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Pemphigus Foliaceus

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Updated: May 5, 2009

Introduction

Background

Pemphigus foliaceus (PF) is generally a benign variety of pemphigus. It is an autoimmune skin disorder characterized by the loss of intercellular adhesion of keratinocytes in the upper parts of the epidermis (acantholysis), resulting in the formation of superficial blisters. It is typified by clinical involvement of healthy-appearing skin that blisters when rubbed (the Nikolsky sign; commonly but incorrectly spelled Nicholsky), a finding named after Dr Piotr Nikolsky, who first described this sign in 1896.[1] Pemphigus foliaceus is characterized by a chronic course, with little or no involvement of the mucous membranes.

Pierre Louis Alphee Cazenave, founder of the first journal dedicated entirely to dermatology, documented the first description of pemphigus foliaceus in 1844 in this journal. The description was of a 47-year-old woman who consulted him at l'Hopital Saint Louis in Paris for a generalized eruption of several years' duration. Nikolsky described lateral extension of the preexisting erosion due to lifting up the collarette (and when applying a lateral pressure to the clinically intact skin), whereas Asboe-Hansen described extension of the intact blister due to pressure that is applied to its roof.

Pemphigus foliaceus has the following 6 subtypes: pemphigus erythematosus (PE), pemphigus herpetiformis (PH), endemic pemphigus foliaceus, endemic pemphigus foliaceus with antigenic reactivity characteristic of paraneoplastic pemphigus (but with no neoplasm), immunoglobulin A (IgA) pemphigus foliaceus, and drug-induced pemphigus foliaceus. See Pemphigus Erythematosus; Pemphigus Herpetiformis; Pemphigus, Paraneoplastic; and Pemphigus, IgA for more information.

Senear and Usher originally described PE in 1926 as an unusual type of pemphigus with features of lupus erythematosus. PE (also known as Senear-Usher syndrome) is best viewed as a localized form of pemphigus foliaceus. Chorzelski et al[2] determined its immunopathology in 1968.

Another pemphigus foliaceus variant with pruritic, flaccid vesicles in an annular pattern has been characterized as IgA pemphigus foliaceus, with antibodies of IgA class providing the basis for diagnosis.

Jablonska and associates[3] coined the term pemphigus herpetiformis for the pemphigus foliaceus variant that often begins as small clusters of pruritic papules and vesicles mimicking dermatitis herpetiformis.

Endemic pemphigus foliaceus, or fogo selvagem (formerly known as Brazilian pemphigus foliaceus because it is evident mainly in the river valleys of rural Brazil), has also been described in Columbia, El Salvador, Paraguay, Peru, and recently in Tunisia. Fogo selvagem (Portuguese for wild fire) displays immunopathologic findings of pemphigus and a distinctive epidemiology suggestive of a disorder triggered by an infectious insect-borne agent (see Fogo Selvagem). A focus of endemic pemphigus foliaceus also exists in El Bagre, Columbia and shares features with Senear-Usher syndrome but occurs in an endemic fashion.[4,5] Heterogeneous antigenic reactivity was observed as in paraneoplastic pemphigus but with no evidence of association with neoplasia. This endemic pemphigus disease in El Bagre had immunologic features similar to pemphigus foliaceus or erythematosus.

Chorzelski et al in 1999[6] described paraneoplastic pemphigus with cutaneous and serologic features of pemphigus foliaceus in a patient with an underlying lymphoma. The authors are not aware of any similar patients with these highly unusual findings.

Drug-induced pemphigus foliaceus is mostly associated with penicillamine, nifedipine, or captopril, medications with a cysteinelike chemical structure.

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A transition from pemphigus vulgaris (PV) to pemphigus foliaceus, or vice versa, is not likely. However, in the experience at the Medical University of Warsaw, PV in the remission period may resemble pemphigus foliaceus. About 7% of patients with pemphigus foliaceus may have the initial features of PH. This figure was 35% in patients with endemic pemphigus foliaceus in Tunisia (see Pemphigus Vulgaris).

Pathophysiology

Superficial blisters in pemphigus foliaceus are induced by immunoglobulin G (IgG) (mainly IgG4 subclass) autoantibodies directed against a cell adhesion molecule, desmoglein 1 (160 kd), expressed mainly in the granular layer of the epidermis. Desmoglein 1 is also a major autoantigen in cases of PH, suggesting that most cases of both PE and PH are clinical variants of pemphigus foliaceus. The mechanism of acantholysis induction by specific autoantibodies may involve phosphorylation of intracellular proteins associated with desmosomes. Complement activation does not play a pathogenic role in pemphigus foliaceus.

Antibodies against desmoglein 3 are also present in patients with paraneoplastic pemphigus (PNP), a severe condition associated with various

antibodies against different components of the cell adhesion complex. Other target antigens, including the acetylcholine receptor, have also been postulated to be relevant in the pathogenesis of pemphigus foliaceus.[7,8,9,10]

Cholinergic control of epidermal cohesion may be important.[11] The regulation of keratinocyte cell-to-cell and cell-matrix adhesion is an important biological function of cutaneous acetylcholine. Recent progress in therapy of pemphigus using cholinergic drugs supports this concept.

Precipitating factors include medications and ultraviolet light radiation. It was recently suggested that both enhanced autoantibody epidermal binding and preferential neutrophil adhesion to UV-irradiated epidermis contribute to acantholysis development in photo-induced pemphigus foliaceus.

Endemic pemphigus foliaceus seems to have an environmental cause. The prevalence of antibodies against desmoglein 1 is high in people residing in endemic areas of Brazil, with disease onset preceded by a sustained antibody response due to an as yet unknown environmental factor.

The role of genetic factors is evident in fogo selvagem in which a strong association exists with some human leukocyte antigen DRB1 (HLA-DRB1) haplotypes, including DRB1*0404, 1402, 1406, and 1401. In France, persons with DRB1*0102 and 0404 are at an increased risk of pemphigus foliaceus.

Pemphigus trigger factors have been meticulously analyzed by Ruocco and Ruocco[12], who have delineated an exhaustive list and stressed the need to detect environmental provoking or precipitating factors. As a superb memory device to facilitate thorough patient evaluation, Ruocco[13] has cleverly observed that PEMPHIGUS should encourage the physician to consider pesticides (PE), malignancy (M), pharmaceuticals (P), hormones (H), infectious agents (I), gastronomy (G), ultraviolet light (U), and stress (S).

