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Pemphigus Erythematosus

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Updated: Oct 20, 2008

Introduction

Background

The various types of pemphigus include pemphigoid, pemphigus vegetans, Hailey-Hailey disease, and pemphigus foliaceus.

Pemphigus erythematosus, also known as Senear-Usher syndrome, is an overlap syndrome with features of lupus erythematosus (LE) and pemphigus foliaceus. Pemphigus is demonstrated by acantholysis and immunoglobulin deposits in the interkeratinocyte substance. The lupus component is demonstrated by circulating antinuclear antibodies (ANA) and sometimes by immunoglobulin and complement deposits at the dermoepidermal junction. The disease has a better prognosis than pemphigus foliaceus, but it can be chronic.

For a thorough description and introduction to the possible causes of pemphigus, see the article " Pemphigus: An Acronym for a Disease with Multiple Causes ", published by the International Pemphigus Society.

Pathophysiology

Patients present with vesiculobullae or superficially eroded lesions, which may ooze and crust, particularly in sun-exposed areas, such as the face, the upper part of the chest, and the back. Pemphigus may be photoactivated. LE is the classic autoimmune disease that demonstrates photosensitivity. It appears that a genetic predisposition to autoimmunity combines with a sensitivity to ultraviolet light leading to an overlap of these 2 diseases in rare cases. Now these are called immunobullous disease.

Frequency

United States

The incidence in the United States is estimated to be similar to that internationally.

International

The incidence of pemphigus is 0.5-3.2 cases per 100,000 population per year. Patients with pemphigus erythematosus comprise only a small subgroup of those with pemphigus. Kumar from India, in a 2008 article, reported a high prevalence (4.4 cases per million population), with a high preponderance (61.5%) in females.[1]

Mortality/Morbidity

With timely diagnosis and treatment, the disease typically has a good prognosis. Some patients may ultimately develop symptoms classified as criteria for systemic lupus erythematosus (SLE) by the American Rheumatism Association (ARA).

Race

Pemphigus erythematosus, like other variants of pemphigus erythematosus and LE, may be increased in patients who express specific human leukocyte antigen (HLA) haplotypes. Those identified to have pemphigus erythematosus are positive for human leukocyte antigen A10 (HLA-A10) or human leukocyte antigen A26 (HLA-A26) and human leukocyte antigen DRW6 (HLA-DRW6).

Sex

Reports generally find no difference in occurrence between the 2 sexes, although some studies from India suggest a male preponderance.

Age

Pemphigus erythematosus may occur at any age, but it is unusual in children.

Clinical

History

- Onset and progression are typically slow.
- Although the distribution of the lesions should suggest induction by sunlight, the patient may be completely unaware of the photosensitive nature of the disorder.

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Physical

- Lesions typically involve the scalp, the face, the upper part of the chest, and the back.
- Patients with pemphigus erythematosus classically present with small, flaccid bullae with scaling and crusting. Occasionally, the appearance may suggest a papulosquamous disorder.
- Secondary infection may occur, resulting in impetiginization, in healing with pigment changes, and in scarring.
- On the face, pemphigus erythematosus presents on the bridge of the nose and on the malar areas as in the butterfly distribution seen in LE.
- With extensive involvement, patients may present with an exfoliative erythroderma.
- The skin may be tender.
- Patients with pemphigus erythematosus do not typically develop mucous membrane involvement, which can be seen in some other variants of pemphigus.
- Electrolyte imbalance and loss of temperature control can occur with extensive skin involvement.

Causes

- Patients with pemphigus develop an autoimmune response directed against desmosomes. In patients with pemphigus foliaceus and its variant, pemphigus erythematosus, the target antigen is desmoglein 1. Desmogleins are desmosomal proteins important in keratinocyte adhesion. The binding of autoantibodies is postulated to result in a cascade of biochemical intracellular events that eventuates in the loss of desmosome function.
- Certain HLA haplotypes (A10 or A26, DRW6) are thought to be associated, suggesting a genetic predisposition.

Differential Diagnoses

Atopic Dermatitis
Lupus Erythematosus, Acute
Lupus Erythematosus, Discoid
Lupus Erythematosus, Subacute Cutaneous
Pemphigus Foliaceus
Pemphigus, Paraneoplastic
Seborrheic Dermatitis

Workup

Laboratory Studies

- Direct immunofluorescence
    - Linear deposits of immunoglobulin G (IgG) and C3 are present in the intercellular space of the epidermis.
    - Granular deposits of C3 and IgG at the dermoepidermal junction are present in 80% of patients, particularly in biopsy specimens from the face or other sun-exposed areas.
- Immunoelectron microscopy: IgG and C3 deposits are localized to the epidermal cell membranes and the upper dermis.
- Patients with pemphigus erythematosus may have other laboratory abnormalities suggestive of SLE; these include anemia, lymphopenia, thrombocytopenia, renal abnormalities, proteinuria, or a positive rheumatoid factor.

