

Review

Pyoderma Gangrenosum

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Abstract

Background: Pyoderma gangrenosum is a chronic, destructive, ulcerating skin disease of unknown etiology. There are four basic pyoderma gangrenosum types: ulcerative variant, pustular variant, bullos variant, superficial granulomatous variant. Apart from these variants, there are some rare variants of pyoderma gangrenosum: malignant pyoderma, pyostomatitis vegetans, peristomal pyoderma gangrenosum, postoperative cutaneous gangrene, genital pyoderma gangrenosum, subcutaneous pyoderma gangrenosum, extracutaneous pyoderma gangrenosum. Pyoderma gangrenosum is often a diagnosis of exclusion as laboratory and histopathological findings are variable and nonspecific. Therapeutic approaches to pyoderma gangrenosum must take into consideration a variety of factors. First and foremost, the onus falls upon the clinician to be cognizant of the underlying systemic disease.

Pyoderma gangrenosum is a chronic, destructive, ulcerating skin disease of unknown etiology. The ulcers are usually painful and, when healed, often produce cribriform scars [1]. Pyoderma gangrenosum is associated with underlying medical disorders in 50% of cases. Whereas it may be an isolated condition [2, 3]. Other conditions associating with pyoderma gangrenosum is given in Table 1 [2]. Among the associating conditions, inflammatory bowel disease is the most frequent, co-existing in 30-40% of patients, besides it may arise 0.5-5% of cases with inflammatory bowel disease, as well [4].

Etiology and Pathogenesis

Pyoderma gangrenosum is an uncommon disorder of uncertain etiology. However there are some hypotheses about its etiology:

Genetic factors: The genetic character of pyoderma gangrenosum is not exactly known but it has been suggested to be autosomal recessive because of in one study two sisters who have pyoderma gangrenosum were reported in a family without pyoderma gangrenosum history [5].

Immunologic factors: It is thought that the immunologic factors have an important role in pathogenesis of pyoderma gangrenosum. Both humoral and cell-mediated abnormalities have been associated with pyoderma gangrenosum. Humoral defects reported include autoantibodies against skin and bowel. A dermonecrotic factor which is present in the serum may give rise to necrosis when injected into the subject's own skin, and a serum factor presents in patients with pyoderma gangrenosum that produces pyoderma gangrenosum-like le-

Table 1. Disorders Associated with Pyoderma Gangrenosum [2]

Inflammatory bowel disease (15%)
Ulcerative colitis
Crohn's disease
Diverticular disease
Regional enteritis
Arthritis (37%)
Seronegative, monoarticular, affecting large joints
Symmetrical polyarthritis
Psoriatic rarely associated
Hematologic disease
Acute and chronic myeloid leukemia
Monoclonal gammopathy (10%)
Large granular lymphocytic leukemia
Myelofibrosis
Waldenström's macroglobulinemia
Polycythemia vera*
Lymphoma: <i>Hodgkin's</i> , non- <i>Hodgkin's</i> and cutaneous T cell
Humoral immune abnormalities
Congenital and acquired hypogammaglobulinemia
Selective, complete and hyperimmunoglobulin E syndrome
Streaking leukocyte factor
Cell-mediated immune abnormalities
Defective neutrophil function: reduced chemotaxis and impaired phagocytosis and oxygen uptake, aberrant neutrophil trafficking
Abnormal monocyte function
Congenital deficiency in leukocyte-adherence glycoproteins
Immuno-deficient/immuno-suppressed
Solid tumors associated with pyoderma gangrenosum
Colon, bladder, prostate, breast, bronchus, ovary, adrenocortical carcinoma
Drugs triggering pyoderma gangrenosum
Alpha-2b-interferon/colony stimulating factors
Others
Chronic active hepatitis, cryoglobulinemia and hepatitis C, thyroid disease, chronic obstructive pulmonary disease, hidradenitis suppurativa, acne conglobata, sarcoidosis, atrophic gastritis, diabetes mellitus, lupus erythematosus, <i>Takayasu's</i> arteritis, dermatomyositis, HIV, <i>Wegener's</i> granulomatosis, sensorineural deafness,
Paroxysmal nocturnal hemoglobinuria, peripheral ulcerative keratitis, lung injury

