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Pemphigus, Drug-Induced

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Introduction

Background

Drug-induced pemphigus is a well-established variant of pemphigus. Since the 1950s, evidence has grown that drugs may cause or exacerbate pemphigus. A drug origin should be considered in every new patient with pemphigus. The most common variant of pemphigus associated with drug exposure is pemphigus foliaceus, although pemphigus vulgaris has been described as well. In penicillamine-treated patients, pemphigus foliaceus is more common than pemphigus vulgaris, with an approximate ratio of 4:1.

Pathophysiology

A variety of drugs have been implicated in the onset of drug-induced pemphigus. Some of these drugs induce antibody formation, which results in acantholysis via a mechanism identical to that found in idiopathic pemphigus. Other drugs are postulated to induce acantholysis directly in the absence of antibody formation.

Drugs that induce pemphigus may be categorized into 2 groups: thiol drugs and nonthiol drugs. Thiol drugs are reported most frequently as the culprits of drug-induced pemphigus. They contain a thiol group (-SH) in their chemical structure. Penicillamine, captopril, and enalapril are the thiol drugs most often associated with drug-induced pemphigus.

Thiol drugs are postulated to induce acantholysis through biochemical mechanisms without antibody formation. Experiments with skin explants have demonstrated that thiol drugs can induce acantholysis directly. These investigations have resulted in several hypotheses regarding thiol-induced acantholysis, including the following:

- Thiol drugs may interfere with critical enzymes, such as keratinocyte transglutaminase, resulting in loss of epidermal cell cohesion.
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- Thiol drugs may activate endogenous proteolytic enzymes, such as plasminogen activators, with subsequent cleavage of desmosomal antigens.
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- Thiol drugs may bind desmoglein 1 or desmoglein 3, creating a neoantigen, which then elicits an immune response.

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- Binding of the pemphigus antigens by thiol drugs may interfere with their normal function, resulting in acantholysis.

Nonthiol drugs include sulfur-containing drugs and drugs without sulfur in their structure. Sulfur-containing drugs, such as penicillins, cephalosporins, and piroxicam, may undergo hydrolytic breakdown in vivo to form thiols; therefore, they are termed masked thiols. An active amide group is found in the structure of many nonthiol drugs, which has resulted in the speculation that this structure may be responsible for the induction of disease.

Nonthiol drugs are more likely to induce acantholysis via immune mechanisms. Studies of cases of non-thiol-induced pemphigus reveal the presence of autoantibodies that recognize pemphigus antigens, in particular desmoglein 3, which is the pemphigus vulgaris antigen. In fact, this group of patients tends to have clinical, histologic, immunologic, and prognostic features similar to idiopathic pemphigus vulgaris.

One case report describes localized pemphigus foliaceus induced by topical imiquimod treatment. Imiquimod does not contain thiol, sulfur, or amide groups in its structure. The exact mechanism of acantholysis induction from this medication is unknown. Because imiquimod is known to cause a localized immune response at the site of application, the generation of antibodies to desmoglein 1 has been postulated as a mechanism of action.

Frequency

International

More than 200 cases of drug-induced pemphigus have been reported, with penicillamine accounting for almost 50%. In patients who take penicillamine for longer than 6 months, it is estimated that 7% develop pemphigus.

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Mortality/Morbidity

- **Mortality rates for drug-induced pemphigus have not been published. A fatal case of acute onset pemphigus vulgaris has been reported in a patient treated with interferon beta and recombinant interleukin 2.**
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- **Significant morbidity may occur. Patients with extensive cutaneous lesions report significant pain and burning sensations. Oral involvement also causes significant pain and results in decreased oral intake. This may result in dehydration.**

Race

Most case series in the literature have not reported the race of patients with drug-induced pemphigus. A number of reports from Israel of drug-induced pemphigus occurring in Jewish persons of Ashkenazi origin suggest an ethnic predominance.

Sex

A recent study evaluating the epidemiology of pemphigus in the Mediterranean region of Turkey found a female predominance (male-to-female ratio, 1:1.4).

Age

Drug-induced pemphigus can occur at any age. In reported cases, patient age has ranged from the third to ninth decade.

Clinical

History

- Most patients develop the eruption a few weeks after starting therapy with the offending agent.
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- In penicillamine use, the eruption may not develop until 6 months after the onset of therapy.
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- Some patients may give a history of a nonspecific eruption prior to the development of pemphigus type lesions.
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Physical

- Clinical manifestations of drug-induced pemphigus depend on the pathomechanism involved.
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- Disease caused by thiol drugs tends to present with the clinical findings of pemphigus foliaceus. Erythematous, scaly, crusted plaques occur primarily on the trunk. Occasional superficial vesicles and bullae may be seen, but usually, they are ruptured. Oral lesions do not occur.
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- Nonthiol drug-induced pemphigus presents predominantly as pemphigus vulgaris. Flaccid bullae and erosions occur on normal-appearing skin and, also, on the oral mucosa.
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Causes

