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Mohd. Adil Tehseen
Associate Professor, Sri Sai RR Institute of Pharmacy, Aligarh, Uttar Pradesh, India

Yatin Kumar
Assistant Professor, Sri Sai RR Institute of Pharmacy, Aligarh, Uttar Pradesh, India

Sangeeta Mahour
Assistant Professor, RG College of Pharmacy, Aligarh, Uttar Pradesh, India

Corresponding Author:
Mohd. Adil Tehseen
Associate Professor, Sri Sai RR Institute of Pharmacy, Aligarh, Uttar Pradesh, India

Comprehensive management of pyoderma ganrenosum

Mohd. Adil Tehseen, Yatin Kumar and Sangeeta Mahour

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Abstract
Pyoderma gangrenosum is an uncommon condition that affects both men and women of all ages, however it is more frequent in people over 50. It is typically related with an inside illness or condition. Its recognized associations include Inflammatory bowel illness (ulcerative colitis, Crohn's disease), Rheumatoid arthritis, myeloid blood dyscrasias, including leukaemia, Monoclonal Gammopathy (typically IgA), Chronic active hepatitis.
Granulomatosis and polyangiitis, PAPA Syndrome, Behçet's disease and other various less common relationships. Treatment for PG typically begins with fast-acting immunosuppressive drugs (corticosteroids and/or cyclosporine) to reduce inflammation, followed by the addition of more slowly acting immunosuppressive drugs with better adverse event profiles, such as biologics. Appropriate wound care is also necessary. Future research should concentrate on PG-specific outcome metrics and PG quality-of-life assessments. Despite the fact that PG is a well-known illness, early diagnosis is frequently overlooked. All doctors should be aware of this syndrome and actively evaluate PG when examining patients with ulcers, since effective and timely therapy at an early stage of the disease can minimize the risks of extended systemic treatment, delayed wound healing, and scarring.

Keywords: Pyoderma gangrenosum, Immunosuppressive and Immunomodulating Drugs, (TNF-α) Inhibitors, IL-1 antagonists, wound management

Introduction
Pyoderma gangrenosum (PG) is an uncommon, persistent, recurrent ulcerative dermatosis now classified as a neutrophilic illness. PG lesions have substantial neutrophilic infiltration on the skin without an infectious etiology or vasculitis, but may also display leukocytoclastic vasculitis. This disorder is potentially fatal and produces significant morbidity. PG ulcers are associated with increased levels of proinflammatory cytokines and chemokines, including IL-6, CXCL-8, and CXCL1-3, in the skin and blood. PG and Sweet's syndrome (SS) lesions show upregulation of matrix metalloproteinases (MMPs). Elevated levels of elfin, a neutrophil elastase inhibitor, and increased Fas/FasL activity can lead to ulcer development and aberrant wound healing. High levels of granulocyte-colony stimulating factor (G-CSF) and pathology may contribute to PG throughout pregnancy and puerperium, according to certain experts. PG cutaneous lesions exhibit elevated levels of IL-17, IL-23, and Th17 cells [1]. There are four main clinical forms of PG that have been identified: Bullous, pustular, ulcerative (classic), and vegetative (superficial). Although just one form is often recognized, a patient may exhibit multiple subtypes at the same time. Furthermore, PG might exhibit characteristics that overlap with those of other NDs. Although the pretibial region of the lower limbs is where PG most frequently manifests, it can also affect the head, neck, breasts, genitalia, and upper extremities. The classical type, also known as ulcerative, is characterized clinically by ulcers that grow quickly, are painful, and have clearly defined, violaceous, undermined borders. Usually composed of granulation tissue, the ulcers' bases might occasionally be necrotic and coated in purulent exudates. Additionally, the perilesional skin is inflamed [1].

Treatment
Wound Management
One of the most important aspects of the treatment is wound care. Changing dressings and properly cleaning with sterile saline or an antiseptic are the fundamentals.

A moist environment that is neither too dry nor too wet should be encouraged by the dressing, which should not stick to the wound bed. It should also be simple to remove in order to avoid stress and the agony that follows. Limiting surgical operations and surgical wound care is necessary to prevent pathergy. Autolytic and mild mechanical debridement are advised. Through improving mobility, compression therapy decreases tissue oedema and localized inflammation, which both directly and indirectly increases blood circulation [2].

