Pyoderma Gangrenosum

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ABSTRACT

Pyoderma gangrenosum is a rare cutaneous ulcerative disease of unknown pathogenesis. The histopathology is non-specific and the diagnosis is by the exclusion of other differentials. This is especially important as potent immunosuppressive treatments are commonly employed. At least half of the patients have associated systemic diseases. As there is a lack of randomized controlled trial for any of the treatments, treatment should be considered individually.

Keywords: Pyoderma gangrenosum, review

INTRODUCTION

Pyoderma gangrenosum (PG) was first described by Brunsting et al.[1] in 1930. Over 500 cases have been reported in the literature, but there are few large-number studies. Recently, two large-number studies by Driesch PD[2] (Review of 44 patients) and Bennett ML et al.[3] (Review of 86 patients) have been published. Both of them provide us with more understanding of this rare disease. An excellent review on the treatment of PG has been provided by Chow RKP et al.[4] In the light of these articles and other recent publications, different aspects of PG will be reviewed in this article.

CLINICAL FEATURES

Pyoderma gangrenosum (PG) is an ulcerative disease of skin, commonly precipitated by trauma (pathergy), occurring at any age, but most commonly in young to middle age. The peak incidence is between the ages of 51 and 60 years. Females are more commonly affected than male, with female to male ratio 2:1 in Driesch's review.[2]

Classical PG present as tender erythematous papules, papulopustules, or vesicles with surrounding inflammatory erythema that develop into painful ulcers. The border of the ulcer is well defined and deeply erythematous to violaceous in color. The lesion extends peripherally and the border often overhangs the ulcer as the inflammatory process spreads within the dermis, causing secondary necrosis of the epidermis. The ulcer frequently extends rapidly and heals with atrophic, cribriform scar. Some patients may develop systemic upset with fever, malaise, myalgia and arthralgia.[5]

A number of variant presentations have been described:[5]

Peristomal PG occurs in patient with ulcerative colitis (UC) or Crohn's disease (CD) having abdominal operation and ileostomy or colostomy. Irritation from stomal appliance may be involved.

Genital PG is typical of PG except for its location, which is vulvar in female, or penile or scrotal in male. It should be distinguished from aphthous ulceration of Behcet's disease by recognition of other features.

Pyostomatitis vegetans presents as chronic, pustular, and eventually vegetative erosion on the mucous membrane, especially oral. Most of the patients have inflammatory bowel diseases.

Atypical/Bullous PG is characterized by more superficial ulceration, with a blue-gray, often bullous margin. The arm and face are more commonly affected than the leg. It is more commonly associated with haematological disease. It can be difficult to distinguish from Sweet's syndrome and both of them may occur in the same patient.

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Superficial granulomatous pyoderma presents as superficial vegetative ulcer with an indolent course. The presence of granuloma causes controversy as to whether this should be classified as a separate disease entity.

Malignant pyoderma presents as aggressive ulceration affecting mainly the head and neck. It is often associated with neurological symptoms. There is no undermined border or surrounding erythema. There is also controversy whether this should be classified as a variant.

In extracutaneous PG, sterile neutrophilic infiltrates have been reported most commonly from the lung. The involvement of heart, central nervous system, gastrointestinal tract, eye, liver, spleen and lymph nodes have also been reported.

Bennett et al.[3] reviewed 86 patients from two institutions and found that lower extremity was most commonly involved in classical PG, while upper extremity was most commonly involved in atypical PG.

HISTOPATHOLOGY

This varies according to the type of PG, age of lesion and site of biopsy. A large sterile abscess with venous and capillary thrombosis, haemorrhage, epidermal necrosis and massive cell infiltration are commonly seen. Numerous neutrophils are seen in the early stage. Mononuclear cells predominate in the chronic form. The advancing border may show features of a leucocytoclastic vasculitis and there is some overlap with this condition. However, if the vasculitis is prominent, a primary vasculopathy is more likely than PG. Upper and mid-dermal edema sometimes amounting to vesiculation, is almost invariable. Bullous PG may show spongiosis, intra-epidermal vesiculation and bullae or subcorneal abscess formation.[6] Although the features are non-specific, they are useful in ruling out other causes of ulceration.