Rarely, a change in pemphigus subtype may occur, accompanied by qualitative and quantitative changes in the anti-Dsg autoantibody profile as detected using antigen-specific enzyme-linked immunosorbent assays (ELISAs). Thus, the antibody profile defines the clinical phenotypes of pemphigus, and that intermolecular "epitope spreading" may be the immunological mechanism underlying a shift between pemphigus foliaceus and PV.[14]

Frequency

International

The incidence of pemphigus foliaceus varies depending on the population studied. Pemphigus foliaceus is rare and sporadic worldwide. In contrast to PV, no predominance of pemphigus foliaceus is found in Jews and in people of Mediterranean descent. An increased incidence of pemphigus foliaceus was noted in Tunisian women (6.6 cases per million per year), whereas, in Western Europe, the incidence of pemphigus foliaceus is about 0.5-1 case per million per year.[15]

Endemic pemphigus foliaceus, or fogo selvagem, occurs with a high frequency in central and southwestern Brazil and in Colombia. The Terena reservation in Brazil, a recently identified focus, has a prevalence of 3.4% of the population. In endemic regions of Brazil, as many as 50 cases per million per year are seen.[16] Other foci may be present in the Maghreb; one was described in Morocco.

Mortality/Morbidity

Pemphigus foliaceus tends to persist for months to years. PE may coexist with thymoma, myasthenia gravis, lupus erythematosus, and other autoimmune bullous diseases.

Race

Pemphigus foliaceus has been described in all races.

Sex

In general, the prevalence of pemphigus foliaceus in men and women is about equal; however, in the Sousse region of Tunisia, an overwhelming predominance of women are affected. The peak incidence of endemic pemphigus foliaceus in women aged 25-34 years in the Sousse region of Tunisia is 15.5 cases per million per year. In El Salvador, a similar female and age predisposition may also be evident.

Age

The mean patient age at onset of pemphigus foliaceus is about 50-60 years; however, it may occur at any age, from infancy onward. Fogo selvagem often occurs in children, young adults, and genetically related family members. The mean patient age at onset is about 20-30 years. The peak incidence of endemic pemphigus foliaceus occurs in women aged 25-34 years in the Sousse region of Tunisia. An increased incidence in genetically related family members does not appear to exist.

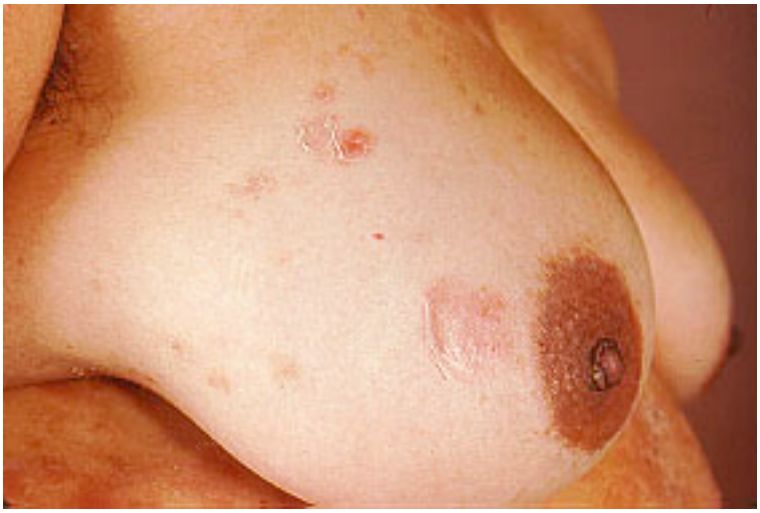
Clinical

History

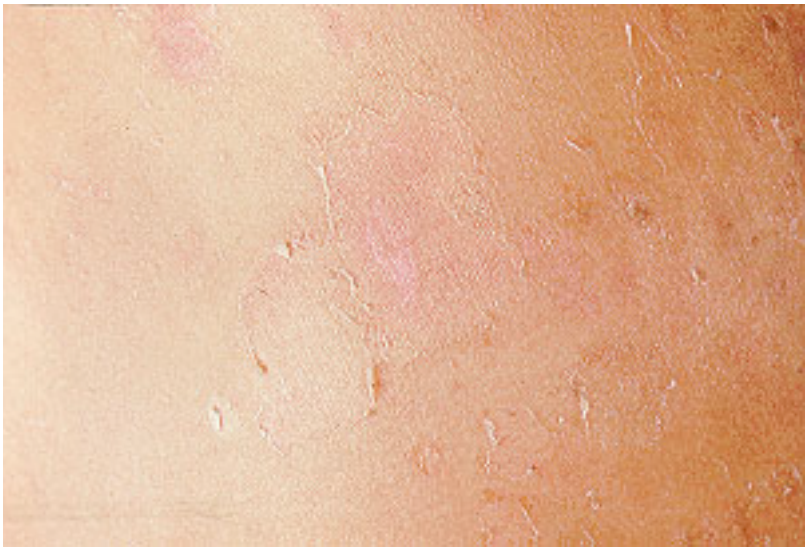
- The bullae usually start on the trunk. The course of the disease is long-term, with the patient's general health being satisfactory.
- Spontaneous remission sometimes occurs, but the lesions can persist for several years.
- A unique clinical pattern may occur in children, with individual lesions appearing as arcuate, circinate, or polycyclic.[17]
- Eyelid skin involvement without conjunctival changes occurs occasionally in patients with pemphigus foliaceus.[18]