Immunosuppressive and Immunomodulating Drugs

- **Systemic Corticosteroids:** About 40-50% of cases respond clinically to systemic corticosteroids (CS) treatment (dosage 0.5-1 mg/kg/day), with complete response rates varying greatly according on the severity of PG and related systemic disorders. Depending on the clinical course, comorbidities, and relapse risk, the CS dose can be reduced over a variable time period (4-6 weeks to 12-24 weeks) after healing is achieved. In addition to helping taper oral CS, pulse therapy with 1000 mg of intravenous methyl prednisolone for three to five days in a row may have a quicker onset of action.
- **Cyclosporine:** An immunosuppressive medication called cyclosporine is the primary line of treatment for PG. A calcineurin inhibitor called cyclosporine prevents the production of ILs, especially IL-2, which is essential for preventing T-lymphocyte activation.
- **Methotrexate:** An immunomodulating medication called methotrexate (MTX) is frequently used to treat long-term inflammatory skin conditions. It works through the following mechanisms increased adenosine release, which suppresses a number of immune and inflammatory responses; uncoupling of nitric oxide synthase, which makes T cells more susceptible to apoptosis; and increased expression of long intergenic non-coding RNA p21, which regulates a number of immune and inflammatory signalling pathways.
- **Mycophenolate Mofetil:** In patients with PG, mycophenolate mofetil has been tested as a first- or second-line steroid-sparing medication. It interferes with the creation of guanosine triphosphate by blocking inosine monophosphate dehydrogenase in the de novo purine synthesis pathway. RNA, DNA, and protein synthesis are consequently hampered by the absence of guanosine nucleotides. The purine salvage route, an alternate mechanism for regenerating adenosine and guanosine, is absent from lymphocytes. Consequently, MMF inhibits lymphocyte growth in a specific manner without affecting other cells. MMF may potentially change adhesion dynamics to endothelial cells by blocking the glycoprotein glycosylation of lymphocytes and monocytes, which would impede leukocyte recruitment to inflammatory areas.
- **Azathioprine:** As an alternative to first-line therapies or as a corticosteroid-sparing drug, azathioprine may be useful in treating resistant or severe PG. Patients with underlying IBD can also benefit from it. Three weeks after starting azathioprine, a patient with diffuse prednisolone-refractory PG showed full ulcer healing. When compared to conventional immunosuppressants, azathioprine has a more favourable therapeutic index and is typically well tolerated [3].

Immunosuppressive Antibiotics

Minocycline, a medication that suppresses protein synthesis by attaching to bacteria's ribosomal subunits, can be used to treat PG. In the current literature, minocycline is typically taken at a dose of 100 mg twice daily and used in combination with other treatments, such as oral prednisolone and sulfasalazine [2].

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is frequently used to treat patients with severe PG who are resistant to first- and second-line medications, with a therapeutic effectiveness rate of approximately 88% (58-60). These patients received IVIG along with systemic corticosteroids, implying that IVIG could be a successful adjuvant therapy for refractory PG [4].

Tumour Necrosis Factor-α (TNF-α) Inhibitors

- **Infliximab:** Infliximab (5 mg/kg) is more effective than placebo for treating PG.
  Open-label treatment with infliximab showed promising results. Infliximab should be evaluated for patients with PG, regardless of coexisting IBD [5].
- **Adalimumab:** Adalimumab delivered subcutaneously, beginning with 80 mg in week 0 and 40 mg in week 1, followed by 40 mg every second week. Under this treatment, the ulcer gradually shrank and healed almost completely within 64 weeks. However, treatment with adalimumab is still underway, with the goal of consolidation and therapeutic success, but application intervals have been increased to four weeks. Adalimumab therapy was well tolerated, with no adverse effects, and resulted in an improved quality of life as judged by the Dermatology Life Quality Index [6].
- **Ustekinumab:** Solitary or multiple pyoderma gangrenosum (PG)-like skin ulcers (PGLUs) were caused by cutaneous ringworm infection (Trichophyton tonsurans). Skin biopsy samples exhibited higher intralesional expression of IL-17A, Il-23, and IL-1β compared to healthy controls. Following a failed treatment with oral methylprednisolone, ustekinumab resulted in ulcer regression and complete cytokine normalization [7].

IL-1 antagonists

- **Canakinumab:** Patients receiving canakinumab therapy experienced a reduction in target-lesion size, PGA, and Dermatology Life Quality Index (DLQI) and reached complete remission. The average diameter of target lesions decreased from 4·32±2·6 cm at visit 1 to 0·78±1·3 cm by visit 7. The average DLQI fell from 15±5 at visit 1 to 8 ± 4 by visit 7 [8].
- **Anakinra:** Anakinra is a recombinant interleukin (IL)-1 receptor antagonist that blocks the activity of IL-1α and IL-1β by competitively inhibiting IL-1 binding to the IL-1 type 1 receptor. We present a series of two patients with recalcitrant PG, who had limited therapeutic options and multiple comorbidities and multiple previous treatment failures, who obtained 100% healing with anakinra. Compared with conventional first-line therapies for PG, the safety profile of anakinra may be preferable for patients with

multiple comorbidities. Further research is needed to assess the safety and efficacy of anakinra for PG [9].

