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Pemphigus, Paraneoplastic

Lynne J Goldberg, MD, Associate Professor, Departments of Dermatology and Pathology, Boston University School of Medicine
Nauman Nisar, MD, Fellow, Department of Dermatology, Section of Dermatopathology, Boston University Medical Center

Updated: Jan 25, 2008

Introduction

Background

Anhalt et al[1] first described paraneoplastic pemphigus in 1990. The authors reported 5 patients with underlying neoplasms who developed oral erosions and bullous skin eruptions. Skin biopsy samples showed both suprabasal acantholysis and interface dermatitis. Direct immunofluorescence (DIF) testing and indirect immunofluorescence (IDIF) testing revealed intraepidermal intercellular staining with immunoglobulin G (IgG); DIF testing also revealed deposition of complement at the dermoepidermal junction. By immunoprecipitation, target antigens were identified from skin extracts with molecular weights of 250, 230, 210, and 190 kd. Since then, many patients with paraneoplastic pemphigus have been reported, and patients previously believed to have other diseases have been retrospectively diagnosed.

A summary of the original criteria for the diagnosis of paraneoplastic pemphigus includes the following:

- Painful mucosal erosions, sometimes with a skin eruption that eventually results in blisters and erosions, in the setting of confirmed or occult malignancy
- Histopathologic changes of acantholysis, keratinocyte necrosis, and interface dermatitis
- DIF observation of immunoreactants, typically IgG and complement (C3) within the epidermal intercellular spaces as well as at the epidermal basement membrane
- IDIF observation of circulating antibodies specific for stratified squamous or transitional epithelia (transitional epithelium)
- Immunoprecipitation of a complex of proteins with typical molecular weights, as described in Other Tests

Because not all patients demonstrate these original criteria, Anhalt[2] has proposed the following new, minimal criteria for the diagnosis of paraneoplastic pemphigus:

- Painful, progressive stomatitis
- Histopathologic changes of acantholysis or lichenoid/interface dermatitis
- Demonstration of antiplakin antibodies
- Demonstration of an underlying lymphoproliferative neoplasm

Note, however, that while a tumor is essential in the diagnosis, patients with tumors other than lymphoproliferative neoplasms can develop paraneoplastic pemphigus. These include thymoma, sarcoma, and lung carcinoma.

Pathophysiology

Paraneoplastic pemphigus is an autoimmune disorder initiated by an underlying lymphoproliferative disorder. Tumor antigens are hypothesized to evoke both a humoral and a cellular immune response that leads to blistering in mucosa and other epithelia. Affected organ systems include the integument, the respiratory tract, and the gastrointestinal tract. It has also been reported to occur in association with benign tumors.

Mortality/Morbidity

Paraneoplastic pemphigus is often fatal, especially when associated with malignancy. Mortality rates approach 90%. Causes of death include sepsis, with resultant multiorgan failure, and respiratory failure due to the direct effects of the disease on the respiratory tract epithelium. The latter is being increasingly recognized, and pulmonary involvement has been found to occur in approximately 30-40% of patients. The susceptibility to infection caused by the loss of skin integrity is exacerbated by the potent immunosuppressive medications used to treat the condition.

Race

No racial predilection is apparent.

Sex

Males and females are affected equally.

Age

The mean age at onset is 60 years. However, paraneoplastic pemphigus can occur in children, and patients ranging in age from 7-76 years have been reported. In children, paraneoplastic pemphigus is often the presenting sign of Casalvato da Windows Internet Explorer 8> Subject: Pemphigus, Paraneoplastic: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 00:39:07 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="----=_NextPart_000_0105_01CA2CF8.1C9CCC70" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. ------=_NextPart_000_0105_01CA2CF8.1C9CCC70 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: http://emedicine.medscape.com/article/1064452-print

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Clinical

History

Paraneoplastic pemphigus is usually associated with malignancy, although it can occur in association with benign neoplasms. The most common malignancy associated with paraneoplastic pemphigus is non-Hodgkin lymphoma.[3,4,5] Other associated malignancies and conditions include chronic lymphocytic leukemia, Castleman disease,[6,7,8] Waldenström macroglobulinemia,[9] thymoma,[7,10] sarcoma,[10] and lung carcinoma.