Physical

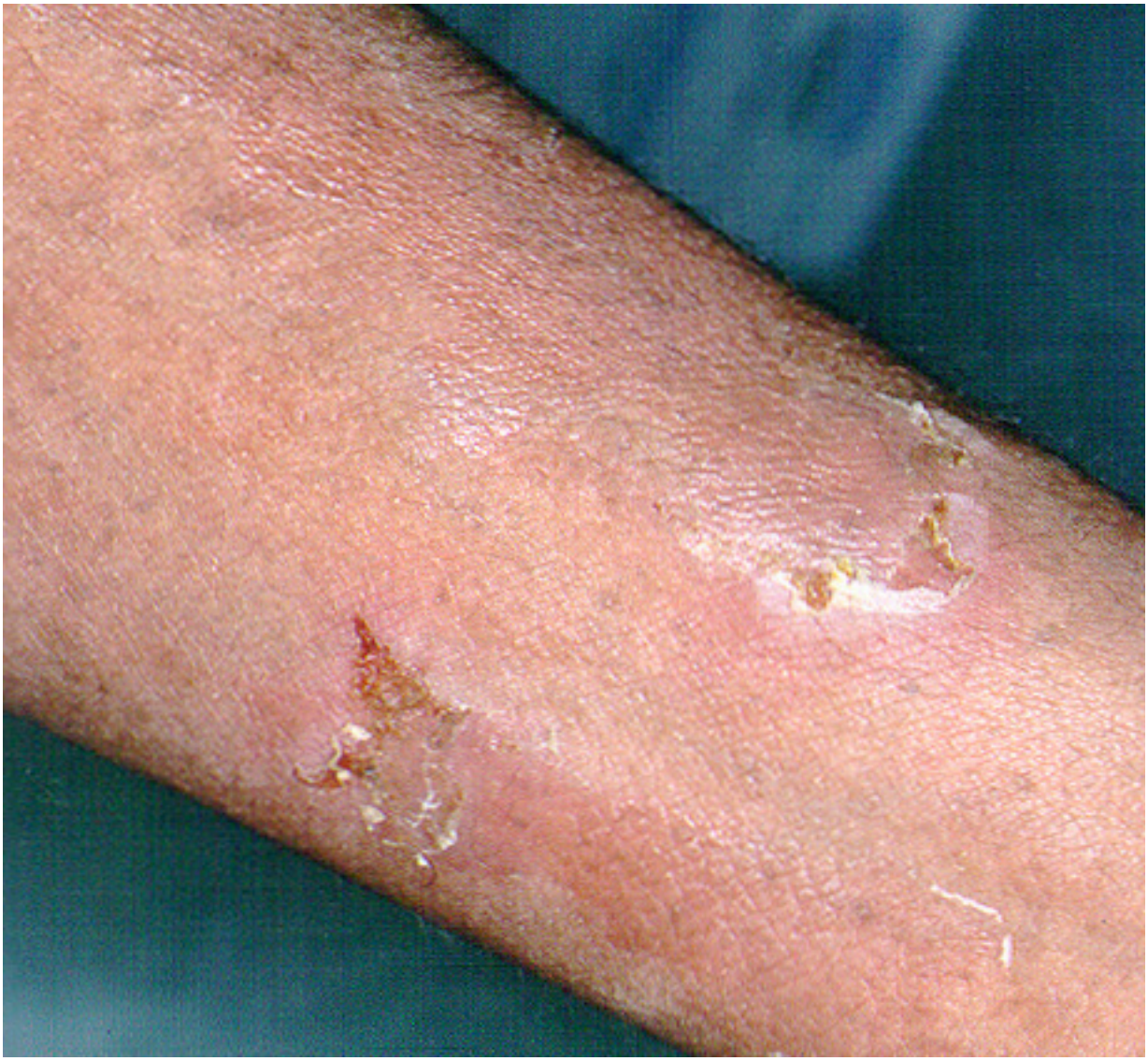
- The primary lesions are small, superficial blisters; however, these flaccid bullae are difficult to find because they are transient and transform into erosions.
    - Typical pemphigus foliaceus has scaly, crusted erosions on an erythematosus base confined mainly to so-called seborrhoic areas (eg, face, scalp, upper part of the trunk).
    - The Nikolsky sign is the finding that physical trauma can shear the pathologic epidermis of the skin of patients with pemphigus foliaceus, resulting in clinical lesions. The Nikolsky sign should probably be regarded as a moderately sensitive but highly specific tool for the diagnosis of pemphigus.[19]
    - The erosions can become numerous, showing a tendency to generalize.
    - Occasionally, erythrodermia develops.
    - Atrophic changes of the nails and the hair are sometimes evident.
    - The erosions may be accompanied by a burning sensation and local pain.
    - In contrast to PV, in pemphigus foliaceus, little or no involvement of the mucous membranes occurs.



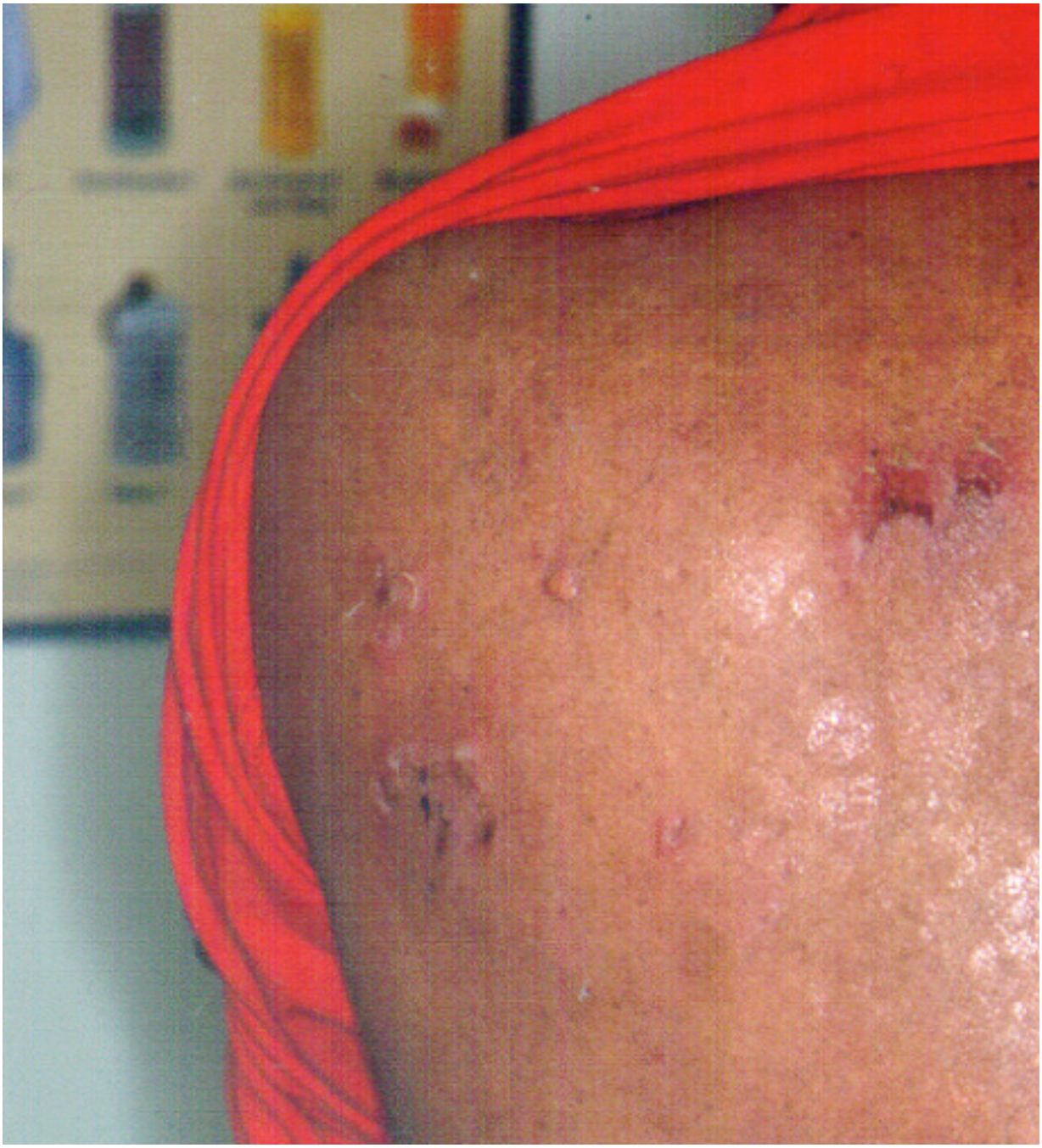
Middle-aged American woman of Mexican lineage with superficial bullae characteristic of pemphigus foliaceus.



