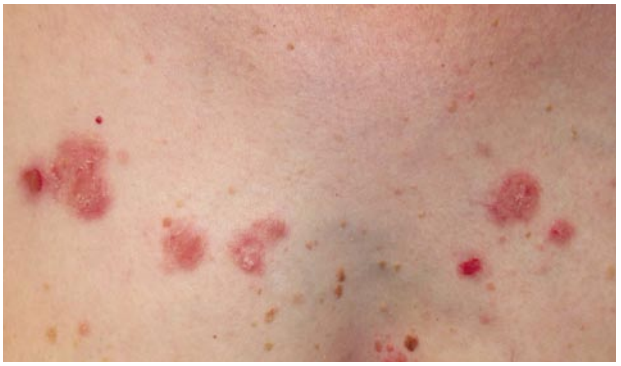
Pemphigus describes a group of autoimmune chronic bullous diseases, originally named in 1791.[1] The term *pemphigus* stems from the Greek *pemphix* meaning blister or bubble.[2] Pemphigus is usually divided into 2 major forms depending on blister location: pemphigus vulgaris (PV) and

pemphigus foliaceus (PF). Pemphigus vegetans is a variant of PV, and pemphigus erythematosus (PE) and fogo selvagem are variants of PF. During the past 3 decades, uncommon forms of pemphigus have been described, including pemphigus herpetiformis, immunoglobulin A (IgA) pemphigus, and paraneoplastic pemphigus.[3] The incidence of pemphigus ranges from 0.76 to 5 new cases per million per year.[2] In a recent analysis of 1209 patients with pemphigus in Iran, the PV to PF ratio was found to be 12:1. However, this ratio varies widely in different parts of the world.[4] In one report, 73% of cases of pemphigus in France were PV.[5] PV also is the most common clinical type of pemphigus in Kuwait, Israel, and Singapore.[6-8] In a report on pemphigus in South Africa, the most common clinical variant was PF, and 80% of these patients were black.[9] Of note, in the Indian population in this region, PV was more common. A high percentage of PF is endemic in rural Brazil, Tunisia, and Columbia.[9]

Case Report

A 58-year-old white woman presented with a 6-month history of superficial erosions on the chest, upper back, hairline, and retroauricular areas. She denied any photosensitivity, and there was no mucosal involvement. The patient's medical history was otherwise unremarkable. Superficial erosions with a positive Nikolsky sign were present on the chest (Figure), upper back, and frontal hairline, as well as in the retroauricular areas bilaterally. Two punch biopsies (one lesional and one perilesional) were performed. Routine histology results showed intraepidermal vesicles in the upper granular layer containing acantholytic cells. Results of direct immunofluorescence demonstrated IgG and complement 3 (C3) in the intercellular spaces in the epidermal cell surface. Of note, antinuclear antibody and anti–double-stranded DNA were negative. These findings were consistent with our clinical diagnosis of PF.

The patient was initially started on a high potency topical corticosteroid (clobetasol propionate ointment) for 4 weeks with no improvement. She was then given prednisone 60 mg/d for approximately one month when new lesions ceased to appear; then the medication was slowly tapered off. Dapsone also was added to her regimen after an initial baseline level of glucose-6-phosphate dehydrogenase and a baseline complete blood count were obtained. Dapsone was initiated at 50 mg/d while prednisone was being slowly tapered. Cacit D3 in a single morning dose (1000 mg calcium and 880 IU vitamin D) also was added to the regimen. Of note, the patient was taking celecoxib for intermittent joint pain, but a literature search at that time did not reveal an association with similar eruptions; our patient was asked to discontinue the celecoxib at the initiation of oral prednisone. She was seen at regular follow-up visits every month. As the patient improved clinically, dapsone was reduced to 25 mg and finally discontinued after about 6 months. Oral prednisone taper continued slowly over a total of 18 months. No lesions were present for the last 3 monthly visits.



Superficial erosions on the chest.