The following articles may be helpful:

- Non-Hodgkin Lymphoma (pediatric focus)
- Chronic Lymphocytic Leukemia
- Waldenstrom Hypergammaglobulinemia
- Thymoma

Patients present with painful oral erosions, often accompanied by a generalized cutaneous eruption. Oral erosions occur early and typically are severe, often involving the lateral tongue and vermilion. The eruption can assume a wide variety of morphologies. A classification system has been suggested, dividing lesions into pemphiguslike, pemphigoidlike, erythema multiforme–like, graft versus host disease–like, and lichen planus–like. Additionally, some patients report pruritus or pain.

Physical

Mucosal findings

The earliest and most constant clinical finding in paraneoplastic pemphigus is painful oral erosions. Of those patients who present with a skin eruption, all go on to develop mucositis at some point during the course of the disease. Some patients only experience oral lesions.

The erosions can occur anywhere in the mouth, including the buccal, labial, gingival, and lingual mucosae. All surfaces of the oropharynx can be affected. Erosions and subsequent crusting on the vermilion of the lips are typical and similar to that seen in persons with Stevens-Johnson syndrome. Genital mucosal surfaces can also be affected. Finally, nasal ulcers may cause epistaxis.

Cutaneous findings

The eruption of paraneoplastic pemphigus is highly variable. Patients may present with diffuse erythema, vesiculobullous lesions, papules, scaly plaques, exfoliative erythroderma, erosions, or ulcerations. The erythema can be macular, urticarial, or targetoid, and it may be polymorphous. Patients may initially present with erythema, and they may subsequently develop bullae and erosions.

Large areas of denudation with a positive Nikolsky sign can occur.

Pustules have been reported. The papular lesions may resemble lichen planus, and the oral lesions may also be mistaken for lichen planus.[11] A single patient has been reported with a solitary, pemphigus vegetans–like lesion that arose in a previous bulla. The palms and the soles may be involved.

Extracutaneous findings

Biopsy-confirmed paraneoplastic pemphigus has been reported in the gastrointestinal tract and the respiratory tract mucosa. The latter has been increasingly recognized and is a significant cause of mortality. Pulmonary involvement manifests as obstructive lung disease and progresses to bronchiolitis obliterans and death. Despite its ominous significance, signs of pulmonary involvement are subtle. Patients develop dyspnea, yet chest radiograph findings are normal.

Ocular involvement ranges from mild conjunctivitis to symblepharon with corneal scarring.[12]

Causes

The association of paraneoplastic pemphigus with malignancy is strong. Only a handful of patients have had no associated diagnosis. Some patients have had benign neoplasms, including thymoma and Castleman disease. Only a single patient without a tumor has met the diagnostic criteria, yet this patient had a rapid demise and may have died with an undiagnosed malignancy. Patients have developed paraneoplastic pemphigus while in remission of their malignancy, leading some authors to prefer the term neoplasia-induced pemphigus.[13]

Treatment of the underlying malignancy does not necessarily halt progression of the paraneoplastic pemphigus, although some have observed that clinical manifestations improve as autoantibody titers decrease following resection of the tumor.

Circulating and tissue-bound antibodies in patients with this disease are directed against a group of molecules with sequence homology and belonging to the plakin family. These molecules are found in the intracellular attachment plaques of desmosomes and hemidesmosomes, and they play a key role in intermediate filament attachment. However, the number of reported target antigens has increased over time and varies between patients. This variability likely accounts for the clinical heterogeneity of this disease. By immunoprecipitation, target antigens (in decreasing order of incidence) include desmoglein 3, desmoglein 1, envoplakin (210 kd), periplakin (190 kd), desmoplakin I (250 kd), desmoplakin II (210 kd), and bullous pemphigoid antigen I (230 kd). Plectin (>400 kd) and an unidentified 170-kd protein have also been found.[14]

How tumors induce autoantibodies to plakin proteins is not known. Tumor cells have been demonstrated to produce autoantibodies that react to epidermal proteins. Other postulates include (1) cross-reactivity of tumor antigens and epidermal antigens and (2) tumor production of plakin proteins that initiate an autoimmune response. Dysregulated cytokine production by tumor cells, specifically interleukin 6, contributing to the autoimmune process is another hypothesis. The concept of epitope spreading, with which patients develop antibodies to multiple structurally related and unrelated proteins, may explain the multitude of antibodies produced in association with this disease.