* Malignant transformation to leukemia common after onset of pyoderma gangrenosum.

sions when injected into guinea pigs. Cell mediated defects have been found including cutaneous anergy to *Candida*, streptokinase and purified protein derivate, as well as altered production of macrophage inhibition factor by lymphocytes. Additional reports have described decreased neutrophil chemotaxis and impaired monocyte phagocytosis in association with pyoderma gangrenosum [6]. However, no uniform pattern of altered cellular immune response has been documented. TNF- α has been considered to be one of the most important pro-inflammatory cytokines involved in the pathogenesis of some immunologically mediated disorders [7].

Vascular factors: There are many factors that point out that pyoderma gangrenosum may represent a type of vascular disorder since it is associated with diseases that often have vasculitis, such as gammopathies and inflammatory bowel disease. Other studies have suggested that the mechanism underlying pyoderma gangrenosum is consistent with *Arthus* or *Schwartzmann* reactions in which circulating immune complexes are deposited in walls of vessels giving rise to activation of classical and alternative complement pathways. Direct immunofluorescence studies to detect immunoglobulins, complement and fibrin deposits in post-capillary venules have yielded inconsistent results. Therefore, it is very difficult to prove a vascular origin [6, 8].

Clinical Features

Clinical features are the mainstay of the diagnosis of pyoderma gangrenosum. While any part of the skin can be involved, the lesions are often take place on the legs. The initial finding is an inflamed, red, often pustular papule or nodule with inflammatory halo which resembles a furuncle or insect bite reaction. Often there is a history of minor trauma. Lesion break down to form a necrotic ulcer that typically has a bluish, undermined ulcer edge and surrounding inflammation [2, 8]. The border is usually undermined and may have tiny pieces of necrotic epidermis still attached [8]. Lesions may be either solitary or multiple [6]. Multiple lesions may fuse together. The ulcers are invariably painful. The course may be explosive and if untreated, may progress to expose muscles, vessels, nerves, fascia and even bones. When the lesion heals, the scarring becomes cribriform or sieve-like, with many little burrows and indentations. A characteristic feature of pyoderma gangrenosum is pathergy reaction, but is often overemphasized. Only about %25 of patients have this feature [5]. Associated symptoms include fever, malaise, myalgia and arthralgia. Extracutaneous involvement has been reported, with sterile neutrophilic infiltrates and pyoderma gangrenosum manifestations occurring in bone and lungs [6].

There are four basic types of pyoderma gangrenosum:

Ulcerative type: It is the classic type of the

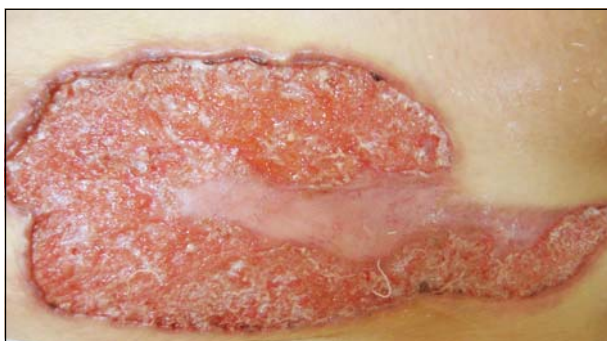


Figure 1. Pyoderma gangrenosum

pyoderma gangrenosum [6]. It can cause patient's death with its destructive and explosive course [9]. In that type ulcer with undermined edge can arise de novo or as a pathergic response to trauma; from an inflammatory pustule or a nodule; or from healthy skin [6, 9]. While any part of the skin can be involved, most lesions are on the legs. Typically, the patient has an age range of 25 to 55 years, in whom lesions manifest as ulcers with a peripheral inflammatory halo most often on the lower extremities or the trunk. Other areas of involvement include vulva and penis, the head and neck region, the breast (**Figure 1**) and ocular sites. The lesions typically begin as small follicular based pustules that break down rapidly. The ulcer that ensues may be a few centimeters in width or may extend as a confluent ulcerated zone along a calf or entire extremity. The ulcer base may be crusted or may have a granular appearance [2]. This variant is more likely associated with inflammatory bowel disease, monoclonal gammopathy and arthritis [8]. Also, it can be associated with hematologic malignancies [2].