Procedures

- Select an early vesicle or bulla for skin biopsy. Perilesional skin is tested on immunofluorescence studies.

Histologic Findings

Intraepidermal superficial bullae are usually within the granular layer or just below it. Acantholysis may occur in the blister floor or roof. Old lesions may have follicular hyperkeratosis with acantholysis and dyskeratosis of the granular layer.

Treatment

Medical Care

Topical therapy

Topical corticosteroids are useful for patients with limited diseases or as an adjunct to systemic therapy. Selection of the appropriate topical steroid strength and vehicle depends on the body site, the age of the patient, and the potential for steroid adverse effects. Use of daily sunscreen and sun protection is necessary.

Systemic therapy

Systemic steroids have been the mainstay of therapy for widespread pemphigus since their first use in 1950. Prednisone 1-2 mg/kg/d as a single morning dose or as intravenous pulses may control the disease. Appropriate monitoring and follow-up care to avoid steroid adverse effects, including glucocorticoid-induced osteoporosis, is critical.

Dapsone is effective in some patients with pemphigus erythematosus. Patients tend to respond relatively quickly, with improvement within several weeks. It can be a steroid-sparing drug. The possible mode of action is stabilization of lysosomal membranes and inhibition of polymorphonuclear leukocyte (PMN) toxicity. The recommended dose is 100-200 mg/d. Hemolytic jaundice may result in people with G-6-PD deficiency. Other adverse effects include agranulocytosis, leading to death, headaches, malaise, hepatitis, hypersensitivity reactions, and neuropathy. Caution is required.

Azathioprine is a potent immunosuppressive agent that has been used as a steroid-sparing agent. The usual doses are 75-150 mg (2-3 mg/kg/d) combined with 40-80 mg of prednisone. After initial control of the disease is obtained, tapering to maintenance doses of azathioprine is recommended. Patients who are thiopurine methyltransferase activity deficient (11% of the population) are at an increased risk of bone marrow toxicity with this agent.

Other useful drugs

- Tetracycline and niacinamide
- Cyclophosphamide
- Methotrexate
- Parenteral gold
- Hydroxychloroquine
- Plasmapheresis
- Mycophenolate mofetil
- Extracorporeal photochemotherapy
- Rituximab

Consultations

A dermatologist with expertise in using and in monitoring of these agents is recommended.

Diet

Patients on long-term glucocorticoids should increase their intake of calcium and vitamin D as well as bisphosphates in an effort to prevent osteoporosis.

Activity

Patients should use appropriate sun-smart behaviors and protective clothing to minimize sun exposure that may exacerbate disease activity.

Medication

The goal of pharmacotherapy is to reduce morbidity and to prevent complications.

Plasmapheresis and immunoadsorption have been shown to be effective in the treatment of pemphigus erythematosus. Plasmapheresis[2,3,4] and, more recently, immunoadsorption,[5,6,7] are extracorporeal treatments that act rapidly on disease activity by lowering the load of the causative autoantibodies in the patient's circulation.

In immunoadsorption, the immunoglobulins are selectively removed from the patient's plasma by adsorbing the antibodies to the matrix in a column of the immunoadsorption apparatus, after which the "cleansed" plasma is returned to the patient. Reportedly, immunoadsorption has higher efficacy and fewer adverse effects compared with plasmapheresis. In one German study,[8] immunoadsorption was effective and safe in treating resistant and severe pemphigus. However, more studies are needed to support these data.

Corticosteroids

The mainstay of treatment of immunobullous diseases is steroids. Generally, high-dose steroids (ie, prednisolone, prednisone, methylprednisolone, dexamethasone), PO or IV, are effective in obtaining rapid disease control. However, high-dose and prolonged treatment with steroids often causes significant adverse effects. Screening and risk assessment of possible adverse effects (eg, diabetes, glaucoma, osteoporosis, blood pressure, history of GI bleeding) are required prior to and during treatment.

Concomitant calcium supplements and antacid drugs (eg, proton pump inhibitors) are recommended throughout therapy. A study[9] of patients with pemphigus vulgaris showed intravenous pulse combined with low-dose oral steroid therapy to be more effective and associated with fewer severe adverse effects than oral high-dose steroid therapy.