Differential Diagnoses

Bullous Pemphigoid
Cicatricial Pemphigoid
Drug Eruptions
Epidermolysis Bullosa
Epidermolysis Bullosa Acquisita
Erythema Multiforme
Lichen Planus
Pemphigus Vulgaris
Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Workup

Laboratory Studies

The evaluation of patients suspected of having paraneoplastic pemphigus includes obtaining samples by skin biopsy for routine microscopy and DIF testing, followed by more sophisticated testing when indicated.

- If the histologic features and DIF results suggest the diagnosis, serum should be sent for IDIF testing. The choice of substrate for the IDIF is important because different substrates express different antigens. Monkey esophagus is considered more sensitive than human skin. Transitional epithelium, such as rat bladder, can also be used. If IDIF results are negative, immunoprecipitation should be performed.[15]
- Immunoprecipitation and immunoblotting are sensitive assays that are very helpful in confirming the diagnosis; they are available at certain immunodermatology research laboratories.
- Once the diagnosis of paraneoplastic pemphigus is established, further evaluation for malignancy may be necessary.

Other Tests

DIF testing

Skin biopsy samples for DIF testing should be taken from noninvolved, perilesional skin. IgG, with or without complement, binds in an intercellular pattern within the epidermis. Immunoglobulin A (IgA) and immunoglobulin M (IgM) also may be detected. Staining can be diffuse or focal.

Some patients have granular or linear deposition of complement, IgG, and/or IgM along the dermoepidermal junction. The combination of intercellular and subepidermal deposition of immunoreactants is a clue to the diagnosis of paraneoplastic pemphigus.

IDIF testing

IDIF testing is performed by using sera obtained from patients suspected of having paraneoplastic pemphigus and is a good screening test for this disease. Patients with high-titer antibodies exhibit both intercellular intraepidermal antibody depositionand deposition along the dermoepidermal junction. Patients with low titers only exhibit deposition intercellularly in a pattern identical to that of pemphigus vulgaris.

Because circulating antibodies that bind to the cell surface of stratified squamous epithelia are common to all forms of pemphigus, other substrates, such as rodent bladder, can be useful in distinguishing paraneoplastic pemphigus from pemphigus vulgaris or pemphigus foliaceus. Binding to rat bladder transitional epithelium is specific for circulating autoantibodies from patients with paraneoplastic pemphigus, with a specificity of 83%[15]; sensitivity ranges from 75-86% depending on the study.

Immunoprecipitation and immunoblotting

Sera from patients with paraneoplastic pemphigus contain autoantibodies directed at several members of the plakin family, including desmoplakin I (250 kd), BPAG I (230 kd), desmoplakin II (210 kd), envoplakin (210 kd), periplakin (190 kd), plectin (500 kd), and an unidentified 170-kd protein.

Desmoglein I and desmoglein III antigens, targeted in pemphigus vulgaris and pemphigus foliaceus, respectively, have also been found in the sera of patients with paraneoplastic pemphigus. These antibodies are directed against transmembrane antigens. Disruption of the keratinocyte membrane may allow formation of antibodies against plakins, which are intracellular.

Immunoprecipitation or immunoblotting is the standard diagnostic test for paraneoplastic pemphigus because either has a higher specificity and sensitivity than IDIF testing. Unfortunately, neither is widely available; however, they can be performed in some research settings.

Sensitivity and specificity

In one study, IDIF identification of autoantibodies with a rat bladder substrate and immunoblotting detection of autoantibodies against periplakin (190 kd) and envoplakin (210 kd) were the most specific and sensitive tests for paraneoplastic pemphigus. Tests that are specific but not highly sensitive are DIF and immunoblot recognition of desmoplakin I and bullous pemphigoid antigen 1.

Histologic Findings

Vesicular lesions express the most characteristic histopathologic features. Oral and cutaneous lesions show variable epidermal necrosis, suprabasal acantholysis, dyskeratotic keratinocytes, vacuolar interface dermatitis, and lymphocytic exocytosis. Substantial inflammation can be present, even in early lesions.

Oral mucosal lesions show the greatest acantholysis, while some skin lesions may not have any acantholysis. Biopsy specimens of severe stomatitis may reveal only ulceration. When present, suprabasal acantholysis can result in clefts and tombstoning, which is the appearance of the basal cell layer below the cleft, and it can be indistinguishable from pemphigus vulgaris.