Pustular type: This variant is often occurs during acute exacerbations of inflammatory bowel diseases. Discrete painful pustules, with a surrounding halo of erythema, develop on normal skin. These pustules commonly arise on the extensor aspects of the limbs and may evolve into typical ulcerations of pyoderma gangrenosum. The lesions often resolve with control of inflammatory bowel disease [6].

Bullous type: This variant is important as it is more likely to be associated with hematologic malignancies, such as hairy cell leukemia, myelogenous leukemia, and other myelodysplastic conditions. The lesions are

more superficial and frequently either start with bullae or have bullae at their borders [8]. Any patient presenting with pyoderma gangrenosum, but particularly one who manifests features of the bullous variant, should be evaluated for an underlying hematologic malignancy irrespective of his or her age. With appropriate therapy of the underlying hematological disorder, bullous pyoderma gangrenosum tends to remit more rapidly than do other forms [2].

Superficial granulomatous type: This variant is called also vegetative variant and that is less explosive from other variants [10]. In 1988, *Wilson-Jones* and *Winkelman* described 25 patients with a superficial granulomatous pyoderma that frequently healed without systemic corticosteroid therapy [11]. Characteristically, these lesions began as a single furunculoid purple abscess, nodule or plaque, most commonly on the trunk, which evolved in an indolent fashion into a granulomatous or pyoderma-vegetative lesion with a heaped up border and had associated draining sinuses and cribriform scarring and generally lacks the violaceous undermined border [6, 8, 11]. However there is a reported case having a nodular lesion in the nasal cavity [10]. Histologically a granulomatous inflammation inconsistent with pyoderma gangrenosum exists [8]. Besides superficial or focal abscesses surrounded by palisading histiocytes or foreign body giant cells may co-exist [11]. Unlike to classic pyoderma gangrenosum association with systemic diseases is rare in vegetative pyoderma gangrenosum [12]. This variant is usually characterized by its responsiveness to simple modalities of therapy and lack of association with underlying systemic disease [11]. Some cases refractory to treatments have been reported. Usually this variant has no association with systemic diseases but some complications such as myeloid leukemia, romatoid arthritis or renal failure may occur. This variant requires careful monitoring and responds well to systemic corticosteroids [10].

Apart from these variants, there are some rare variants of pyoderma gangrenosum:

Malignant Pyoderma: Initially this condition was considered to be separate from pyoderma gangrenosum because it was on

the head and neck, was rarely associated with underlying diseases, and lacked the erythematous border. Today, it is considered to be a variant of pyoderma gangrenosum [8].

Pyostomatitis Vegetans: This pustular vegetative disease of the oral mucosa is also associated with inflammatory bowel disease and may be oral pyoderma gangrenosum [8].

Peristomal Pyoderma Gangrenosum: Peristomal pyoderma gangrenosum can cause serious morbidity in patients who require the placement of a stoma, as it can occur near the site of the stoma following resection in patients with abdominal malignancy, as well as patients with IBD [13]. This variant's pathogenesis is considered to be an immune system defect [14]. Patients with inflammatory bowel disease may develop extensive ulcerations by their stoma site or on the wound. In addition, the pustular eruption of ulcerative colitis is probably a type of pyoderma gangrenosum [8]. In one study a patient has been with pyoderma gangrenosum at surgical site of enterocutaneous fistula operation has been described [14]. However, it is frequently misdiagnosed as a stitch abscess, contact dermatitis, irritation from leaking feces or urine, extension of the underlying IBD or a wound infection. Thus, the differential diagnosis of recalcitrant peristomal skin disease should include peristomal pyoderma gangrenosum [13].