Direct immunofluorescence staining reveals positive staining of vessels with antisera against complement factor C3 in 83%, against IgM in 78%, against IgA in 17%, and against IgG in 11% of cases.[2]

Microbiological examination of swabs from the ulcers reveals sterility in 50% of cases. In the remaining half, a number of organisms most commonly Staphylococcus aureus are found.[2]

DIAGNOSIS

The work-up of patients presumed to have PG should have two objectives. The first is to rule out other causes of ulceration and the second is to detect any associated systemic diseases. The list of differential diagnosis of PG is long (Table 1).[3]

As there is no specific histopathological or laboratory test, diagnosis is based on history, physical examination, histology, microbiologic tissue culture and exclusion of the above differential diagnosis.

Laboratory investigations include: complete blood picture with differential, liver and renal function tests, blood sugar and haemoglobin A1, hepatitis markers, serum protein electrophoresis or immuno-electrophoresis, quantitative serum IgA, IgM and IgG level, antinuclear antibodies, rheumatoid factor, complement factors C3 and C4, antineutrophil cytoplasmic antibodies (ANCA), anticardiolipin antibodies, Venereal Disease Research Laboratory test (VDRL) and activated partial thromboplastin time (APTT), complete urinalysis with determination of Bence Jones protein, stool for occult blood, proctoscopy, and chest X-ray. Further tests include gastrointestinal studies such as upper gastrointestinal endoscopy, sigmoidoscopy, colonoscopy and barium enema; bone marrow biopsy, ultrasonography and computed tomography. Patients with lesions on their legs should have detailed analysis of their arterial and venous vessels by Doppler sonography. Arteriogram and venogram are performed if pathological findings are obtained.[2]

PATHOGENESIS AND ASSOCIATION

The pathogenesis of PG is uncertain. Decreased or abnormal immune responses have been described. Patients with PG have been shown to have a failure to induce a contact hypersensitivity response to topically applied dinitrochlorobenzene, suggesting a defect in type 4 immune response. Association of PG with diseases of decreased immune status like monoclonal gammopathies and HIV further supports this. No clear antigenic trigger has been identified.[6] Aberrant integrin oscillation on neutrophil has been demonstrated recently.[7]

Table 1. Differential diagnosis of PG[3]

Infection	Bacteria especially syphilis Mycobacterium Fungus Parasite especially amoebae Virus especially herpes simplex
Insect bite reaction	
Sweet's syndrome	
Malignancy	Squamous cell carcinoma Basal cell carcinoma Cutaneous T-cell lymphoma
Halogenoderma	
Factitious ulceration	
Ulcerative necrobiosis lipoidica	
Vascular disease	Venous or arterial insufficiency Antiphospholipid antibody associated occlusive disease Thrombophlebitis with gangrene
Syndrome with vasculitis	Systemic lupus erythematosus Rheumatoid arthritis Behcet's disease Wegener's granulomatosis

About 50% of patients with PG have at least one relevant associated systemic disease (Table 2).[6] The most common ones are irritable bowel disease, rheumatoid arthritis, paraproteinaemia, and haematological malignancy.[5] In fact, haematological diseases or malignancies account for more than half of the association in atypical PG.[3]

TREATMENT

This had been reviewed in detail by Chow RKP et al.[4] The most important objectives are to make the correct diagnosis by exclusion of other diseases, and to detect associated condition. Infection has to be excluded especially because corticosteroid and immunosuppressants are commonly used in treatment. Treatment of associated condition may also aid in healing of PG.[4] Because of the rarity of PG, none of the treatments has been subjected to proper controlled study. Treatment success comes mainly from isolated reports or at most small open trials. Dermatologists taking care of patients with PG should consider each patient individually. General measures and local therapy should be given. If these are insufficient systemic corticosteroid may be considered. If there is inadequate response or severe side-effects, first line steroid-sparing agent can be considered. If it is still not working, second line steroid-sparing agent can be tried. Each of the individual groups of treatment will be mentioned below.

