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Pyoderma Gangrenosum,Treatment Challenges

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Abstract: **Evidence on treatment of Pyoderma gangrenosum (PG) were reviewed aiming to describe the proper management option for PG, also in this review intended to discuss the diagnosis, and pathophysiology of PG, to have great understanding for present concerned dermatological disease. PubMed, Embase databases were searched for relevant articles, related to the Pyoderma gangrenosum (PG), wether concerned with treatment challangest or diagnostic approach or even clinical features of PG, which are published before the end of 2016, and contained only human subjects. No language restriction was applied in this search. Pyoderma gangrenosum is a serious however uncommon ulcerating skin disease, the treatment of which is mainly empirical. Pyoderma can provide to a range of health specialists and a number of versions exist that may not be recognised immediately. The finest recorded treatments are systemic corticosteroids and ciclosporin A. Combinations of steroids with cytotoxic drugs are used in resistant cases. The combination of steroids with sulfa drugs or immunosuppressants has been utilized as steroid-sparing methods. Anti-tumor necrosis alpha treatment in Crohn's disease showed a fast response of PG.**

Keywords: **Pyoderma gangrenosum (PG), dermatological disease, treatment, human subjects.**

1. INTRODUCTION

Pyoderma gangrenosum (PG) is an unusual disease, however frequently related to important morbidity. PG was first assumed to be contagious, but is now thought about an inflammatory neutrophilic disease, typically related to autoimmunity, and with chronic inflammatory and neoplastic diseases. PG sores are defined by prominent neutrophilic seepage of the skin in the absence of transmittable cause or vasculitis, although they can reveal evidence of leukocytoclastic vasculitis [(1,2)]. PG has actually been approximated to take place in three to ten individuals/million. Nevertheless, it is tough to determine the specific disease occurrence, as precise epidemiological data are missing out on. PG is most frequently observed in young to middle-aged adults, with females being more affected.5 Cases in elderly people have been reported sometimes, and childhood PG represent approximately 4% of the cases [(3,4)].

Classically, sores begin as tender papulopustules, vesicles or papules, progressing into painful and rapidly enlarging ulcers. Healing often leaves a cribriform scar, which may result in significant disfiguring [(5)]. The ulcer edge is often weakened (worn and damaged) and the surrounding skin is indurated and erythematous (**Figure 1**) [(6)]. The ulcer frequently begins as a small papule or collection of papules, which break down to form little ulcers with a "cat's paw" appearance. These coalesce and the main area then goes through necrosis to form a single ulcer [(6)]. The condition is possibly deadly and causes substantial morbidity. It goes unrecognized or is misdiagnosed in as much as 30% of cases and can take place at any age, with a peak of occurrence between 20 - 50 years of age. Women are a little more vulnerable to the disease than guys [(7,8)]. Pediatric PG represents 4% of all cases [(9)]. It typically presents as a papule or pustule that develops into several painful ulcers with violaceous and weakened borders [(10)]. Several versions are recognized. Considering that there are no accepted agreement diagnostic criteria and the medical diagnosis is one of exclusion, recognition of PG is typically postponed and tough. This is made harder by there being no medical trials that have actually examined the effectiveness of the different substance abuse in the treatment of PG due to the rarity of the disease; therefore, there is no 'gold requirement' treatment [(8,9,10)].

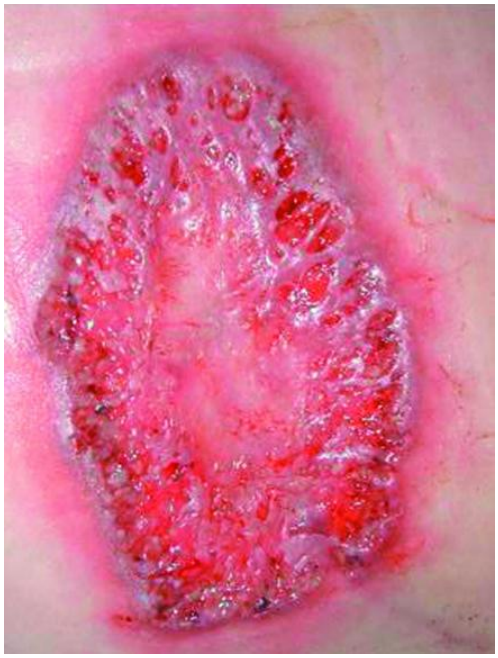

Figure 1: Classic PG [6]

Objective:

Evidence on treatment of Pyoderma gangrenosum (PG) were reviewed aiming to describe the proper management option for PG, also in this review intended to discuss the diagnosis, and pathophysiology of PG, to have great understanding for present concerned dermatological disease.