A distinctive feature of paraneoplastic pemphigus is dyskeratosis. Dyskeratosis is a constant feature, but the number of dyskeratotic keratinocytes is variable. Dyskeratotic keratinocytes are found at all levels in the epidermis, especially within the zones of acantholysis, and they can be found in cutaneous adnexa. The presence of dyskeratosis in a person with a suprabasal acantholytic bullous disorder is a clue to the presence of paraneoplastic pemphigus.

Interface dermatitis is a frequent finding in persons with paraneoplastic pemphigus, and it can be found both with and without acantholysis. Exocytosis of inflammatory cells into the epidermis is common, and the amount and degree are directly proportional to the degree of dyskeratosis. Satellite cell necrosis (a lymphocyte adjacent to a necrotic keratinocyte) can occur. Lesions showing marked vacuolar alteration are accompanied by melanophages in the papillary dermis.

Dermal changes include a superficial perivascular infiltrate of variable intensity, which is mostly composed of lymphocytes. The inflammation can sometimes be lichenoid, leading to a misdiagnosis of lichen planus. Papillary dermal edema is present in early lesions, whereas older lesions may exhibit mild dermal fibrosis.

Treatment

Medical Care

Response to treatment is generally poor, especially for mucosal lesions. Initial care is aimed at treating superinfection, if present. Warm compresses, nonadherent wound dressings, and topical antibiotic ointment are helpful. Potent immunosuppressive agents are required to decrease blistering, but they are often ineffective. High-dose corticosteroids are first-line therapy,[4] followed by steroid-sparing agents such as azathioprine, cyclosporine, and mycophenolate mofetil. In general, skin lesions are more responsive to therapy than mucosal lesions.

Other therapeutic options include plasmapheresis, immunophoresis, intravenous gammaglobulin,[16] and stem cell ablation therapy with high-dose cyclophosphamide[3] without stem cell rescue. Rituximab has been tried in several patients with mixed results.[17] Treating the underlying malignancy may control autoantibody production, and intravenous gammaglobulin at the time of surgery may help prevent the development of bronchiolitis obliterans.

Surgical Care

For solid neoplasms, curative resection should be attempted when appropriate, but this does not halt disease progression. If surgery results in decreased autoantibody production, the disease may improve. Intravenous immunoglobulin (IVIG) before, during, and after the surgery may block autoantibody released from the tumor.

Consultations

Respiratory therapy may be beneficial when pulmonary involvement causes respiratory insufficiency. Consultations from a pulmonary medicine specialist, an ophthalmologist, a gastroenterologist, and an otolaryngologist should be obtained when appropriate.

Medication

The medications used to treat paraneoplastic pemphigus are potent immunosuppressive agents with numerous adverse effects. All patients taking these medications require periodic monitoring of laboratory values.

Immunosuppressives

These agents diminish the production of autoantibodies and decrease resultant blistering and erosions.

Prednisone (Deltasone, Orasone, Sterapred)

Affects all organ systems. On a cellular level, affects cell activation, replication, differentiation, and mobility. Net result is inhibition of immediate and delayed hypersensitivity. Suppression of antibody production requires higher doses than suppression of monocyte function.

Dosing

Adult

1-2 mg/kg/d PO; 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

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

Interactions

Ketoconazole, erythromycin, clarithromycin, estrogens, and birth control pills may increase levels; aminoglutethimide, phenytoin, phenobarbital, rifampin, cholestyramine, and ephedrine may decrease levels
Levels of potassium-depleting diuretics (potentiate potassium loss and digitalis toxicity) and cyclosporine may increase; isoniazid, insulin (resistance is induced), and salicylate levels may decrease
Monitor anticoagulant therapy and theophylline levels

Contraindications

Absolute: Systemic fungal infection; herpes simplex keratitis; hypersensitivity (usually with corticotropin; occasionally with intravenous preparations)
Relative: hypertension; active tuberculosis, CHF; prior psychosis; positive intermediate purified protein derivative test result; glaucoma; severe depression; diabetes mellitus; active peptic ulcer disease; cataracts; osteoporosis; recent bowel anastomosis; pregnancy

Precautions

Pregnancy

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

Precautions

Use lower dose in hypothyroidism, liver disease, and obesity (cortisol-binding globulin levels decreased, and free fraction of steroid increased); pregnancy, hyperthyroidism, and concurrent estrogen therapy may increase cortisol-binding globulin levels

Patients requiring long-term glucocorticoid use should have measurements of baseline weight and blood pressure, placement of a purified protein derivative test, ocular examination, and, when appropriate, stool ova and parasite examination for *Strongyloides* organisms; consider measurements of bone density for patients at risk for osteoporosis; patients receiving glucocorticoids for long periods may require acutely increased dosages during periods of major stress; abrupt discontinuation may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur with glucocorticoid use

Azathioprine (Imuran)

Often used in conjunction with prednisone for dermatologic purposes as a steroid-sparing agent. Purine analog with cytotoxic properties. Prodrug metabolized to 6-mercaptopurine. Inhibits RNA and DNA synthesis.