General measures

Normal saline or potassium permanganate can be used for daily dressing. Hydrophilic occlusive dressing can maintain clean and moist wound, provide relief of symptoms, and possibly promote re-epithelialization. Topical antimicrobial agents such as antibiotics, povidone-iodine, hydrogen peroxide, and benzoyl peroxide can be used to decrease the risk of secondary infection, but their effectiveness has not been confirmed. Long-term use of them should be avoided because it may result in bacterial resistance and retard wound healing. Aggressive surgical debridement or skin grafting is discouraged because of the risk of pathergy. However, cultured keratinocyte autografts and allografts, and split-thickness skin grafting had been reported to be useful.[4]

Table 2. Association of PG[6]

Parainflammatory	inflammatory bowel diseases
	rheumatoid arthritis
	ankylosing spondylitis
	Behcet's disease
	Wegener's granulomatous
	chronic active hepatitis
	sarcoidosis
	subcorneal pustular dermatosis
	Takayashu's arteritis
Hematological	malignancies (lymphoma, myeloma, leukemia, myelofibrosis, polycythemia rubra vera)
	myelodysplasia
	paraproteinaemia
	congenital and acquired hypogammaglobulinaemia
Others	diabetes mellitus
	solid tumors (breast, colon, prostate, bladder, ovary)
	granulocyte colony stimulating factor therapy

Local therapy

It may be sufficient for early or mild lesion. In severe lesion, it may aid systemic therapy. It is summarized in Table 3.

Systemic corticosteroids

This is the drug of choice for PG not responding to general measures and local therapy. It can be given by oral route or intravenous (IV) pulse. The mechanism of action is not entirely known. It may exert its effect by anti-inflammmatory or immunosuppressive properties. On the other hand, restoration of normal monocyte responsiveness may be involved. Initial oral dose ranges from prednisolone 40-80 mg (up to 120 mg) daily. When PG is under control, the dose is reduced slowly. A rapid decrease (>10 mg per week) or premature withdrawal may precipitate severe flare. Complications of prolonged steroid treatment are well known.

Intravenous steroid pulse usually consists of methylprednisolone 1 gm in 150 ml 5% dextrose intravenous infusion daily for 3-5 days. It must be administered in a hospital with cardiac monitoring during and for 24 hours after infusion.

Complications include sudden death of presumed cardiac origin, anaphylaxis, seizures, acute electrolyte abnormalities, transient hypertension, hyperglycaemia, petechiae, and adrenal suppression. It is contraindicated in patients with impaired renal function, poor electrolyte balance, a history of cardiac arrhythmia, and patients taking frusemide.[4]

First line steroid-sparing agents

These include sulfa drugs, clofazimine, minocycline and thalidomide.

Sulfa drugs

These include sulfonamides and sulfones. The most commonly used sulfonamides are sulfasalazine and sulfapyridine (active metabolite of sulfasalazine). The usually used sulfone is dapsone.

Sulfasalazine is usually initiated at 1-4 gm daily. It is reduced to a maintenance dosage of 0.5-1 gm daily. Sulfapyridine is used at a daily dose of 4-8 gm. A drug level of 6-8 μg/ml should be achieved to ensure an adequate dosage because oral absorption is erratic. Dapsone is initiated at 100-200 mg (up to 400 mg) per day.