2. METHODOLOGY

PubMed, Embase databases were searched for relevant articles, related to the Pyoderma gangrenosum (PG), wether concerned with treatment challangest or diagnostic approach or even clinical features of PG, which are published before the end of 2016, and contained only human subjects. No language restriction was applied in this search.

3. RESULTS

❖ **Pathophysiology and clinical feature of Pyoderma gangrenosum:**

Both the etiology and pathogenesis of PG are not yet completely understood. An abnormal immunological response to undefined triggers and factors may integrate and be accountable for the medical manifestations. The pathergy phenomenon, an aberrant exaggerated inflammatory action, is characteristically observed in as much as 30% of PG cases [7].

PG is often connected with inflammatory bowel disease (IBD). This supports the hypothesis of possible cross-reactivity between cutaneous and intestinal antigens. Dysregulation of the regular T cell response likewise appears to be linked. When treated with immunosuppressive drugs and tumour necrosis factor (TNF) inhibitors, this is supported by the observation that PG sores recover. Lesions may appear throughout treatment with etanercept or infliximab, although this is unusual [11,12]. PG is thought about to be within the spectrum of the neutrophilic dermatoses (NDs). This group consists of a number of heterogeneous conditions characterised by inflammatory skin sores that, observed histologically, show an intense inflammatory infiltrate composed primarily of neutrophils, with no evidence of infection [1,2]. These entities most likely share a typical pathophysiological system that involves an unusual recruitment or haemostasis of polymorphonuclear neutrophils. An elevation of the cutaneous and/or flowing levels of proinflammatory cytokines and potent attracting chemokines, specifically interleukin (IL) -6, chemokine (C-X-C motif) ligand (CXCL) 8, and CXCL1- 3, are observed in PG ulcers [13,14].

Particularly, in the traditional ulcerative type, two unique phases are explained: the active ulcerative stage and the injury recovery stage. At the ulcerative stage, the injury has a peripheral erythematous inflammatory halo and the edges are erythematous, raised, and sometimes lethal, with an under mining border, whose size reveals how quickly the ulcer edge

will evolve. Alternatively, the ulcer can extend through the look of surrounding pustules. In contrast, at the healing phase, the edges reveal string-like projections of epithelium, which straddle the border in between the ulcer bed and the regular surrounding skin-- Gulliver's indication (**Figures 2**) [15,16]. The lesions commonly take place on the lower legs, classically the pre-tibial region, but can happen on any anatomical area consisting of: trunk, head, neck, breasts, upper limbs, genitalia, mucous membranes and peristomal circulation [17,18]. Sores have actually been reported to take place simultaneously on various physiological locations2. Typically, the lesions start as a little blemish or sterilized pustule30 which increase the size of into well-demarcated ulcers, which can extend to the fascia with violaceous margins (red-blue) weakened border, surrounding erythema and induration. Normally the lesions have necrosis at the base, friable granulation tissue with a purulent or haemoserous exudate [3]. The ulcers are typically described as "necrolytic", a procedure whereby as the tissue is destroyed, the liquefactive necrosis exposes a redblue undermined injury edge30. Invariably the lesions are very agonizing. Atrophic cribriform pigmented scarring can take place as the sores heal, especially with delayed diagnosis and treatment [2,4]. PG has also been described in association with pathergy, a process that takes place as a result of trauma. This has actually been reported in injuries ranging from small trauma to surgical incision sites [18].