Postoperative Cutaneous Gangrene: Postoperative pyoderma gangrenosum was first described by *Cullen* in 1924 in an abdominal wound following drainage of an abdominal abscess. A case has been described who had postoperative pyoderma gangrenosum mimicking wound infection, occurring in sequential pacemaker scars [15]. Another case was presented with pyoderma gangrenosum after median sternotomy and aortic valve replacement [16]. Postoperative pyoderma gangrenosum should be strongly suspected if a sterile, painful, non-healing ulcer develops following any injury or surgical procedure, which is unresponsive to antimicrobial therapy and regular wound care [15]. Other patients may also develop pyoderma gangrenosum-like changes following surgery. Usually, a bacterial wound infection is

suspected, but the rapid course and failure to respond to antibiotics should suggest a different condition [8].

Genital Pyoderma Gangrenosum: Vulvar, penile [17], and scrotal pyoderma gangrenosum have all been identified. Often the differential diagnosis of Behçet's syndrome is suggested, but the ulcers are extensive. Once again, mixed synergistic bacterial infections has to be excluded [8].

Subcutaneous Pyoderma Gangrenosum: The disease process may start in the fat, causing massive destruction and then breaking through to the skin. There is usually a massive purulent discharge and, not surprisingly, far deeper destruction [8].

Extracutaneous Pyoderma Gangrenosum: Although constitutional symptoms such as pyrexia, malaise and arthralgia are commonly seen in pyoderma gangrenosum, together with a neutrophilia and raised inflammatory markers, discrete extracutaneous abscesses are extremely rare. The lung is the organ which is frequently involved, with 24 reports of pulmonary disease in association with pyoderma gangrenosum. The vast majority of these consist of patchy unilateral or bilateral infiltrates. Pulmonary cavities have been reported in three patients. Aseptic neutrophilic infiltrates have also been described in bone, presenting as a sterile osteomyelitis, and joints, as sterile synovial effusions in association with a seronegative arthropathy. The central nervous system has been involved in two cases of pyoderma gangrenosum, in one as a pituitary mass and in the other as aseptic meningitis. Ocular involvement, as episcleritis or scleral ulcers, has been rarely reported, as has inflammation in the periorbital tissues and sinuses [8]. Splenic abscesses have been described in two patients prior to this case. The extracutaneous abscesses usually occur concurrently with the skin lesions, but may precede them, making diagnosis even more difficult [18]. Sterile neutrophilic deposits have been described in the heart, lungs, gastrointestinal tract, and CNS. Often they are first identified at autopsy [8].

Pyoderma Gangrenosum in Children

Pyoderma gangrenosum commonly occurs between 25 to 54 years of age and is ex-

tremely rare in pediatric population. Approximately 4% of reported cases were children. Infants alone represent a small fraction (8.8%) of pediatric pyoderma gangrenosum [5]. Pyoderma gangrenosum is very rare in children under 1 year of age. Among eight cases that have been reported, none had any of the associating conditions. However, HIV infection and *Takayasu* arteritis have been reported in two patients [19]. In children pyoderma gangrenosum usually occurs in association with inflammatory bowel disease, immunodeficiency, and immunosuppression and HIV infection. In a series of 46 infants and children with pyoderma gangrenosum, ulcerative colitis was the most common associated condition, seen in 74% of patients. However, in 20–30% of instances no underlying systemic disease could be identified [5, 20, 21]. Leukemia is the most frequent associated malignancy, acute myeloid leukemia is being the most common form. However, its association with lymphoid malignancy is very rare. In one study a children with ALL and pyoderma gangrenosum was reported [21]. The perianal and genital areas in infants, and the face, head and gluteal region in children are the most common sites of involvement [5, 20]. In children a preponderance of pustular lesions, and preexisting trauma have been reported [19]. Most infants and children with pyoderma gangrenosum have been successfully treated with oral corticosteroids, mainly prednisone [5, 19, 20]. Despite the fact that all infants reported so far have responded very well to treatment, and many of them have been reported to be healed, the long-term outcome of pyoderma gangrenosum in infants is uncertain. The symptom-free period in the reported patients has been 2 years, and long-term course is unclear [19]. Alternative treatments especially in refractory pediatric cases, include dapsone, sulfapyridine, cyclosporine, methotrexate, clofazimine, minocycline, and colchicine [20].