Pemphigus foliaceus. Middle-aged American woman of Mexican lineage with superficial bullae formation.



A 41-year-old woman of Puerto Rican origin with a 9-year history of pemphigus foliaceus, often with erythroderma flares.



A 41-year-old woman of Puerto Rican origin with a 9-year history of pemphigus foliaceus, often with erythroderma flares.

- IgA pemphigus foliaceus begins as pruritic, flaccid vesicles in an annular pattern.
- PH commences as intensely pruritic, grouped papules and vesicles suggestive of dermatitis herpetiformis. Erythematous patches with peripheral vesicles may be present. Sometimes, oral erosions are seen.
- PE starts as erythematous patches with border vesiculation, often in a butterfly distribution on the cheeks and the forehead, with similar patches on the sternal and interscapular skin. Crusted plaques may appear in the healing phase.
- PNP is a subset of pemphigus combining the clinical features of PV variably associated with those of erythema multiforme, bullous pemphigoid, and lichen planus. Chorzelski and associates[6] in 1999 described a most unusual case of PNP with the

immunopathologic findings of pemphigus foliaceus. The clinical pattern appears to be correlated with that of the antibody profile; therefore, patients with antibodies directed against desmoglein 1 tend to have the clinical features of pemphigus foliaceus.

Causes

- Endemic pemphigus foliaceus, or fogo selvagem, seems to be induced by a viral infection transmitted by insects.
- In some patients, pemphigus foliaceus may be precipitated by extensive UV exposure or burns and by various drugs (eg, penicillamine,[20,21] inhibitors of angiotensin convertase, nonsteroid anti-inflammatory agents).[22] Pemphigus foliaceus induced by bucillamine has been described.[23]

Differential Diagnoses

Contact Dermatitis, Allergic
Contact Dermatitis, Irritant
Drug-Induced Bullous Disorders
Drug-Induced Photosensitivity
Epidermolysis Bullosa
Epidermolysis Bullosa Acquisita
Erysipelas
Erythema Multiforme
Erythroderma (Generalized Exfoliative Dermatitis)
Fogo Selvagem
Glucagonoma Syndrome
Herpes Simplex
Impetigo
Insect Bites
Linear IgA Dermatosis
Lupus Erythematosus, Bullous
Lupus Erythematosus, Drug-Induced
Lupus Erythematosus, Subacute Cutaneous
Papular Urticaria
Pemphigus Erythematosus
Pemphigus Herpetiformis
Pemphigus Vulgaris
Pemphigus, Drug-Induced
Pemphigus, IgA
Pemphigus, Paraneoplastic
Pseudoporphyria
Subcorneal Pustular Dermatosis

Other Problems to Be Considered

A mixed immunoblistering disorder exhibiting features of bullous pemphigoid and pemphigus foliaceus (PF), associated with the food supplement Spirulina, was described in an 82-year-old woman.[24]

Workup

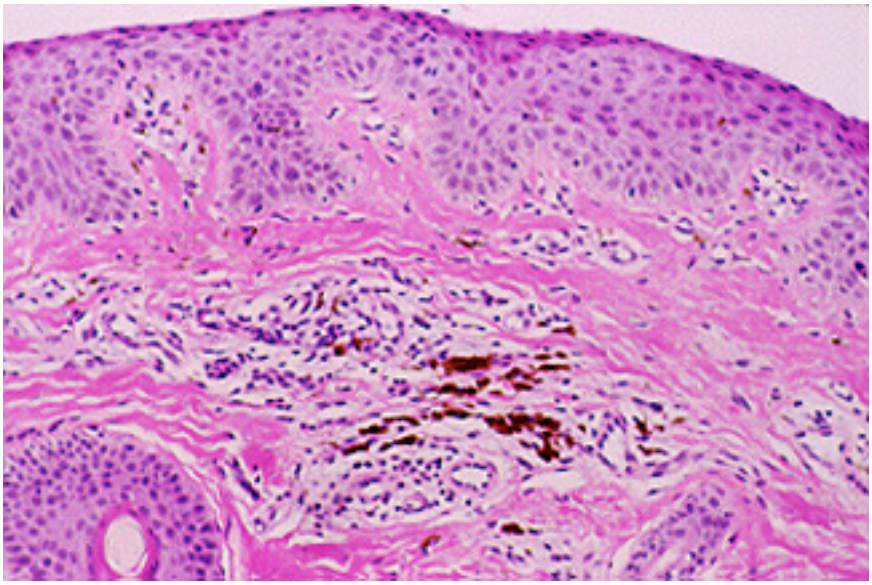
Laboratory Studies

- Immunofluorescence using both direct techniques and indirect techniques is the most reliable method to diagnosis pemphigus.[25] Because of the rare occurrence of pemphiguslike antibodies, pemphigus cannot be diagnosed by indirect immunofluorescence (IIF) alone and must be confirmed by direct immunofluorescence (DIF). With the use of 2 appropriate substrates (ie, monkey esophagus [or human skin] and guinea pig esophagus and standardized conjugates), in IIF, PV and pemphigus foliaceus patterns are different; PV stains throughout the epidermis, and pemphigus foliaceus stains only in the upper epidermis, whereas, with DIF, the patterns are similar. With a DIF study, cell surface immune deposits are often present throughout the entire epidermis in both pemphigus foliaceus and PV.
    - Immunologic examination with DIF testing shows IgG in the intercellular space, mainly in the upper parts of the epidermis; an IIF study documents the presence of circulating pemphigus antibodies, especially with a guinea pig esophagus used as a substrate. One IIF study suggested that using both a monkey esophagus and the human skin increases the sensitivity and aids in distinguishing pemphigus foliaceus from PV.
    - In PH, IgG deposits are evident in the upper epidermis, with circulating IgG to the epidermal cell surface. The subcorneal pustular dermatosis type of IgA pemphigus foliaceus has IgA deposition on the upper epidermal cell surfaces and circulating IgA antibodies to the epidermal cell surfaces.
    - Desmogleins 1 and 3 are the major cell surface target molecules in patients with PH.
    - In the unusual instance when PV becomes pemphigus foliaceus, or vice versa, the clinical alteration is associated with a shift in the antidesmoglein autoantibody profile.