The mechanism of action of sulfa drugs is not known but appears not to be related to their antibacterial action. Demonstrated effects include inhibition of neutrophil chemotaxis, inhibition of neutrophil myeloperoxidase-hydrogen peroxide-halide-mediated cytotoxic system, and reduction of inflammation-

Table 3. Local therapy of PG

Therapy	Method	Comment
Topical corticosteorid[4]	Daily application of potent corticosteroid with occlusion	Generally ineffective
Intralesional corticosteroid[4]	Triamcinolone acetonide 10 mg/ml with or without 1% lidocaine	Early treatment of small ulcer. Important adjunct to systemic treatment. Avoid aggressive injection/introducing infection
Topical 5-aminosalicylic acid[4]	Daily application of 5% cream	
Topical sodium cromoglycate[4]	1-4% aqueous solution three times daily	
Topical nitrogen mustard[4]	Daily application of 20% aqueous solution	
Intralesional cyclosporine[4]	Isotonic saline solution	Pain
Topical nicotine[13]	Patch of 10 mg directly on ulcer, replace every 24 hours	Systemic adverse effect usually mild. Avoid using large area
Topical tacrolimus[14]	Daily application of 0.1% ointment with or without occlusion	Early treatment of small ulcer. Adjunct to systemic treatment. No significant anti-proliferative effect or interference with collagen synthesis
Perilesional granulocyte-macrophage colony stimulating factor (GM-CSF)[15]	Weekly perilesional injection	Anecdotal report of aggravation[16]

inducing oxygen intermediates through suppression of their generation by neutrophil or through a scavenger-like effect. They may also stabilize lysosomal membranes and possibly decrease glycosaminoglycan viscosity.

Complications include hemolysis, methemoglobinemia, leukopenia, and rarely, agranulocytosis. Glucose-6-phosphate dehydrogenase deficiency should be screened beforehand. Patient taking sulfapyridine should drink large amount of water because it may precipitate in the kidneys, producing crystalluria and hematuria.[4]

Clofazimine

It is given at a dosage of 200-400 mg per day. Besides being an anti-inflammatory agent, it also enhances neutrophil phagocytosis, as measured by the oxygen consumption rate, and macrophage function. Whether these actions account for its effect on PG is not known. Complications include a reversible pigmentation of skin, conjunctiva and body fluid; dryness of skin, eosinophilic enteropathy and bowel obstruction; crystal deposition in the gut, lymph node, and spleen that may result in splenic infarction.[4]

Minocycline

It is initiated at a dosage of 200-300 mg per day. It is then reduced for maintenance. It decreases the chemotactic responsiveness of neutrophils, possibly through inhibition or binding of chemotactic factors.[4] Complications include gastrointestinal upset, vestibular dysfunction, headache, and pigmentary disturbance. More severe complications include hypersensitivity reaction, serum-sickness like reaction, drug induced lupus, pneumonitis and benign intracranial hypertension.

Thalidomide

This is initiated at a dosage of 400 mg per day. Its mechanism of action in PG is unknown. There is selectively inhibition of tumor necrosis factor α production, and inhibition of macrophage phagocytosis and neutrophil chemotaxis. Complications include teratogenicity and peripheral neuropathy.[4]

Second line steroid-sparing agents

These include azathioprine, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, plasma exchange, and human intravenous immune globulin.

Azathioprine

This is a purine analogue that inhibits DNA synthesis in lymphoid cells. It also inhibit T-cell function, cell-mediated immunity, and to a lesser extent, B-cell function and antibody production. It possesses anti-inflammatory properties and is the most frequently used immunosuppressant for PG. The recommended dosage is 1-3 mg/kg per day. Azathioprine is said to be slow acting. Its steroid-sparing effect may be delayed for 6-8 weeks, and any course of treatment less than 12 weeks may not be adequate.[4] The reason behind this can be explained briefly below.