- Speculation exists that genetic predisposition may be important in non-thiol-triggered pemphigus.
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- Human leukocyte antigen DR4 (HLA-DR4) is associated with idiopathic pemphigus; however, few studies have provided data concerning HLA typing in cases of drug-induced pemphigus.
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- Drugs implicated in drug-induced pemphigus are as follows:
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- Thiols
 - Penicillamine
 - Bucillamine
 - Captopril
 - Lisinopril
 - Pyritinol
 - Thiopronine
 - Piroxicam
 - Thiamazole
 - 5-Thiopyridoxine
 - Gold sodium thiomalate
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- Antibiotics
 - Penicillin and derivatives
 - Cephalosporins
 - Quinolones
 - Rifampicin
-
- Pyrazolone derivatives
 - Phenylbutazone
 - Aminopyrine
 - Azapropazone
 - Oxyphenylbutazone
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- Miscellaneous drugs
 - Propanolol
 - Levodopa
 - Heroin
 - Progesterone
 - Carbamazepine
 - Phenobarbital
 - Lysine acetylsalicylate
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Differential Diagnoses

Pemphigus Erythematosus

Pemphigus Foliaceus

Pemphigus Herpetiformis

Pemphigus Vulgaris

Pemphigus, Paraneoplastic

Workup

Other Tests

- **Indirect immunofluorescence: Circulating autoantibodies are present in approximately 70% of patients with drug-induced pemphigus. When positive, indirect immunofluorescence findings usually reveal low titers of antibodies, which do not correlate with the severity of the disease.**

These antibodies recognize the pemphigus foliaceus antigen (desmoglein 1), pemphigus vulgaris antigen (desmoglein 3), or both. Circulating autoantibodies have been demonstrated to be more likely to occur in patients with non-thiol-induced pemphigus. In this group, the immunologic pattern and clinical course are similar to that of idiopathic pemphigus vulgaris.

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- **Direct immunofluorescence:** Tissue-bound intercellular immunoglobulin G antibodies are diagnostic of pemphigus and are found in most patients (75-90%) with drug-induced pemphigus.
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Histologic Findings

Histologic features of established lesions correlate with the clinical appearance. Lesions resembling pemphigus foliaceus reveal superficial epidermal acantholysis, while those resembling pemphigus vulgaris reveal suprabasal acantholysis. Eosinophilic spongiosis may be present. It is not possible to distinguish between idiopathic and drug-induced pemphigus based on histologic features.

Treatment

Medical Care

Withdrawal of the offending agent is the first step in treatment. Most, but not all, patients go into remission once the offending agent is stopped. Some patients may follow a chronic course identical to that of idiopathic pemphigus vulgaris. These patients require systemic corticosteroids and/or immunosuppressive therapy.

Consultations

- **Burn unit consultation:** For patients who have erosions involving a significant portion of the body surface area, the burn unit is helpful in providing wound care (cleansing, application of topical antibiotics, and bandaging).

Diet

Mucosal lesions may be exacerbated by eating hard or crunchy foods, such as potato chips, crackers, fresh fruits, and uncooked vegetables.

Medication

For patients in whom the disease does not resolve upon withdrawal of the offending agent, medical therapy is necessary. Generally, systemic corticosteroids or other immunosuppressants are required. Anecdotal reports support the use of alternate immunomodulating agents (eg, antimalarial drugs,

rituximab, intravenous immunoglobulin, mycophenolate mofetil). Recent reports suggest targeting cholinergic drugs as antiacantholytic therapy for idiopathic pemphigus.

Corticosteroids

Systemic corticosteroids (eg, prednisone) should be initiated in patients with disease that persists after the implicated agent has been discontinued. Since most cases of drug-induced pemphigus involve an immune mechanism, the anti-inflammatory and immune modulating properties of corticosteroids are beneficial. In idiopathic pemphigus vulgaris and pemphigus foliaceus, high doses of systemic corticosteroids may be needed. This also may be necessary for cases of drug-induced pemphigus.

Prednisone (Deltasone, Orasone, Sterapred)

Initial DOC for severe or recalcitrant cases of drug-induced pemphigus. Immunosuppressant for treatment of autoimmune disorders; may decrease inflammation by reversing increased capillary permeability and suppressing PMN activity. Stabilizes lysosomal membranes and suppresses lymphocytes and antibody production. Up-regulates keratinocyte adhesion molecules desmoglein 1 and 3.