Dosing

Adult

1-3 mg/kg/d PO; clinical efficacy takes several wk; 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

May be best to base dose on TPMT level.

Pediatric

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

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

Interactions

Allopurinol increases risk of pancytopenia; captopril/ACE inhibitors may increase risk of anemia and leukopenia; increase in warfarin dose may be necessary; increased dose of pancuronium may be needed for adequate paralysis; live virus vaccines; co-trimoxazole (increased risk of hematologic toxicity); rifampicin (transplants possibly rejected); clozapine (increased risk of agranulocytosis)

Contraindications

Absolute: Documented hypersensitivity; pregnancy or attempting pregnancy; clinically significant active infection

Relative: Concurrent use of allopurinol; prior treatment with alkylating agents (eg, cyclophosphamide, chlorambucil, melphalan) because of high risk of neoplasia; pediatric patients (safety and efficacy in pediatric population not established)

Precautions

Pregnancy

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

Precautions

Previous treatment with alkylating agents as part of chemotherapeutic regimen increases risk of secondary malignancy; low levels of TPMT, which metabolizes azathioprine, increase risk for toxicity; initial baseline and weekly blood cell counts and kidney and liver function tests required; rarely causes a hypersensitivity syndrome, which manifests as fever, malaise, constitutional symptoms, and hepatitis; patients receiving azathioprine are susceptible to infection even with normal WBC counts

Cyclosporine (Sandimmune, Neoral)

Demonstrated to be helpful in a variety of skin disorders. Potent immunosuppressive agent most often used in organ transplantation. Diminishes production of autoantibodies and decreases resultant blistering and erosions. Acts by inhibiting T lymphocytes and lymphokine production.

Dosing

Adult

1-4 mg/kg/d IV divided bid; alternatively, 2-5 mg/kg/d PO in divided doses

Pediatric

Administer as in adults

Interactions

Erythromycin, clarithromycin, azithromycin, norfloxacin ciprofloxacin, cephalosporins, doxycycline, ketoconazole, itraconazole, fluconazole, ritonavir, indinavir, saquinavir, nelfinavir, diltiazem, verapamil, nicardipine, cimetidine, methylprednisolone, dexamethasone, thiazides, furosemide, allopurinol, bromocriptine, danazol, amphotericin B, metoclopramide, oral contraceptive pills, warfarin, and grapefruit juice may increase levels
Rifampin, rifabutin, nafcillin, carbamazepine, phenobarbital, phenytoin, valproate, octreotide, and ticlopidine may decrease levels
Tobramycin, gentamicin, ketoconazole, azapropazone, trimethoprim/sulfamethoxazole, vancomycin, sulindac, amphotericin B, indomethacin, naproxen, cimetidine, ranitidine, diclofenac, tacrolimus, and melphalan may potentiate renal toxicity
Decreases renal clearance may lead to digitalis toxicity with coadministration of digoxin or myositis with coadministration of lovastatin; decreased renal clearance may lead to convulsions with coadministration of methylprednisolone or prednisolone; coadministration with ACE inhibitors, potassium supplements, or potassium-sparing diuretics increases risk of hyperkalemia

Contraindications

Absolute: Significantly decreased renal function; uncontrolled hypertension; documented hypersensitivity; clinically cured or persistent malignancy (except nonmelanoma skin cancer)
Relative: Age <18 y or >64 y (transplant recipients as young as 1 y have been treated with no unusual effects; however, safety in patients <18 y not established); controlled hypertension; planning to receive a live attenuated vaccine; active infection or evidence of immunodeficiency; concurrent phototherapy, coal tar, methotrexate, or other immunosuppressive agents; pregnancy or breastfeeding; unreliable patient; severe hepatic dysfunction

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

Frequent laboratory monitoring is essential, especially when dose is changed or other medications are started; decrease dose for any relevant clinical or laboratory abnormalities; monitoring blood concentration is sometimes helpful; nephrotoxic and hepatotoxic; causes hypertension and predisposes patients to secondary malignancy

Cyclophosphamide (Cytoxan, Neosar)

Recent reports suggest that cyclophosphamide in combination with systemic steroids is a useful regimen for paraneoplastic pemphigus. Has been used to ablate bone marrow, followed by stem cell rescue (peripheral blood stem cell transplantation). Chemically related to nitrogen mustards. As an alkylating agent, mechanism of action of active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells. Many PO/IV regimens exist, depending on disease being treated and status of patient.