Azathioprine is metabolized by the enzyme thiopurine methyltransferase (TPMT). There is a wide inter-patient variation in the activity of this enzyme. About 90% of the patients have high level of activity and rapid conversion of azathioprine to inactive compounds. About 10% of the patients have lower activity and subsequent risk of over-dosing causing myelosuppression. One in 300 patients has in significant activity and possibility of life-threatening myelosuppression. Therefore, the drug is usually started at a low dose and increased slowly. This may result in under-dosing with the majority of patients. TPMT activity can now be measured in selected laboratories and it is hoped that this will clarify the usage and the role of azathioprine.[8]

Complications include nausea and vomiting, hepatotoxicity, opportunistic infections, increased incidence of neoplasia particularly non-Hodgkin's lymphoma and cutaneous squamous cell carcinoma, and most importantly myelosuppression. The myelosuppression is dose-related and may be delayed.

Cyclophosphamide

This is an alkylating agent that blocks DNA replication by forming covalent linkages with various nucleophilic substances. It is given orally at a dosage of 100-150 mg per day. It can also be given in intermittent high-dose pulses at a dosage of 500 mg/m^2.

Complications include myelosuppression with leukopenia that peaks at 10-14 days after treatment; hemorrhagic cystitis in 5-10% which can be life-threatening; increase risk of malignancy that is higher than azathioprine; increased susceptibility to infections, sterility, gastrointestinal upset, aphthous ulceration, alopecia, and, rarely, hepatotoxicity, cardiotoxicity, and pulmonary fibrosis.[4]

Cyclosporine

This is a macrolide antibiotic with immuno-suppressive properties. It inhibits the formation of several cytokines including IL2, IL3, IL4, GMCSF, and tumor necrosis factor α.

During T-cell activation, antigen binds to its specific T-cell receptor. This results in an influx of calcium that binds to calmodulin activating the phosphatase calcineurin. Activated calcineurin dephosphorylates the cytoplasmic sub-unit of nuclear factor in activated T-cell (NF-AT). The dephosphorylated (activated) cytoplasmic NF-AT translocates from the cytoplasm into the nucleus and forms a complex with the nuclear sub-unit of NF-AT. This then binds to the promoter region of several cytokine genes (as mentioned above) and induces their transcription.

After entering the cell, cyclosporine complexes with its cytosol binding protein. This complex inhibits the function of activated calcineurin, resulting in a suppression of NF-AT-dependent cytokine gene transcription.[9] It is usually given at a dosage of <5 mg/kg per day, but dosage up to 10 mg/kg per day has been used. The reason why some patients respond only to high dosage may be due to poor bioavailability. Complications include nephrotoxicity, hypertension, hypertrichosis, gastrointestinal upset, increased susceptibility to infections, and increased risk of malignancies.[4]

Tacrolimus

This is also a macrolide antibiotic with immunosuppressive properties. The mechanism of action is similar to cyclosporine.[13] It is given at a dosage of 0.15-0.3 mg/kg per day.[10] Complications include neurotoxicity, nephrotoxicity, diabetes mellitus, increased susceptibility to infections, and increased risk of malignancies.[11]

Mycophenolate mofetil

This is an ethyl ester of (a product of numerous Penicillium species) with increased bioavailability. It is usually given at a dosage of 1 gm twice daily orally

and is rapidly hydrolyzed in the liver into its active metabolite, mycophenolic acid.

Mycophenolic acid selectively inhibits, in a non-competitive way, the type 2 isoform of inosine monophosphate dehydrogenase enzyme in the de novo pathway of purine synthesis. This enzyme is primarily found in lymphocytes, and is responsible for the conversion of inosine monophosphate into xanthine monophosphate, an intermediate metabolite in the synthesis of guanosine triphosphate. Lymphocytes minimally use the hypoxanthine/guanine phosphoribosyltransferase salvage pathway for purine synthesis, so the inhibition of the de novo pathway of purine synthesis would have a potent cytostatic effect in the nucleic acid synthesis of T and B cell.