- Other methods, such as ELISA[26] and immunoblot assays,[27] can be used, but they require highly purified antigens to give similar results. The sensitivity for PV and pemphigus foliaceus antibodies is more than 98% in at least the renowned laboratory of Jarzabek-Chorzelska and associates,[25] with their many decades of experience. Histologic examination is useful, but it is not the preferred method for diagnosing pemphigus foliaceus because it cannot replace a highly reliable DIF method.
- Another less experienced laboratory found ELISA to be superior to an IIF study for serodiagnosis of pemphigus foliaceus at various stages of disease activity.[28]
- Pemphigus foliaceus arising during the administration of D-penicillamine was described in an elderly patient in whom withdrawal of D-penicillamine resulted in improvement of the skin lesions and ELISA scores for anti–desmoglein 1 antibodies revealed a rapid decline.[29]

Histologic Findings

Pemphigus foliaceus begins as acantholysis of the upper epidermis, often resulting in a subcorneal cleft. It usually enlarges and detaches without bullae formation, though a bulla may form showing acantholysis at both the roof and the floor. More established lesions may have acanthosis and mild-to-moderate papillomatosis. Hyperkeratosis and parakeratosis may also be evident, with dyskeratotic cells within the granular layer. These features may be particularly pronounced in long-standing PE. A mild dermal lymphocytic infiltrate occurs, often with the presence of eosinophils. Eosinophilic spongiosis may also be noted, especially in PH.



Histologic view shows the typical pattern of a detached stratum corneum without bullae formation (same patient as in Media File 4). Pigmentary incontinence is prominent in the dermis, reflecting the patient's 9-year history of recurrent superficial bullae.

Treatment

Medical Care

Present information is probably inadequate to ascertain the optimal therapy for pemphigus foliaceus (PF), including the optimal glucocorticoid dose, the role of adjuvant immunosuppressive medications, and long-term adverse events to improve the risk-to-benefit ratio.[30] Therapy for pemphigus foliaceus is usually less aggressive than that of PV because of lower morbidity and mortality rates.[31]

First results indicate that nonsteroidal treatment of pemphigus is possible. Mestinon may be used to slow down progression of the disease and to treat mild cases with chronic lesions on limited areas. Antimalarial therapy may be effective monotherapy in some patients. However, a major obstacle in comparing therapeutic outcomes is the lack of generally accepted definitions and measurements for the clinical evaluation of patients with pemphigus.[32] Common terms and endpoints of pemphigus are needed to accurately measure and assess disease extent, activity, severity, and therapeutic response.

- Topical glucocorticosteroids may be sufficient in cases of limited involvement.[33]
- In more extensive cases (similar to PV), adjuvant immunosuppressants, including systemic corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, and cyclosporin A, may be necessary.[34,35]
- In some cases, such as PE, combined therapy is beneficial with the use of corticosteroids and sulfones or antimalarial agents.
- Topical treatment with antibiotics and corticosteroids, such as topical clobetasol cream or ointment 0.05% twice a day, is helpful. Other vehicles that may be useful are creams, foams, liquids (for scalp lesions), and aerosols. Antibiotics, such as minocycline 50 mg daily, may be effective. Nicotinamide 1.5 g/d and tetracycline 2 g/d have also been reported to be beneficial in a small number of patients. Antibiotics and nicotinamide are purported to have anti-inflammatory effects.[36]
- Photoprotection is appropriate for some patients because UV-B may trigger acantholysis and cause a flare-up of the disease.
- Successful anti-CD20 antibody treatment has also been described.[37]
- Plasmapheresis is another therapeutic option in patients with recalcitrant disease. It may decrease autoantibody titers in some patients and favorably influence the clinical outcome, especially in patients with otherwise therapy-resistant pemphigus foliaceus. It is often used in conjunction with cytostatic agents, such as cyclophosphamide or azathioprine, to reduce a predictable rebound increase in autoantibody synthesis. Potential complications, including the need for maintaining venous access, a bleeding tendency, electrolyte shifts, pulmonary edema, fever, chills, hypotension, and septicemia, should be considered.
- Amagai et al reported that a single cycle of intravenous immunoglobulin at 400 mg/kg/d for 5 days is effective and safe for patients with pemphigus that is relatively resistant to systemic steroid therapy.[38] Toth and Jonkman also reported on successful therapy with intravenous immunoglobulin (low dose).[39]

Medication

A number of medications are used to treat patients with pemphigus foliaceus. They are often used in combination. Refractory pemphigus foliaceus as been treated with the anti-CD20 monoclonal antibody rituximab.[40,41]

Corticosteroid agents

These agents have anti-inflammatory properties and cause profound and varied metabolic effects. Corticosteroids modify the body's immune response to diverse stimuli.

Prednisone (Deltasone, Orasone)

Synthetic adrenocortical steroid with predominantly glucocorticoid properties. Immunosuppressant for the treatment of autoimmune disorders; may decrease inflammation by reversing increased capillary permeability and suppressing PMN activity. Stabilizes lysosomal membranes and suppresses lymphocyte and antibody production.

Dosing

Adult

60-100 mg PO every morning or more often as required to abort acantholysis; alternatively, 0.5-2 mg/kg/d PO; taper as condition improves; single morning dose is safer for long-term use, but divided doses have more anti-inflammatory effect

Pediatric

0.14-2 mg/kg/d PO divided tid/qid (4-60 mg/m^2/d)

Interactions

Coadministration with estrogens may decrease clearance; when used with digoxin, digitalis toxicity secondary to hypokalemia may increase; phenobarbital, phenytoin, and rifampin may increase the metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics; coadministration with ritonavir may significantly increase serum concentrations of prednisone; concomitant therapy with montelukast may result in severe peripheral edema; clarithromycin may increase risk of psychotic symptoms

Contraindications

Documented hypersensitivity; viral, fungal, tubercular skin, or connective tissue infections; peptic ulcer disease; hepatic dysfunction; GI disease

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

May unmask hypertension or diabetes or exacerbate peptic ulcer disease and tuberculosis; long-term sequelae associated with long-term steroid use include osteoporosis, cataracts, and pituitary-hypothalamic axis suppression; with high doses, patients may develop a steroid psychosis and are at increased risk of infections, particularly when oral steroids are used in conjunction with other immunosuppressants; frequently monitor patient's blood glucose level, blood pressure, and weight; monitor for Cushing syndrome

Antibiotic agents

Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting.

Minocycline (Dynacin, Minocin)

Semisynthetic derivative of tetracycline. Treats infections caused by susceptible gram-negative and gram-positive organisms, in addition to infections caused by susceptible *Chlamydia, Rickettsia,* and *Mycoplasma* species. Was found to be effective in some nontuberculotic mycobacterial infections.