Diagnosis

Pyoderma gangrenosum is often a diagnosis of exclusion as laboratory and histopathological findings are variable and nonspecific. Patient evaluation should include a detailed history, physical examination and skin biopsies for histopathology and culture as well as appropriate laboratory tests to rule out other possible etiologies. Infectious

ulcers may mimic pyoderma gangrenosum. Histological stains and cultures of skin biopsies for bacteria, mycobacteria, fungi and occasionally viruses can aid in excluding these etiologies. Syphilis serology and anti-cardiolipin antibody may be indicated because syphilitic gummatous ulcers and antiphospholipid syndrome can simulate ulcerative or vegetative pyoderma gangrenosum. *Sweet's* syndrome can often be distinguished by its rather sudden onset of non-ulcerating lesions that generally heal without scarring. Syndromes with vasculitis such as WG, *Behçet's* disease and SLE can also be confused with pyoderma gangrenosum; however, leukocytoclastic vasculitis is not a feature of pyoderma gangrenosum [6]. Some authors also suggest screening for hepatitis and human immunodeficiency virus (HIV); more than five HIV-related cases have been reported [22].

Histopathology

Although the histopathological findings of pyoderma gangrenosum are often variable and non-specific, they can be useful in excluding other possible etiologies. Several variables must be considered when evaluating this histopathology, including the type of lesion, the site of the lesion from which the biopsy is obtained, the stage of evolution of lesion, and therapy. Typical findings include central necrosis and ulceration of the epidermis and dermis surrounded by an intense acute inflammatory cell infiltrate, with a peripheral mixed to chronic inflammatory cell infiltrate [6]. A biopsy of the advancing edge of the lesion may, if one is lucky enough, reveal neutrophils and fibrin in superficial vessels. In one large series, about 40% of patients had histologic evidence of vasculitis. Thrombosis of small vessels may also be seen [8]. Each clinical variant has additional more specific histopathological findings. In the ulcerative variant of pyoderma gangrenosum, there is a massive dermal-epidermal neutrophilic infiltrate with abscess formation; in pustular pyoderma gangrenosum, a perifollicular neutrophilic infiltrate with subcorneal pustule formation; the bullous variant shows a neutrophilic infiltrate with intraepidermal vesicle formation; and in vegetative pyoderma gangrenosum, granulomatous reaction with peripheral palisading histiocytes and giant cells exists. The presence of vascular involvement in pyoderma gangrenosum has

been a subject of discussion. Although many investigators have reported findings consistent with a neutrophilic vascular reaction or leukocytoclastic vasculitis, granulomatous vasculitis and lymphocytic vasculitis, these findings are not supported by all studies [6].

Direct immunofluorescence testing: Direct immunofluorescence testing indicates the role of vasculopathy in progression of lesions by means of perivascular deposition of IgM, C₃ or fibrin in some cases. However this finding does not directly correspond with vascular pathology since non-specific vessel injury may cause a similar finding [2].

Laboratory Findings

No laboratory findings are specific and thus diagnostic of pyoderma gangrenosum. Laboratory tests are only useful to search for possible underlying disorders. Bacterial and deep fungal infections should be excluded, but confusion is very rare [8, 23].

Course and Prognosis

If the underlying disease is treatable, the outcome is good. In patients with idiopathic pyoderma gangrenosum, the disease shows a relapsing course for years [8].

Association with Systemic Disease

Pyoderma gangrenosum may occur as a disease confined to the skin in 40 to 50 percent of cases (idiopathic pyoderma gangrenosum), but it may sometimes manifest itself in extracutaneous sites. The heterogeneity of these conditions makes to find a common pathogenetic mechanism difficult [23].

Ulcerative colitis and Crohn's disease

Pyoderma gangrenosum was associated with ulcerative colitis ranging from 30 to 60 percent. Also, pyoderma gangrenosum occurs only rarely in ulcerative colitis, with a reported prevalence ranging from 0.6 to 5 percent. Nonetheless, together with erythema nodosum, pyoderma gangrenosum represents the most common dermatologic disorder accompanying ulcerative colitis. pyoderma gangrenosum is also associated with Crohn's disease. In inflammatory bowel disease, the most frequent localization of pyoderma gangrenosum is on the lower legs and around the stoma [23].