Dosing

Adult

Ablative dose of 50 mg/kg IV qd for 4 d has been used; pulses of 500 mg IV qd for 3 d and 150 mg qd, in conjunction with 100 mg of PO prednisolone or dexamethasone; alternatively, 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 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

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

Secondary malignancies develop; can cause sterility, amenorrhea, hemorrhagic cystitis, and immune suppression; regularly examine hematologic profile (particularly neutrophils and platelets) to monitor for hematopoietic suppression; regularly examine urine for RBCs, which may precede hemorrhagic cystitis

Immunomodulatory agents

IVIG is being increasingly used in high doses to treat many dermatologic inflammatory and autoimmune diseases, including autoimmune bullous disorders and dermatomyositis. However, few controlled trials exist, and it is costly and time consuming to administer. IVIG has been used as monotherapy and as adjunctive therapy.

Immune globulins intravenous (Gammagard, Gamimune, Sandoglobulin)

Prepared from pooled plasma of 10,000-20,000 donors. Has many mechanisms of action, which are mediated by the Fc portion of IgG or the antigen-binding and variable regions of the F (ab') 2 portion. Has been used for dermatomyositis, pemphigus foliaceus, pemphigus vulgaris, epidermolysis bullosa acquisita, bullous pemphigoid, and herpes gestationis. High dose is needed for treatment of inflammatory and autoimmune disorders in comparison to replacement therapy for patients with deficiency.

Dosing

Adult

2 g/kg IV over 2-5 d monthly

Pediatric

Administer as in adults

Interactions

Increases toxicity of live virus vaccine (MMR); do not administer within 3 mo of vaccine

Contraindications

Documented hypersensitivity; IgA deficiency; anti-IgE/IgG antibodies

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

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, patients with diabetes, patients with volume depletion, and those with 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

Follow-up

Complications

The main complication of paraneoplastic pemphigus is impaired skin barrier function, which can lead to localized infection, sepsis, and death. Additionally, painful oral and pharyngeal ulceration can interfere with eating, which can compromise nutritional status. Finally, involvement of respiratory tract epithelium can lead to respiratory insufficiency due to bronchiolitis obliterans and can result in death.

Prognosis

In general, the prognosis of paraneoplastic pemphigus is poor; however, the prognosis is somewhat better when the disease is associated with benign tumors.

The mortality rate when associated with malignancy is estimated at 90%. Nearly all patients with the 2 most common associated tumors, non-Hodgkin lymphoma and chronic lymphocytic lymphoma, are dead of disease within 2 years of diagnosis. Note, however, that outcome does not parallel the course of the underlying malignancy. Both the presence of an underlying neoplasm and the adverse effects of the potent medications required to treat the disease add to both the morbidity and the mortality.

Paraneoplastic pemphigus is the only form of pemphigus that affects epithelia other than squamous. Involvement of respiratory mucosa, which manifests clinically as dyspnea with normal chest radiograph findings, is an ominous finding that progresses via an unknown mechanism to bronchiolitis obliterans. The most recent estimates are that approximately one third of the deaths from paraneoplastic pemphigus are due to pulmonary insufficiency.

Patient Education

As with any serious illness, patients should be made aware of the poor prognosis. For excellent patient education resources, visit eMedicine's Procedures center. In addition, see eMedicine's patient education article Skin Biopsy.

Miscellaneous

Medicolegal Pitfalls

The biggest legal pitfall in paraneoplastic pemphigus is making the correct diagnosis. The eruption is polymorphous. Light microscopy findings can be easily misinterpreted as lichen planus, erythema multiforme, or pemphigus vulgaris; immunofluorescent findings of intercellular deposition of complement exclude the first 2 diagnoses. Immunoprecipitation findings confirm the diagnosis, aided by a high degree of suspicion and careful clinicopathologic correlation. In one study, an initial diagnosis of pemphigus vulgaris was made in 27% of cases.

References

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