Dosing

Adult

50-100 mg PO bid

Pediatric

<8 years: Not recommended

>8 years: 4 mg/kg PO initially, followed by 2 mg/kg q12h

Interactions

Bioavailability decreases with antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate; can decrease effects of PO contraceptives, causing breakthrough bleeding and increased risk of pregnancy; tetracyclines can increase hypoprothrombinemic effects of anticoagulants; concomitant use of vitamin A supplementation or oral retinoids (eg, isotretinoin) not recommended; additive risk of pseudotumor cerebri; simultaneous administration of cinnamon and tetracycline may slow tetracycline absorption; bacteriostatic drugs (eg, tetracyclines) may interfere with bactericidal effect of penicillin

Contraindications

Documented hypersensitivity; severe hepatic dysfunction

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Photosensitivity may occur with prolonged exposure to sunlight or tanning equipment; reduce dose in renal impairment; consider drug serum level determinations in prolonged therapy; tetracycline use during tooth development (last half of pregnancy through age 8 y) can cause permanent discoloration of teeth; Fanconilike syndrome may occur with outdated tetracyclines; hepatitis or lupuslike syndromes may occur; autoimmune syndromes; drug-induced lupus–like syndrome, hepatitis, and vasculitis reported with long-term use; caution in preexisting renal impairment; risk of azotemia, hyperphosphatemia, and acidosis due to drug accumulation; minocycline use may result in false elevations of urinary catecholamine levels due to interference with the fluorescence test

Dapsone (Avlosulfon)

Bactericidal and bacteriostatic against mycobacteria; mechanism of action is similar to that of sulfonamides where competitive antagonists of PABA prevent formation of folic acid, inhibiting bacterial growth. Used to control the dermatologic symptoms of dermatitis herpetiformis. Can be used for patients with pemphigus and may be DOC for PH and IgA PF. May be provided as monotherapy or in combination with systemic steroids and immunosuppressants.

Dosing

Adult

50-200 mg PO qd

Pediatric

Not established

Interactions

May inhibit anti-inflammatory effects of clofazimine; hematologic reactions may increase with folic acid antagonists, eg, pyrimethamine (monitor for agranulocytosis during second and third months of therapy); probenecid increases toxicity; trimethoprim with dapsone may increase toxicity of both drugs; because of increased renal clearance, levels may significantly decrease when administered concurrently with rifampin

Contraindications

Documented hypersensitivity; known G-6-PD deficiency (assay for G-6-PD activity prior to initiation of therapy)

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Associated with a variety of systemic toxicities, including agranulocytosis, anemia, methemoglobinemia, hepatitis, and neuropathy; patients may experience headache and/or GI distress on initiation of therapy; perform weekly blood counts (first mo), then monthly WBC counts (6 mo), then semiannual WBC counts; discontinue if a significant reduction in platelets, leukocytes, or hematopoiesis occurs; caution in methemoglobin reductase deficiency, G-6-PD deficiency, or hemoglobin M because of high risk for hemolysis and Heinz body formation; caution in patients exposed to other agents or conditions (eg, infection, diabetic ketosis) capable of producing hemolysis; peripheral neuropathy can occur (rare); phototoxicity may occur when exposed to UV light; pancreatitis may occur; various forms of renal complications including acute renal failure, acute tubular necrosis, and oliguria have occurred with dapsone use

Antimalarial agents

Hydroxychloroquine has immunosuppressive effects.

Hydroxychloroquine (Plaquenil)

4-Aminoquinoline derivative active against a variety of autoimmune disorders. Inhibits chemotaxis of eosinophils, locomotion of neutrophils, and impairs complement-dependent antigen-antibody reactions. Hydroxychloroquine sulfate 200 mg is equivalent to 155 mg hydroxychloroquine base and 250 mg chloroquine phosphate.

Dosing

Adult

400 mg PO qd or divided bid (mg/kg same as pediatric dosing)

Pediatric

Not to exceed 6.5 mg/kg/d PO

Interactions

May increase penicillamine levels; serum levels of hydroxychloroquine may increase with cimetidine; magnesium trisilicate may decrease absorption; concurrent use of aurothioglucose and antimalarial agents may induce blood dyscrasias and may also result in additive risk of this effect; concurrent digoxin may result in increased serum digoxin concentrations

Contraindications

Documented hypersensitivity; psoriasis; retinal and visual field changes attributable to 4-aminoquinolones

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Crosses placenta and may cause ocular, CNS, or ototoxicity in fetus; do not use in breastfeeding; limit pediatric use to established safe doses to avoid potential fatality; perform regular ophthalmologic examinations (including visual acuity, slit lamp, funduscopic, and visual-field tests); caution in patients with G-6-PD deficiency; check blood cell counts periodically (perhaps biannually)
Hemolysis, aplastic anemia, agranulocytosis, and leukopenia can occur; not recommended for long-term use in children; perform periodic (6 mo) ophthalmologic examinations; test periodically for muscle weakness

Immunomodulatory agents

These agents have antiproliferative and immunosuppressive effects.

Azathioprine (Imuran)

May be used alone or as steroid-sparing agent. Antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins. May decrease proliferation of immune cells, which results in lower autoimmune activity.

Dosing

Adult

100-200 mg PO qd in combination with prednisone; alternatively, 1 mg/kg/d PO for 6-8 wk; increase by 0.5 mg/kg q4wk until response or dose reaches 2.5 mg/kg/d

Pediatric

Not established

Interactions

Toxicity increases with allopurinol; concurrent use with ACE inhibitors may induce severe leukopenia; may increase levels of methotrexate metabolites and decrease effects of anticoagulants, neuromuscular blockers, and cyclosporine; coadministration with mycophenolate may increase toxicity; alfalfa, black Cohosh, and echinacea may reduce immunosuppressive drug effectiveness

Contraindications

Documented hypersensitivity; deficiency of thiopurine methyltransferase (can result in severe myelosuppression and leukopenia); history of treatment with alkylating agents

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Adverse effects include teratogenicity, hepatitis, bone marrow suppression, and increased risk of cancer; before initiating therapy and regularly thereafter, perform urine analysis, complete blood cell count, renal and liver function tests, and serum electrolyte levels; increases risk of neoplasia; caution with liver disease and renal impairment; hematologic toxicities may occur

Cyclophosphamide (Cytoxan, Neosar)

May be used as monotherapy or as a steroid-sparing agent. Chemically related to nitrogen mustards. As an alkylating agent, the mechanism of action of the active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells.

Dosing

Adult

50-100 mg IV qd in combination with prednisone; 2.5-3 mg/kg/d PO divided qid

Pediatric

Not established

Interactions

Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects; may potentiate doxorubicin-induced cardiotoxicity; may reduce digoxin serum levels and antimicrobial effects of quinolones; chloramphenicol may increase half-life while decreasing metabolite concentrations; may increase effect of anticoagulants; coadministration with high doses of phenobarbital may increase rate of metabolism and leukopenic activity; thiazide diuretics may prolong cyclophosphamide-induced leukopenia and neuromuscular blockade by inhibiting cholinesterase activity; concurrent use of NSAIDs has resulted in increases in cyclosporine levels, nephrotoxicity, and increased plasma creatinine concentrations; concomitant use of ACE inhibitors may decrease renal function; coadministration with nevirapine and St. John's wort may reduce immunosuppressive drug effectiveness
Increased risk of infection by live vaccine; coadministration with trastuzumab may increase cardiac toxicity; coadministration with tamoxifen may increase risk of thromboembolism