Arthritis

Arthritis is frequently associated with pyoderma gangrenosum and usually precedes it. In one review, arthritis was found in 30 percent of patients with pyoderma gangrenosum. Some patients have classic seropositive rheumatoid arthritis; others have the arthritis associated with inflammatory bowel disease, which is seronegative, acute, oligoarticular, and nondestructive; others have a seronegative rheumatoid-like arthritic syndrome; still others have spondylitis [23]. In Turkey, an association of pyoderma gangrenosum with rheumatoid arthritis was reported [9]. An association of pyoderma gangrenosum with the synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome and with psoriatic arthritis has been described [23]. In addition, pyoderma gangrenosum is a clinical manifestation of the autosomal dominant PAPA syndrome that is characterized by pyogenic sterile arthritis, pyoderma gangrenosum, and acne and is a rare autosomal dominant autoinflammatory disorder characterized by early onset of recurrent and destructive inflammation of joints, skin, and muscle that has been reported in three different families worldwide [24].

Monoclonal Gammopathy

Pyoderma gangrenosum is often associated with paraproteinemia, mostly of the IgA type, but also of the IgG and IgM types. Although patients with a monoclonal gammopathy do not show progression to malignancy over the short term, some patients with pyoderma gangrenosum have myeloma at presentation or develop it subsequently [23].

Myeloproliferative Disorders

Pyoderma gangrenosum occurs in myelodysplasia, as well as in acute myeloblastic, myelomonocytic, or chronic myeloid leukemia. A few cases have been associated with the other myeloproliferative disorders [23].

Other Conditions

Several studies have documented patients with pyoderma gangrenosum and Behçet's syndrome. The two diseases share certain features, and the phenomenon of pathergy. pyoderma gangrenosum has occurred in association with PAPA syndrome, vasculitis, erythema elevatum diutinum, Wegener's granulomatosis, Takayasu's disease. And

pyoderma gangrenosum has occurred rarely in association with sclerosing cholangitis, type 1 diabetes mellitus, sarcoidosis, and hidradenitis suppurativa [23, 25, 26, 27].

Differential Diagnosis

The clinical presentation of an ulcer on the lower extremities raises the possibility of an ischemic or infective etiology [2]. Three most frequent primary cutaneous disease types that produce ulcers resembling pyoderma gangrenosum are infections, neoplasms, and rheumatologic diseases. Clues which can help to distinguish pyoderma gangrenosum from other ulcerative entities that mimic pyoderma gangrenosum include the anatomic location of the lesions and the patient's past medical history.

Pyoderma gangrenosum ulcers are located on the lower extremities about 75% of cases. When the ulcer is located elsewhere on the body, particularly on the upper limbs and trunk, the clinician should have a higher index of suspicion of an etiology other than pyoderma gangrenosum, such as infection or malignancy-associated ulcers. Ulcers occurring at unusual sites, such as the genitalia, fingers, or venipuncture sites, should raise suspicion of a factitious ulcer. These patients usually have a history of psychiatric disorder. An erroneous diagnosis of pyoderma gangrenosum can be avoided by performing a wound culture, skin biopsy, and evaluation for rheumatologic disorders [28]. Bacterial infections, sporotrichosis and other deep mycoses, factitial dermatitis, panniculitis are the other conditions to be differentiated.

Pyoderma gangrenosum may mimic Sweet's syndrome, although the latter is rarely folliculocentric, and clinical features often make distinction possible. As the lesions of pyoderma gangrenosum are frequently follicular-based, the differential diagnosis should also include other causes of necrotizing pustular follicular reactions with an accompanying vasculopathy, such as mixed cryoglobulinemia, Behçet's disease and rheumatoid vasculitis, rare cases of eosinophilic folliculitis, pustular drug reactions and herpetic folliculitis. Such cases should not be misinterpreted as bacterial folliculitis [2, 6].