Comment

PF comprises 2 major categories: endemic and sporadic. The endemic form, also known as *fogo selvagem*, primarily affects children and young adults in rural Brazil. In contrast, the sporadic form of PF is generally a disease of middle-aged individuals and the elderly. Of note, there are several cases of nonendemic PF occurring in children,[10] and 2 cases reported in the neonatal period.[11] Many patients with PE show serologic findings suggestive of systemic lupus erythematosus (SLE), especially the presence of antinuclear antibodies.[2,12]

PF is an autoimmune blistering disease of unknown etiology with antibodies produced against desmoglein 1 (Dsg1).[13] Dsg1 is an adhesive cadherin protein found in the desmosomal cell junction in the suprabasal layers of the epidermis.[14,15] Binding of the antibody results in the loss of cell adhesion or acantholysis and formation of the clinical picture of PF.[16] The blisters are subcorneal, occurring in and around the granular cell layer of the epidermis.[13] Blister formation is superficial because the most differentiated layer of the epidermis is the only area in which Dsg1 is critically important to cell adhesion, and there is no protection redundancy of adhesion molecules by coexpression of Dsg3.[17] Of interest, one study has demonstrated that the autoantibodies in up to 7% of patients with PF and up to 50% of patients with PV recognize both Dsg1 and Dsg3 isoforms.[18] It also is

reported that some patients can progress from PF to PV or vice versa, though the latter is less common.[19] It has been shown that this transition correlates well with the qualitative and quantitative changes in the profile of Dsg1 and Dsg3 antibodies.[20] Patients with PF have been reported to have a predominance of circulating IgG4 antiepidermal autoantibodies, followed by a lesser degree of IgG1, IgG2, and IgG3 subclasses.[21] PF has shown a strong association with several HLA-DRB1 haplotypes.[22,23] Most recently, an association with HLA-DRB1*0101 was found in the Mexican population.[24] Sunlight exposure[25] and several drugs such as penicillamine[26,27] have been identified as possible triggering factors for the disease. In children, bacteria, cytomegalovirus, and otitis also have been implicated.[10] Similarly, an unusual case of childhood PF apparently triggered by conjunctivitis was reported.[28]

PF manifests clinically as recurrent shallow erosions accompanied by erythema, scaling, and crusting.[29] Lesions usually are found in a seborrheic distribution (central face, neck, chest, or upper back).[30] Patients develop superficial fragile vesicles, which often are not seen. In contrast to PV, PF patients rarely have mucosal involvement.[11] The onset of disease may be slow, starting with only a few transient scattered crusted lesions.[2] The condition may then stay localized for years or progress into generalized involvement, sometimes resulting in an exfoliative erythroderma.[31] In general, patients are not severely ill but often complain of burning and pain associated with the skin lesions.[2]

Fogo selvagem, formerly known as *Brazilian PF*, occurs in an endemic fashion in certain regions of Brazil.[32] The condition has been described in certain regions of Brazil since the turn of the century.[33] The prevalence in some rural areas of Brazil is as high as 3.4%.[34] There also have been reports of other possible foci of endemic PF in Tunisia and Columbia.[35,36] Endemic PF differs from sporadic PF in its geographic distribution, high familial incidence, and young age of onset.[36] The clinical manifestations, histology, and immunopathologic features are indistinguishable from sporadic PF.[29,32] The distinct epidemiology of the condition is suggestive of an environmental or infectious agent. Studies have identified that most patients are young peasants or children who live in close proximity to rivers, which exposes the children to the hematophagous insect belonging to the *Simulium nigrimanum* species, also known by its popular name borrachudo (blackfly).[37,38]

PE was first described by Senear and Usher[39] in 1926. Originally, the term *PE* was introduced to describe patients with immunologic features of both SLE and pemphigus.[2] Many patients with PE show serologic findings suggestive of SLE, especially the presence of antinuclear antibodies.[12,40] However, there are only a few reports of PE occurring in patients who have clearly defined SLE.[41,42] In most of these cases, the diagnosis of SLE had been established months to years earlier.[42] PE also may be associated with a variety of autoantibodies and may require extensive immunotherapy.[43] PE has characteristic findings on direct immunofluorescence, usually IgG and C3 at the basement membrane zone of erythematous facial skin, in addition to the epidermal cell surface IgG.[12,44] Clinically, the lesions of PE resemble those of PF but are most commonly restricted to the upper trunk, head, and neck.[42] PE may remain localized for years, or it may evolve into more generalized PF.[40] PE also has been associated with myasthenia gravis and thymomas.[45]