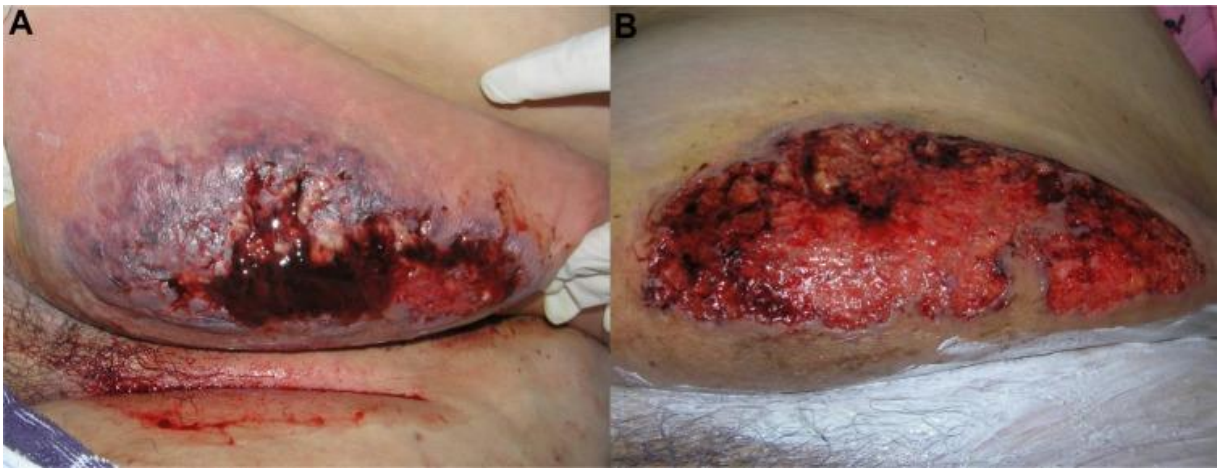

Figure 2: PG (A) Ulcerative stage (B) The healing stage ulcer

❖ **Diagnosis of Pyoderma gangrenosum:**

Histopathology and lab findings in PG are nonspecific; therefore, the diagnosis is based upon medical history, health examination and verified through a process of elimination. There must be a high index of suspicion in patients with non-healing ulcers, specifically in the presence of systemic diseases [2,3]. The clinician must, nevertheless, err on the side of care as a lot of the associated diseases might not be overtly obvious4. In order to increase PG acknowledgment and enhance diagnostic specificity, diagnostic criteria have actually been proposed, initially by von den Driesch, and later on by Su et al [19] (**Table 2**). They are quite similar and require the exact same 2 significant criteria (a characteristic PG classical type ulcer, and the exemption of other reasons for cutaneous ulcer), combined with at least two small requirements: suggestive history of pathergy or a cribriform scar (product just provided in the most recent diagnostic criteria), presence of a pertinent involved disease, suitable histopathological findings, or reaction to systemic steroid treatment [20,21].

Table 1: Proposed diagnostic criteria for classic ulcerative pyoderma gangrenosum,

➢ **Major criteria**
– Rapid progression of a painful, necrolytic, cutaneous ulcer with an irregular, violaceous, and undermined border.
– Exclusion of other causes of cutaneous ulceration.
➢ **Minor criteria**
– History suggestive of pathergy.
– Clinical finding of cribriform scarring.
– Systemic diseases associated with pyoderma gangrenosum.
– Histopathologic findings (sterile dermal neutrophilic infiltration, ± mixed inflammation, ± lymphocytic vasculitis).
– Treatment response (rapid response to systemic steroid treatment).

There are a number of differential diagnoses, and ulcerative cutaneous lesions that mimic PG (**Table 2**) including: malignancy, infectious disease, antiphospholipid antibody-associated occlusive disease, vasculitis, and drug responses [2,4]. Lab investigations are not diagnostic for PG; patients often have neutrophil leukocytosis [22]. The inflammatory process is shown with elevated erythrocyte, C-reactive protein, and protein electrophoresis [23]. It is essential to target lab examinations for involved diseases, such as IBD or arthritis, and to leave out other ulcerating conditions; for instance, other autoimmune connective tissue diseases, or anticardiolipin syndrome [22,23]. Tissue biopsy for histopathology should be carried out to leave out other conditions such as malignancy or vasculitis. A biopsy can likewise be carried out for culture, level of sensitivity and microbiology (MC&S), particularly trying to find irregular mycobacteria, fungis and parasites. Although carrying out a tissue biopsy can cause pathergy, the treatment must be performed, as this will help in dismissing other aetiologies [2,4].