To reduce the adverse effects of systemic steroids, French researchers compared the efficacy and adverse effect profile of topical steroids with that of systemic steroids in the treatment of moderate-to-severe bullous pemphigoid.[10] Topical steroids were more effective than oral therapy and

were associated with far fewer severe complications. However, a recent report warns of the development of steroid-induced skin atrophy and striae after this regimen.[11]

Prednisone (Deltasone, Meticorten, Orasone, Sterapred)

Immunosuppressant for treatment of autoimmune disorders; may decrease inflammation by reversing increased capillary permeability and suppressing PMN activity. Stabilizes lysosomal membranes and also suppresses lymphocyte and antibody production.

Dosing

Adult

1-2 mg/kg/d PO qam; alternatively, 0.5-2 mg/kg/d; taper as condition improves; single morning dose is safer for long-term use, but divided doses have more anti-inflammatory effect

Pediatric

Administer as in adults

Interactions

Coadministration with estrogens may decrease clearance; concurrent use with digoxin may cause digitalis toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics

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

Monitor adrenal insufficiency when tapering drug; abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, growth retardation, and infections are possible complications of glucocorticoid use

Antineoplastic agents

These agents inhibit cell growth and proliferation. Intravenous pulse cyclophosphamide (500 mg qd) has also been suggested as adjunctive therapy after plasmapheresis to prevent "rebound" (marked increase of antibodies compensating for the antibodies depleted by plasmapheresis).[4]

High-dose immunoablative cyclophosphamide without stem cell rescue was effective in 2 patients with resistant pemphigus. However, considering the serious adverse effects of this high-dose regimen, it should be reserved for patients who are resistant to other treatments.[12,13,14]

Cyclophosphamide (Cytoxan, Neosar)

Several regimens with cyclophosphamide have been described in the treatment of immunobullous disorders. Cyclophosphamide is a potent cytotoxic agent that can cause severe cytopenia and hemorrhagic cystitis (bladder inflammation).
Oral low-dose cyclophosphamide is usually used as a steroid-sparing agent.
Intravenous cyclophosphamide (500 mg qd for 1 d) plus low-dose oral (50 mg qd) has been combined with intravenous pulse dexamethasone (100 mg qd for 3 d) to achieve rapid disease control.
Intravenous pulse cyclophosphamide (500 mg qd) has also been suggested as adjunctive therapy after plasmapheresis to prevent "rebound" (marked increase of antibodies compensating for the antibodies depleted by plasmapheresis).
More recently, high-dose immunoablative cyclophosphamide without stem cell rescue was effective in 2 patients with resistant pemphigus. However, considering the serious adverse effects of this high-dose regimen, it should be reserved for patients who are resistant to other treatments.
More studies are needed to outline the risk of adverse effects vs benefits of this regimen.

Dosing

Adult

10 mg/kg/d IV; 2.5-3 mg/kg/d PO 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 of cyclophosphamide while decreasing metabolite concentrations; may increase effect of anticoagulants; coadministration with high doses of phenobarbital may increase rate of metabolism and leukopenic activity of cyclophosphamide; thiazide diuretics may prolong cyclophosphamide-induced leukopenia and neuromuscular blockade by inhibiting cholinesterase activity

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

Sulfone antibiotics

Dapsone's anti-inflammatory mechanism of action differs from the antibacterial mechanism of action. Suppression of neutrophils by inhibiting the halide-myeloperoxidase system is the most likely mechanism of action for anti-inflammatory effects.

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.

Dosing

Adult

50-300 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 the second and third mo 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

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

Perform weekly blood counts (first mo), then perform WBC counts monthly (6 mo), and then semiannually; discontinue if 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, particularly at high dose; phototoxicity may occur when exposed to UV light

Immunosuppressants

These agents are effective in the treatment of autoimmune diseases. See Glied and Rico[15] and Tan et al[16] for references regarding adverse effects (eg, abnormal LFT results) related to triphosphate-methyltransferase (TPMT).

Azathioprine (Imuran)

Among the slowly acting adjuvant therapies, azathioprine is a useful and safe steroid-sparing agent, provided TPMT assay is performed prior to treatment. TPMT is an enzyme that converts azathioprine into its inactive metabolites.
If TPMT is lacking or present in a much lower concentration, patient is at high risk for bone marrow suppression and thus anemia, thrombocytopenia, and leukopenia. Therefore, analysis of TPMT levels is recommended before starting treatment.
Other adverse effects (eg, abnormal LFT results) are not reflected by this enzyme level.