Dosing

Adult

0.5-2 mg/kg/d PO; high doses (eg, 150-200 mg/d PO) may be needed; taper as condition improves; single morning dose is safer for long-term use, but divided doses have more anti-inflammatory effect

Pediatric

4-5 mg/m²/d PO or 0.05-2 mg/kg PO divided bid/qid; taper over 2 wk, as symptoms resolve

Interactions

Coadministration with estrogens may decrease prednisone clearance; when used with digoxin, digitalis toxicity secondary to hypokalemia may increase; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics; postmarketing surveillance reports indicate that risk of tendon rupture may be increased in patients receiving concomitant fluoroquinolones and corticosteroids, especially elderly persons; concomitant use with amphotericin B liposome may potentiate hypokalemia; concomitant therapy with montelukast may result in severe

peripheral edema; coadministered ritonavir may significantly increase serum concentrations of prednisone

Contraindications

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

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Abrupt discontinuation of glucocorticoids may cause adrenal crisis; adverse effects include weight gain, cushingoid appearance, osteoporosis, avascular necrosis, increase risk of infection, peptic ulcer disease, posterior subcapsular cataract formation, psychosis, agitation, insomnia, depression, hypertension, and skin changes including atrophy, acneiform eruption, striae, poor wound healing, and hirsutism

Immunosuppressants

For patients who do not respond to moderate doses of systemic steroids or for patients in whom steroids are contraindicated. Also used as steroid-sparing agents.

Azathioprine (Imuran)

Antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins. May decrease proliferation of immune cells, which results in lower autoimmune activity. Useful in steroid-resistant patients. Less toxic than some other immunosuppressants. Generally, used in conjunction with low doses of systemic corticosteroids.

Prior measurement of thiopurine methyltransferase (TPMT) levels can be useful in guiding initial dose.

Dosing

Adult

1-3 mg/kg/d PO/IV; 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

Initial dose: 2-5 mg/kg/d PO/IV

Maintenance dose: 1-2 mg/kg/d PO/IV

Interactions

Toxicity increases with allopurinol; concurrent use with ACE inhibitors may induce severe leukopenia; angiotensin-converting enzyme inhibitors, warfarin, may increase levels of methotrexate metabolites and decrease effects of anticoagulants, neuromuscular blockers, and cyclosporine; alfalfa, black cohosh, and echinacea may reduce immunosuppressive drug effectiveness

Contraindications

Documented hypersensitivity; history of treatment with alkylating agents; low levels of serum TPMT; pregnancy, breastfeeding

Precautions

Pregnancy

D - Unsafe in pregnancy

Precautions

May cause leukopenia, thrombocytopenia, hemorrhagic cystitis, liver toxicity, nausea and vomiting, and increased risk of infection; increases risk of neoplasia; check TPMT level prior to therapy and follow liver, renal, and hematologic function; pancreatitis rarely associated; hepatotoxicity and pancreatitis may occur

Cyclophosphamide (Cytosan, Neosar)

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. Effective in treating pemphigus; however, this drug also is very toxic.

Dosing

Adult

1-2 mg/kg/d PO; alternatively, 2.5-3 mg/kg/d PO qid; intermittent IV pulse also has been used

Pediatric

Administer as in adults

Interactions

Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects of cyclophosphamide; 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; may increase risk of infection by live vaccines; may increase risk of developing noncutaneous solid malignancies when coadministered with etanercept; coadministration with indomethacin may cause fluid retention; nevirapine and St. John's wort may decrease plasma concentrations of cyclophosphamide

Contraindications

Documented hypersensitivity; severely depressed bone marrow function; pregnancy; breastfeeding

Precautions

Pregnancy

D - Unsafe in pregnancy

Precautions

Hematologic myelosuppression, primarily leukopenia, thrombocytopenia, anemia, gastrointestinal adverse effects, urologic adverse effects, and hemorrhagic cystitis may occur; encourage fluid intake; 45-fold increase in bladder cancer exists; interferes with oogenesis and spermatogenesis; may cause sterility in both sexes but may be irreversible in some patients; may increase risk of malignancy and increased risk of infections; may cause oligospermia or azospermia, cardiomyopathy, infectious disease, or interstitial pneumonia; increased risk of malignancy; possibility of increased toxicity in adrenalectomized patients; tamoxifen may increase risk of thromboembolism

Follow-up

Complications

- **Secondary infections may occur because of the disruption of the skin barrier. Extensive erosions may promote entrance of bacteria, resulting in cutaneous infections, bacteremia, or sepsis.**
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Prognosis

- Patients with thiol-induced pemphigus and patients lacking cell surface autoantibodies have a more favorable prognosis. Up to 50% of thiol-induced pemphigus cases remit upon withdrawal of the drug.
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- Patients with pemphigus induced by nonthiol drugs are more likely to have cell surface antibodies and to have a chronic course similar to idiopathic pemphigus vulgaris.
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Patient Education

- Educate patients about their disease and their medications, including adverse effects from therapy.
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- The International Pemphigus and Pemphigoid Foundation, a nonprofit support group for patients with pemphigus and their families, offers an active web site and a quarterly newsletter, as well as local chapters in many parts of the country.

Miscellaneous

Medicolegal Pitfalls

- Failure of dermatologists and other providers to be alert to the role of drugs in causing pemphigus. Offending agents must be stopped and the patient treated appropriately.
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