Complications include gastrointestinal upset, slight elevation of liver aminotransferases, myelosuppression, increased incidence of opportunistic infections, and increased incidence of lymphoproliferative diseases. Hematological and infectious complications have usually occurred when the dosage exceeds 2 gm per day.[12]

Plasma exchange

This involves removing large volume of the patient's plasma and replacing it with exogenous plasma or plasma substitutes. The rationale behind its use in PG is unclear because no abnormal plasma constituent has ever been consistently demonstrated in PG. In fact, patients without associated systemic disease have shown incomplete or no response to the treatment. It is given once to three times weekly. Complications include vasovagal reaction, hypovolemia or fluid overload, electrolyte disturbance, infection of indwelling lines, bleeding tendency caused by depletion of platelets or clotting factors, and, in patient given plasma as replacement fluid, allergic reactions and transfusion related infections. Vascular access is a further problem because PG may develop at venepuncture site.[4]

Human intravenous immune globulin

This is given at a dosage of 1 gm/kg daily for two days. It can be repeated every four weeks. At this high dose it possesses immunosuppressive properties through poorly understood mechanism. Complications include headache, chills, fever, and transfusion related infections. Another disadvantage is the high cost.[4]

A number of other treatments have also been reported and these include hyperbaric oxygen, chlorambucil, melphalan, potassium iodide, cyproheptadine, and nicotine gum.[4]

PROGNOSIS

Bennett ML et al. reviewed 86 patients from two institutions. They found that patients with PG showed absence of inflammation after 6.0±9.8 months of treatment, and complete remission after 11.5±11.1 months. Patients with atypical PG showed absence of inflammation after 4.5±10.7 months of treatment, and complete remission after 9.0±13.7 months.[3] Concerning long term behavior, patients with idiopathic PG and those with associated parainflammatory diseases are similar. Association of PG with hematological diseases and malignancies is associated with a poor prognosis.[2]

Learning points:

About 50% of pyoderma gangrenosum have associated systemic disorders, including inflammatory bowel diseases, rheumatoid arthritis, paraproteinaemia, and haematological malignancy.

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Answers to Dermato-venereological Quiz on page 197

Answer (Question 1)

1. Examination showed erythematous plaques and nodules symmetrically over buttocks, thighs and the extensor surface of knees. Hyperpigmentation was noted. Differential diagnoses include erythema elevatum diutinum, psoriasis and Sweet's syndrome.

2. Erythema elevatum diutinum. It is a rare form of chronic idiopathic leucocytoclastic vasculitis in adult. It is characterized by persistent red-brown nodules and plaques symmetrically over the extensor surface of limbs and buttocks. The lesions are initially soft in consistency and become harder with fibrosis. The disease progresses in most cases for more than 10 years to eventual resolution. Hyperpigmentation often results with healing.

3. Dapsone is the treatment of choice but the effect is suppressive only. Prompt recurrence may occur with withdrawal of treatment. Intralesional and topical high-potency corticosteroids may be used in very limited disease to decrease the size of lesions.

Answer (Question 2)

1. The clinical pictures showed an erythematous maculopapular rash over chest and upper limbs. Pustules are noted over the chest area. The diagnosis is toxic pustuloderma due to carbamazepine. Other possibilities include pustular psoriasis and subcorneal pustular dermatosis. The rash typically occurs within a few days of commencing the implicated drug. It presents as a generalized erythematous maculopapular rash which becomes confluent. Superficial non-follicular pustules occur mainly on head and neck area. Fever and leucocytosis are present.

2. Toxic pustuloderma are mostly drug-induced. Antibiotics like penicillins, cephalosporins and macrolides account for the majority. Other drugs include carbamazepine, nifedipine, diltiazem, allopurinol, ofloxacin etc.

3. Management includes discontinuation of the offending drug and supportive treatment. Systemic corticosteroids are sometimes used empirically. Resolution of the pustules and desquamation occur promptly with withdrawal of the drug.