Dosing

Adult

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

Initial: 2-5 mg/kg/d PO/IV
Maintenance: 1-2 mg/kg/d PO/IV

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

Contraindications

Documented hypersensitivity; low levels of serum TPMT

Precautions

Pregnancy

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

Precautions

Increases risk of neoplasia; caution in liver disease and renal impairment; hematologic toxicities may occur

Intravenous immunoglobulins

Latest development in the armamentarium for treating immunobullous disorders. IVIGs have proven beneficial in achieving rapid disease control in patients with immunobullous diseases.[17,18,19,20,21,22]

Immune globulin intravenous (Gamimune, Gammagard, Sandoglobulin)

Consists of IgG collected from a pool of thousands of blood donors (virus-free), thus providing a wide range of immunologically different IgG. Theoretically, they bind and neutralize pathogenic autoantibodies.
Administered IV, with each cycle lasting 3-5 d, at a dose of 1-2 g/kg/cycle. Several cycles are usually required.
Cost and availability limit use. IVIG costs approximately $5500 (approximately £3000) for a 5-d course based on a 70-kg patient. Generally used in resistant and severe bullous diseases in addition to immunosuppressive therapy or as monotherapy in patients with contraindications for immunosuppressive drugs.

Dosing

Adult

1-2 g/kg/cycle IV, each lasting 3-5 d; several cycles may be required

Pediatric

Not established

Interactions

Globulin preparation may interfere with immune response to live virus vaccine (MMR) and reduce efficacy (do not administer within 3 months of vaccine)

Contraindications

Documented hypersensitivity; IgA deficiency

Precautions

Pregnancy

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

Precautions

Administer only to resistant cases; check serum IgA before IVIG (use an IgA-depleted product, eg, Gammagard S/D); infusions may increase serum viscosity and thromboembolic events; infusions may increase risk of migraine attacks, aseptic meningitis (10%), urticaria, pruritus, or petechiae (2-30 d postinfusion)
Increases risk of renal tubular necrosis in elderly patients and in patients with diabetes, volume depletion, and preexisting kidney disease; laboratory result changes associated with infusions include elevated antiviral or antibacterial antibody titers for 1 mo, 6-fold increase in ESR for 2-3 wk, and apparent hyponatremia

Anti-inflammatory agents

Anti-inflammatory agents (eg, dapsone, gold, tetracyclines) are also being used to treat certain immunobullous disorders. However, they are generally used in patients with mild-to-moderate disease, with the exception of those with dermatitis herpetiformis and linear IgA disease, in

whom dapsone is still first-line treatment. Dapsone can be started after glucose-6-P-dehydrogenase screening. Low levels are associated with a high risk of methemoglobinemia. When using tetracyclines, some authors have reported minocycline-induced pigmentation in patients with pemphigus and pemphigoid, with a prevalence that appears to be much higher than in persons with acne or rheumatoid arthritis.[23]
Targets a cell-specific protein and may represent a promising novel therapeutic option for refractory immunobullous diseases.[24,25,26,27]

Rituximab (Rituxan)

Monoclonal anti-CD20 antibody (CD20 is a protein on the surface of lymphocytes), reported to be effective in treating resistant pemphigus foliaceous and vulgaris. May deplete B lymphocytes (antibody-producing cells) and rapidly removes desmoglein antibodies (antibodies causing pemphigus) from circulation.

Dosing

Adult

375 mg/m^2 IV qwk for 4 doses on days 1, 8, 15, and 22

Pediatric

Not established

Interactions

None reported

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

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Precautions

Hypotension, bronchospasm, and angioedema may occur; discontinue treatment if life-threatening cardiac arrhythmias occur

Follow-up

Deterrence/Prevention

Sun avoidance and sun protection are recommended.

Complications

The types of medications used to control severe pemphigus erythematosus may lead to serious iatrogenic disorders.

Prognosis

The prognosis of pemphigus erythematosus is better than that of pemphigus vulgaris. With good dermatologic care, patients with pemphigus erythematosus are often able to live normal lives.

Patient Education

Patient education about possible triggers for the disease is important. Patients should minimize sun exposure. Additionally, as in all photosensitive disorders, patient education on the use of sunscreens, protective clothing, and sun-smart behaviors is a cornerstone of therapy.

Miscellaneous

Medicolegal Pitfalls

- Failure to explain the toxicity and adverse effects of steroids, cyclophosphamide, or other drugs
- Failure to explain the disease's prognosis before treatment
- Medscape Medical Malpractice and Legal Issues Resource Center

Special Concerns

- A delay of pregnancy is recommended during treatment and for a minimum of 2 years after stopping treatment with immunosuppressants.
- Wound healing may be delayed in patients on glucocorticoids.

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