Table 1: Differential diagnosis of the unspecific ulcerative lesions of pyoderma gangrenosum

➢ **Infections**
Bacterial
Mycobacterial (eg, Buruli ulcer)
Fungal infection (eg, sporotrichosis)
Parasitic (eg, cutaneous amebiasis)
Viral (eg, chronic ulcerative herpes simplex or cytomegalovirus ulcer)
➢ **Sweet's syndrome (bullous forms)**
➢ **Insect bites**
➢ **Cutaneous primary tumors/metastasis**
➢ **Skin lymphomas**
➢ **Halogenoderma (iododerma/bromoderma)**
➢ **Ulcerative necrobiosis lipoidica**
➢ **Vascular occlusive disease or ulcers of chronic venous insufficiency**
➢ **Autoimmune diseases with vasculitis**
Antiphospholipid antibody syndrome
Systemic lupus erythematous
Behçet's disease
Wegener granulomatosis
Polyarteritis nodosa
Factitious ulceration

❖ **Treatment of pyoderma gangrenosum:**

Outside dermatology, the medical diagnosis of PG is frequently thought about just after several and unsuccessful treatment attempts, with antibiotics and surgical debridement. Lesions typically progress when dealt with as infection, and due to pathergy, get worse after surgical procedures [24]. Treatment is challenging; there is no universally accepted "gold requirement" and although a small trial has been released, comparing infliximab to placebo, no randomized regulated trials have actually been carried out for the usual systemic therapies [25,26]. Little proof supports a rational therapeutic technique to this scientific entity, and currently, treatments are mainly attempting to target a broad spectrum of inflammatory cells and immunologic arbitrators, shown to be involved in PG, consisting of lymphocytes, cytokines, and neutrophils.

Topical and systemic corticosteroids are considered the very first healing option, whereas other immunosuppressors and cytostatics can be used as steroid-sparing agents. Multidrug routines have not been well explained in the literature, however they represent a good alternative for patients with refractory disease [27].

➢ **Treatment of the underlying disease and topical treatment**

Treatments differ between patients with idiopathic disease and those who have a hidden condition. In the latter case, the fundamental technique is the control of the associated condition, which is, however, not always possible. Treatments serving this purpose may consist of: colectomy in patients with chronic ulcerative colitis, plasmapheresis or granulocyte apheresis in patients with leukemia, or thalidomide in patients with myelodysplastic syndromes [28,29].

Anti-inflammatory and immunosuppressive drugs can be effective both in PG and the underlying disease, as the example of the IL1 villain anakinra for PG in the context of PAPA syndrome, [30,31] and of infliximab and other anti-TNF representatives in the context of Crohn's disease and ulcerative colitis [27]. Among the anti-TNF biologics, etanercept is the only one reported not to be efficient in IBD, which should be taken into account when dealing with these patients. In many case reports describing successful treatment of PG, it is not possible to determine whether treatment had a direct effect on PG, or an indirect result by managing the associated condition [32]. Extremely powerful topical corticosteroids (occasionally underneath occlusive dressings) may suffice to induce remission [33]. Triamcinolone 40 mg/ml might be injected into the ulcer edge, either alone or as an accessory to systemic treatment [34]. Recently, topical tacrolimus has been revealed to be effective in patients with peristomal disease. This is now offered as a 0.1% and 0.03% lotion [35].

➢ **Systemic treatment & Corticosteroids for managing PG:**

A lot of patients require systemic treatment to cause remission and physicians typically start patients on oral corticosteroids at an early stage. Prednisolone is the drug of option and is generally begun at high dosages (60-120 mg) (level B proof) [36,37]. Patients exposed to these dosages for a long time are at risk of steroid associated side effects and might take advantage of the addition of a bone safeguarding representative. Minocycline 100 mg two times daily may be of some benefit, typically as an accessory to oral steroids (level C evidence) [38]. Rapid enhancement has actually been reported in patients with extreme disease given intravenous methylprednisolone as pulse therapy of 1 g daily for 3 to 5 days (level B proof), and numerous series and examines assistance this treatment [37,39]. For a more extensive or quickly progressive disease, systemic treatment is compulsory. Corticosteroids in moderate to high dosages (eg, prednisolone, 0.5-2 mg/kg/day) and cyclosporine (3- 6 mg/kg/day) are the most often used drugs.

4. CONCLUSION

Pyoderma gangrenosum is a serious however uncommon ulcerating skin disease, the treatment of which is mainly empirical. Pyoderma can provide to a range of health specialists and a number of versions exist that may not be recognised immediately. The finest recorded treatments are systemic corticosteroids and ciclosporin A. Combinations of steroids with cytotoxic drugs are used in resistant cases. The combination of steroids with sulfa drugs or immunosuppressants has been utilized as steroid-sparing methods. Anti-tumor necrosis alpha treatment in Crohn's disease showed a fast response of PG.

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