The histologic changes of PF, PE, and fogo selvagem are identical.[2] Early blisters indicate acantholysis just below the stratum corneum and in the granular layer. The stratum corneum often is lost from the surface of these lesions. The deeper epidermis, below the granular layer, remains intact. Another frequent finding is subcorneal pustules, with neutrophils and acantholytic epidermal cells in the blister cavity.[12]

Immunofluorescence using both direct and indirect techniques is the most reliable method of diagnosing pemphigus.[46] Most patients with pemphigus have IgG and C3 deposits at the epidermal cell surfaces and circulating IgG against the same components.[47] However, the cell staining pattern of both direct and indirect immunofluorescence is virtually identical in PV and PF, making it difficult to distinguish between them.[48] One innovation has been the introduction of an antigen-specific ELISA (enzyme-linked immunosorbent assay) test for the diagnosis of pemphigus: if a serum is positive against Dsg3, the test results indicate a diagnosis of PV, regardless of reactivity against Dsg1; if a serum is negative for Dsg3 and positive for Dsg1, the test results indicate a diagnosis of PF.[48]

The differential diagnosis of PF includes other forms of pemphigus, bullous impetigo, subcorneal pustular dermatosis, linear IgA dermatosis, and seborrheic dermatitis.[2,30]

Before the advent of glucocorticoid therapy, PF was fatal in about 60% of patients.[12] The aim of current therapy is to suppress the production of pathogenic antibodies, stop the development of new lesions, and heal old lesions.[49] The therapy of PF differs from that of PV only in that treatment can be less aggressive because morbidity and mortality are lower.[26] In all patients, a complete review of medications should be done to exclude the possibility of

drug-induced PF. The most commonly implicated medications are penicillamine,[27] captopril,[50] lisinopril,[51] nifedipine,[52] and topical imiquimod.[53]

Because PF may be localized for many years and the prognosis without systemic therapy may be good, patients do not necessarily require systemic therapy. This patient group may be treated successfully with topical corticosteroids.[29,54] Patients with active and widespread disease require systemic therapy.[16] An initial dose of prednisone at 1.0 mg/kg can usually be tapered down toward an alternate-day dosage within 1 to 3 months.[29] One patient has been kept on a low dose of corticosteroids successfully as maintenance over an extended period.[55]

Patients with the most severe disease (ie, disease unresponsive to corticosteroids) should be considered for adjuvant immunosuppressive drugs as steroid-sparing agents.[29,49] The goal of immunosuppressive therapy is to suppress the production of antibodies. One of the medications used is mycophenolate mofetil, which is shown to be an effective steroid-sparing agent.[56,57] Oral cyclophosphamide, which also is an effective adjuvant alkylating agent in the treatment of severe and refractory PV and PF, can be combined with pulse intravenous corticosteroids. However, the use of alkylating agents should be done with care because of the risk of side effects such as hemorrhagic cystitis, susceptibility to infection, potential infertility, mutagenic potential, and lifetime risk for transitional cell carcinoma of the bladder and hematologic malignancies.[58] Other immunosuppressive medications that have been used include azathioprine,[59,60] methotrexate,[61,62] and cyclosporine.[63,64] In patients for whom conventional therapies have failed, alternative therapies such as intravenous immunoglobulin,[65] plasmapheresis,[66] and extracorporeal photochemotherapy[67,68] have been employed successfully. A single case of PF occurring after unrelated cord blood transplantation was reported to be successfully treated with rituximab, an anti-CD20 antibody.[69]

Dapsone has been used both as monotherapy and in combination regimens. In a study of 9 patients, 5 had at least 50% improvement.[70] Only patients with low titers or undetectable circulating antibodies responded to monotherapy. The value of dapsone in the treatment of PF remains to be clearly established.[71] There have been a few case reports indicating that a combination of tetracycline and niacinamide is an effective alternative to steroids in superficial pemphigus.[72] Other agents reported in the literature include gold,[43,73] chlorambucil,[74] and hydroxychloroquine sulfate.[75]

It is commonly perceived that PF is more benign than PV. Although uncommon, there are several reports of death occurring in PF.[65,76] Infection is often the cause of death, and therapy is frequently a contributing factor because it causes the immunosuppression necessary to treat active disease.[77] The effective management of PF requires a knowledge of the pathophysiology and pharmacologic effects of the agents used, an ability to make an accurate diagnosis, and an understanding of the patient's expectations.[49]

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