Treatment

Therapeutic approaches to pyoderma gan-

grenosum concern a variety of factors. Firstly, underlying conditions, if exist, have to be identified. Secondly, the type and course should be defined for an efficient treatment approach. As an example coexisting inflammatory bowel disease, the management may be carried as far as resection of the involved bowel. In broad terms, the treatment of pyoderma gangrenosum lesions can be classified as local or systemic in type [2, 6].

Local Therapeutic Options

For early or mild lesions, topical therapy may be sufficient. This includes wet compresses, hydrophilic occlusive dressings, antimicrobial agents and topical corticosteroids [6]. Topical steroids are generally ineffective in treatment of pyoderma gangrenosum, but clobetasole 0.05% cream or lotion proved successful in a few cases of parastomal pyoderma gangrenosum patients [1]. Very early lesions can be treated with intralesional or very potent topical corticosteroids [5, 6]. Triamcinolone acetonide injected around the active rim of pyoderma gangrenosum ulcers or into the primary nodule may provide dramatic reduction in pain and inflammation in as little as 48 hours and definite healing at 72 hours. Primary or small lesions respond well to intralesional steroids, but even large ulcers may respond to weekly injections of triamcinolone in concentrations of 8-10 mg/ml to the advancing border [1]. Both topical cyclosporine and tacrolimus have been helpful in selected cases [6, 8]. In some cases topically tacrolimus used successfully at 0.1% and 0.5% concentrations [29]. Also, four patients successfully treated with tacrolimus 0.3% in carmellose sodium paste applied to the active ulcer borders have been reported [1].

Systemic Therapeutic Options

Many patients have already been treated with antibiotics before the diagnosis, but they usually have no effect. The mainstay of therapy is systemic corticosteroids, usually starting with prednisone 60-80 mg daily. If this does not promptly arrest the progression of the disease, higher dosages (up to 120 mg daily) or intravenous methylprednisolone pulse therapy should be considered. Most patients with severe pyoderma gangrenosum develop corticosteroid-related problems. For this reason, many steroid-sparing agents have been employed [8].

Antimicrobial Treatment: Sulphones and other antimicrobials such as dapsone, clofazimine and minocycline have been found to be useful in treating pyoderma gangrenosum. Their mode of action is likely related to their anti-inflammatory effects or their alteration of neutrophil function [6]. Dapsone is helpful in less severe cases and for maintenance, usually in dosages of 50-150 mg daily. Sulfasalazine has been endorsed, even for patients without inflammatory bowel disease. Clofazimine 100-300 mg daily has also helped some patients [8]. Minocyclin in doses of 100-200 mg/day along with topical steroids may be useful in mild cases of bullous or granulomatous pyoderma gangrenosum. Tetracyclines have anti-inflammatory and antichemotactic effects, the probable mechanism of activity in pyoderma gangrenosum [1].

Immunosuppressive Therapy: Immunosuppressive agents have been found to be useful as adjunctive or alternative therapy in corticosteroid-sparing agents [6]. Subsequent reports achieved healing of pyoderma gangrenosum ulcerations starting with doses of 4 mg/kg/day, which were later tapered to as little as 1 mg/kg/day. The other agent is a tacrolimus that is a potent macrolide immunosuppressive support agent, used in a dosage range of 0.15-0.3 mg/kg/day, is reported to induce remission of recalcitrant pyoderma gangrenosum ulcers in a small number of cases [1].

Alkylating Agents: Cyclophosphamide, melphalan and chlorambucil appear to be effective in the limited number of patients reported [6]. Cyclophosphamide 100-150 mg/day is effective in healing recalcitrant pyoderma gangrenosum ulcerations, and also acts as a steroid sparing agent. Azathioprine, a purine analog, has a very slow onset of action (8-12 weeks) and when effective, it required long-term maintenance, since the pyoderma gangrenosum relapsed when the drug was discontinued or reduced in dosage. For these reasons today azathioprine was no longer used for treatment of pyoderma gangrenosum [1]. In recent years mycophenolate mofetil has shown special promise, but controlled studies are lacking [8]. In two reported cases, mycophenolate mofetil 1.0 gr twice a day was required to promote healing of the ulcers [1].