Future directions

Platelet rich plasma is autologous conditioned plasma high in growth factors and platelet concentrate. It has been used to promote healing and lower inflammation. PRP has been used well in dermatology to treat alopecia, acne scars, skin renewal, and skin ulcers. According to treatment standards, PRP is the third-line therapeutic option for pyoderma gangrenosum. To avoid pathergy, use a PRP-soaked calcium alginate dressing rather than an intralesional injection. Treatment occurred once weekly for 6 weeks; by the end of treatment, the ulcer size was decreased by more than 50%, and the pain was gone [10].

Several problematic cases of PG treated with supplementary HBOT resulted in full wound healing with minimal scarring and wound re-epithelialization. Indeed, after only four days of treatment, a case of peristomal PG was completely cured with re-epithelialization of peristomal tissue. HBOT resulted in healing after a knee arthroplasty where delayed diagnosis and repeated debridement caused considerable tissue loss. In both cases, HBOT effectively reduced wound size, increased wound granulation, encouraged re-epithelialization, and alleviated pain.

It is uncertain how HBOT works in PG. HBOT raises the partial pressure of oxygen in tissue, which can boost the generation of reactive oxygen species due to hyperoxia. The Undersea and Hyperbaric Medical Society currently approves HBOT for the treatment of disorders, including radiation harm to tissue, compromised skin grafts and flaps, necrotizing soft tissue infections, and nonhealing diabetic ulcers. These data points to the benefits of treating PG with supplementary HBOT to achieve complete remission [11].

After one week of tannin topical therapy, the severity of pyoderma symptoms decreased by at least 90%. On the seventh day of treatment, there was no soreness, and stinging and burning had decreased by 93.2%. Excoriation decreased by 80% after seven days of use. The medications had a strong anti-inflammatory impact; on the seventh day of administration, erythema symptoms were reduced by 89.8%, and dampness and oedema were absent in 100% of the patients. The size of the skin lesions decreased by 73%. Microbial culture confirms tannin preparation's antibacterial efficacy against the major and conditionally pathogenic microorganisms of skin pyoderma. Fixed topical tannin formulations have been shown to be highly effective and safe in treating primary and secondary pyoderma in adults, children, and newborns. A comparative evaluation of modern medical compositions based on synthetic tannins with classic aniline dyes allows us to suggest the "neotanin" product line as a more effective topical formulation than carbol-fuchsin (both alone and in conjunction with systemic antibacterial medications) [12].

Natural topicals containing essential oils, plant-extracted essential fatty acids, and N-acetylcysteine effectively treated superficial pyoderma in dogs without the need for systemic antimicrobials. Such solutions can be used in conjunction with drugs like chlorhexidine and miconazole to treat CSP. Natural topical products containing plant-derived essential fatty acids, essential oils, and N-acetylcysteine with antibacterial or antibiofilm properties can replace medicated shampoos with chlorhexidine and miconazole for treating CSP [13].

Colchicine's antimitotic, anti-inflammatory, and immunomodulating qualities may explain why it is useful in PG patients. Most people find colchicine useful and well tolerated at modest dosages. Furthermore, it is less expensive and safer for long-term use than corticosteroids and other immunosuppressive medications. Colchicine thus may be used as a single agent or as a corticosteroid-sparing drug in the early treatment of PG [14].

There have been numerous anecdotal instances of thalidomide being used to treat resistant pyoderma gangrenosum. Thalidomide dosages ranged from 100 to 400 mg per day. Several modes of action for thalidomide have been proposed. It may affect cytokine production and the expression of cell surface adhesion molecules. It has been found to reduce polymorphonuclear cell chemotaxis and monocyte phagocytosis. It can also reduce TNF-α production, possibly by lowering messenger RNA levels. It has also been demonstrated to be a powerful angiogenesis inhibitor in a rabbit cornea model [15].

Skin allografts are widely known for accelerating healing in difficult-to-heal lesions. Composite grafts are tailored to wound specific features: the acellular DED, due to its low immunogenicity, acts as an ideal scaffold, guiding host cell proliferation and preventing scarring, while the overlying epidermal grafts maintain optimal wound humidity and allow for re-epithelization. Glycerolized skin allografts, in particular, offer additional benefits: because they are hypocellular, they can be partially absorbed into the PG wound bed, promoting re-epithelialization; and glycerol can greatly reduce local pain, as both patients have experienced [16].

Conclusion

Pyoderma gangrenosum is a chronic, neutrophilic, progressive skin necrosis with no known cause. It is frequently accompanied with systemic disease and, on occasion, skin damage. The diagnosis is clinical. Wound treatment is provided, as well as anti-inflammatory drugs or immunosuppressants, depending on the severity. The ongoing research focuses on the disease's unknown etiology and pathophysiology, with theories including neutrophil malfunction, immune system dysregulation, and genetic predisposition. Treatment research involves enhancing established medications like corticosteroids and immunosuppressants, as well as studying emerging possibilities including anti-TNF-α drugs and biologics, which often have varied effects. Ongoing research seeks to enhance diagnosis, better understand the genetic causes underlying the disease, and find more effective and tailored treatments to improve outcomes and prevent recurrence.

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