Contraindications

Documented hypersensitivity; severely depressed bone marrow function

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Regularly examine hematologic profile (particularly neutrophils and platelets) to monitor for hematopoietic suppression; regularly examine urine for RBCs, which may precede hemorrhagic cystitis; adverse effects include oligospermia or azoospermia, cardiomyopathy, infectious disease, interstitial pneumonia, increase risk of malignancy, possibility of increased toxicity in adrenalectomized patients

Follow-up

Complications

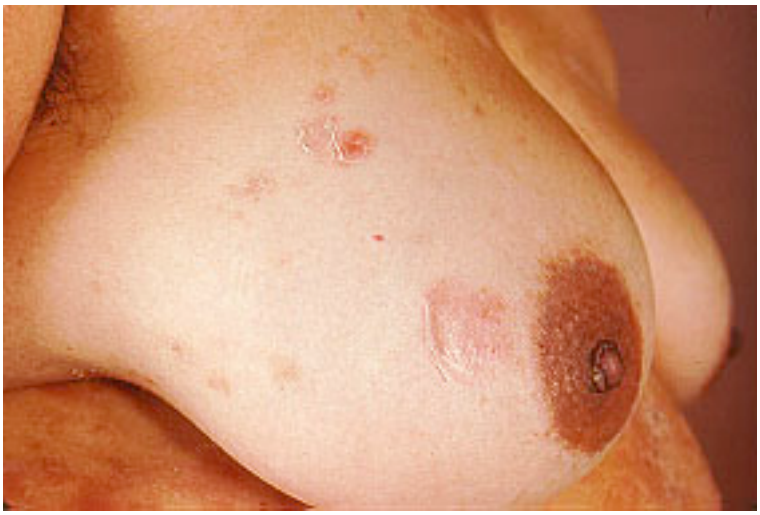
- Monitor pemphigus foliaceus (PF) patients for other autoimmune disorders, particularly thymoma and myasthenia gravis.

Miscellaneous

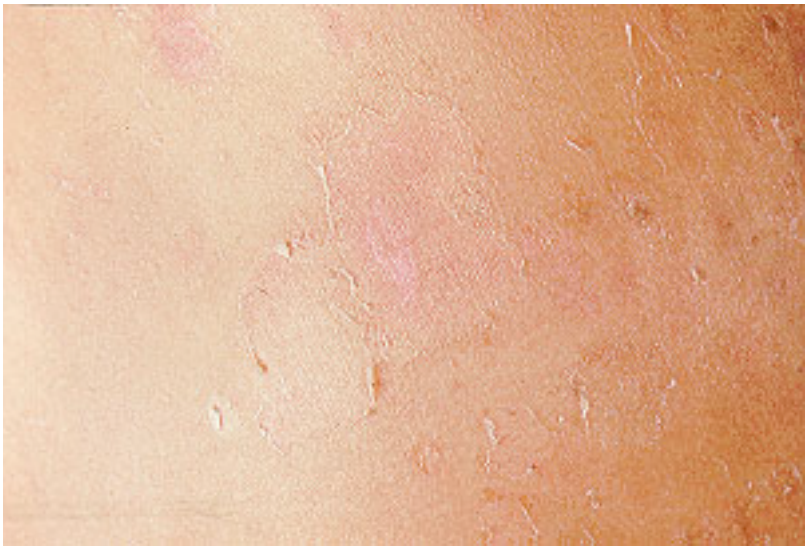
Medicolegal Pitfalls

- Because PE may coexist with thymoma, myasthenia gravis, lupus erythematosus, and other autoimmune bullous diseases, failure to diagnose this disease or its associations can be problematic. Likewise, for paraneoplastic pemphigus, a diagnosis must be established and the underlying malignancy must be located.