Biological Agents: Methotrexate may be useful in patients with underlying arthritis or inflammatory bowel disease, and new biological TNF- α inhibitors such as infliximab and etanercept are now being used [6]. Infliximab is made up of a constant human fraction and a variable fraction of murine origin and etanercept is a fusion protein of a TNF- α receptor, which binds TNF- α and TNF- β molecules, preventing them from combining with their receptors [7]. Infliximab, a chimeric monoclonal antitumor necrosis factor antibody, has been used with success in many patients with inflammatory bowel disease. It has also been used in patients with pyoderma gangrenosum in association with inflammatory bowel disease, with good resolution of both bowel and skin disease, and has additionally been reported to clear peristomal pyoderma gangrenosum. One group recently reported successful treatment of vegetating pyoderma gangrenosum. Infliximab is generally well tolerated, but in one report infusion reactions of varying severity were reported to occur in about 10% of patients [18]. In 2001, Tan et al. reported two patients with Crohn's disease and pyoderma gangrenosum who were treated with infliximab for resistant fistulous disease, with improvement in both disorders. Since then, other cases of pyoderma gangrenosum treated with infliximab have been reported. Etanercept seems to be a promising drug for the treatment of severe pyoderma gangrenosum that is resistant to conventional treatment. However, controlled studies are necessary to determine whether anti-TNF therapy is safe and effective in the treatment of pyoderma gangrenosum and other inflammatory disorders [7]. Adalimumab is the first fully human anti-TNF- α antibody. Theoretically, antibody formation and subsequent infusion reactions should be less likely to occur. In one study, the presence of antibodies to adalimumab in the treated group was found to be 12%. However, there were no differences in the pattern or frequency of adverse events between patients with or without these antibodies [18].

Other Therapeutic Measures: Other treatment for pyoderma gangrenosum include thalidomide, IVIG and plasma exchange. Doses of thalidomide of 100-400 mg/day may be effective in recalcitrant pyoderma gangrenosum [1]. IVIG has also been effective

tive; classical protocol includes 1.0 g/kg daily for 2 days, repeated monthly for four to six courses [8].

Granulocyte monocyte adsorption aphaeresis may be used for treat pyoderma gangrenosum. Granulocyte monocyte adsorption aphaeresis is an extracorporeal-type granulocyte and monocyte aphaeresis unit that employs a column designed to remove pathogenic granulocytes. The column contains 220 g of 2 mm diameter cellulose acetate beads. The GCAP therapy was performed 10 times at 5 day intervals. At each treatment session, blood was drained from the cubital vein of one arm, circulated through the column, and returned to the cubital vein of the other arm. The flow rate was 30 mL/min and the duration of each circulation was 60 min [30].

LCAP has been used successfully in ulcerative colitis patients, but the mechanism of its effectiveness is not fully understood. One case of pyoderma gangrenosum reported was successfully treated with LCAP. LCAP is considered to improve ulcerative colitis by removing the activated leucocytes effectively through the column [31].

Surgical therapy: As a treatment strategy, surgery may have some indications in pyoderma gangrenosum. Debridement should be avoided because it may induce tissue pathergy. Skin grafting also carries a risk of pathergy at the donor site, prompting use of tissue culture to maximize epithelial yield while minimizing donor site area. Hyperbaric oxygen, may be employed as a primary therapeutic modality, and may induce in suppressing donor site pathergy. Pathergy may also be less problematic if the underlying systemic disorder is first brought into remission [2]. There are, however, reports of the successful use of split-thickness skin grafts to speed healing of pyoderma gangrenosum ulcers that are very large or in areas such as the breast. A recent report of four cases of pyoderma gangrenosum successfully treated with skin grafting stresses the need for adequate control of the inflammatory process with high dose corticosteroid to prevent pathergy and the loss of graft in the donor sites. Other methods reported to help to promote more rapid healing of pyoderma gangrenosum ulcers include hyperbaric oxygen, cultured

keratinocyte autografts, and allografts [1].

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