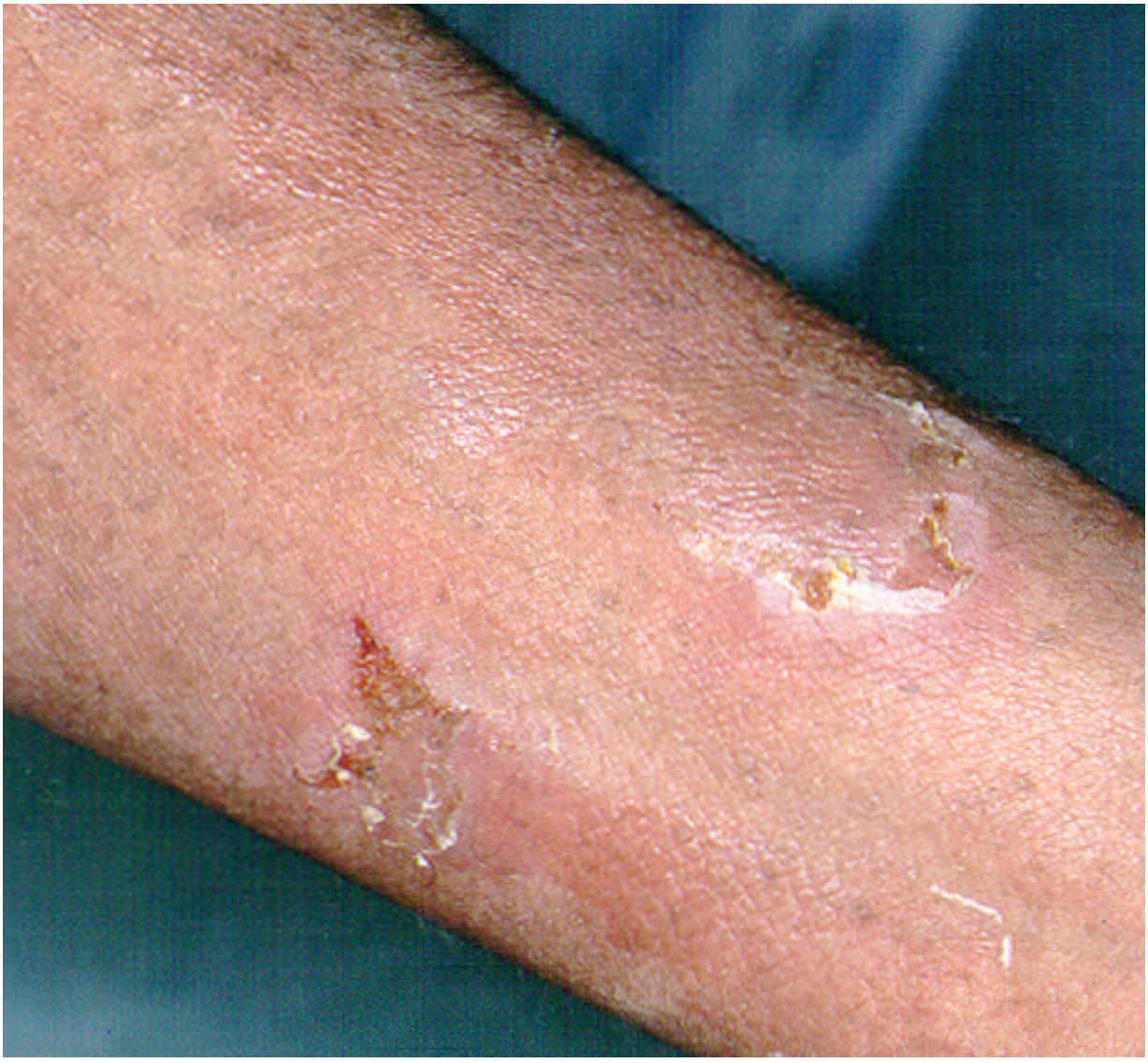
Multimedia



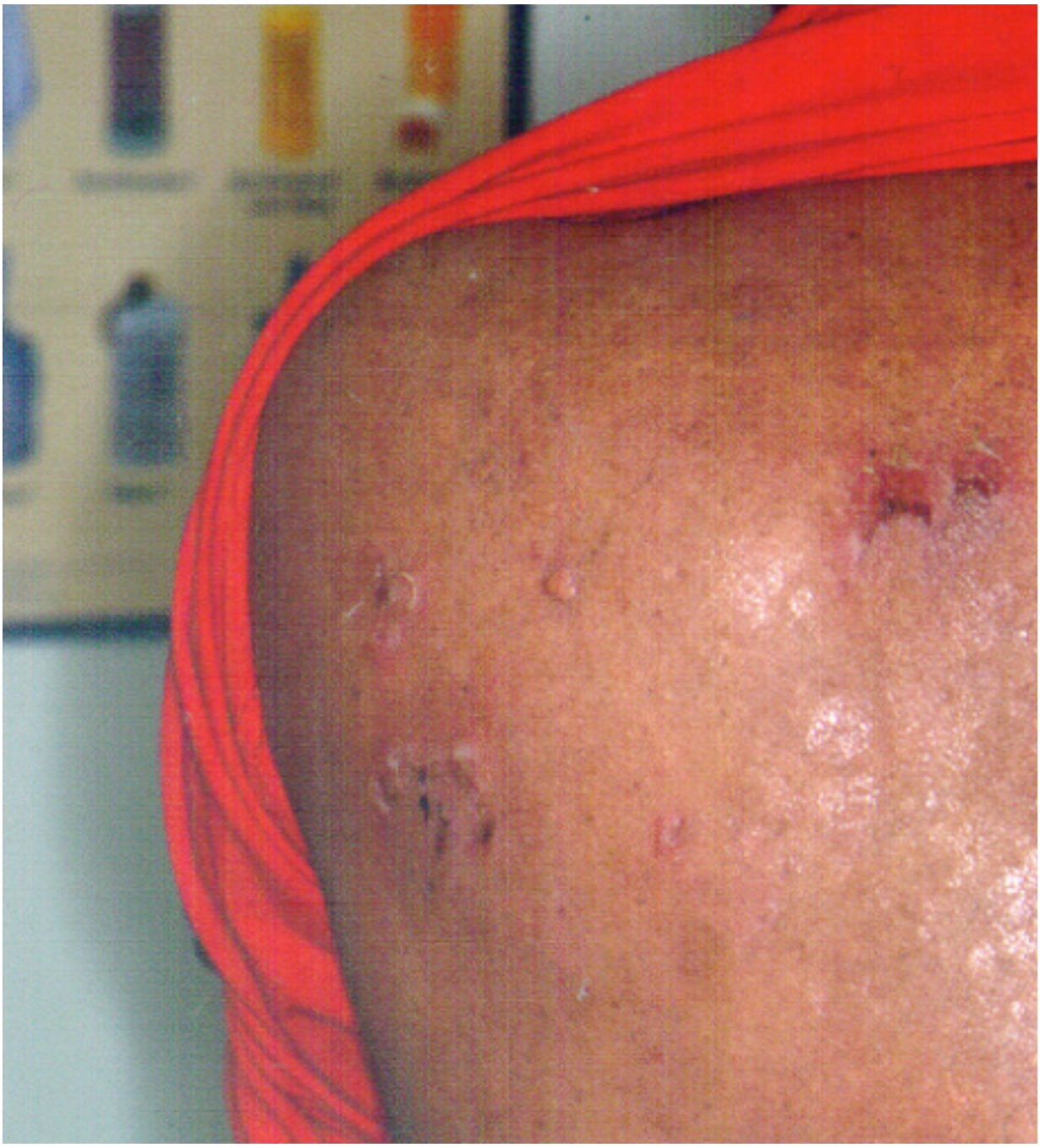
Media file 1: Middle-aged American woman of Mexican lineage with superficial bullae characteristic of pemphigus foliaceus.



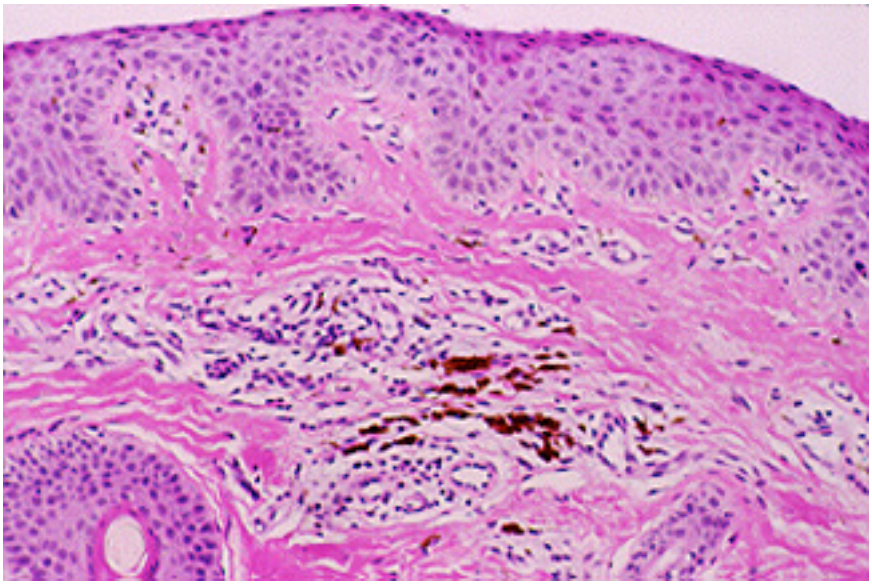
Media file 2: Pemphigus foliaceus. Middle-aged American woman of Mexican lineage with superficial bullae formation.



Media file 3: A 41-year-old woman of Puerto Rican origin with a 9-year history of pemphigus foliaceus, often with erythroderma flares.



Media file 4: A 41-year-old woman of Puerto Rican origin with a 9-year history of pemphigus foliaceus, often with erythroderma flares.



Media file 5: Histologic view shows the typical pattern of a detached stratum corneum without bullae formation (same patient as in Media File 4). Pigmentary incontinence is prominent in the dermis, reflecting the patient's 9-year history of recurrent superficial bullae.

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