International Journal of Computational and Experimental Science and ENgineering (IJCESEN)

Vol. 9-No.3 (2023) pp. 307-312
http://dergipark.org.tr/en/pub/ijcesen

ISSN: 2149-9144

Research Article

Pyoderma Gangrenosum: Retrospective Evaluation of Clinical Features and Treatment Responses in 23 Cases

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Article Info:

DOI: 10.22399/ijcesen.1363934
Received : 21 September 2023
Accepted : 27 September 2023

Keywords

pyoderma gangrenosum
concomitant systemic diseases
treatment

Abstract:

Pyoderma gangrenosum (PG) is a rare inflammatory disease in the spectrum of neutrophilic diseases characterized by rapidly progressive, painful and large ulcers. In this study, we aimed to investigate the relationship between the clinical characteristics and treatment responses of patients diagnosed with PG, treated and followed up in our clinic. Between 2018 and 2023, 23 patients diagnosed with PG in our clinic were included in the study. Medical file records were retrospectively analyzed and various demographic and clinical characteristics, comorbid systemic diseases, treatment protocols and treatment responses of the patients were recorded. Twelve (52.2%) of the patients were female and 11 (47.8%) were male, with a mean age of 42.4±12.9 years. The median disease duration was 52 months (range: 10-540 months). Systemic diseases accompanying PG were present in 14 patients (60.9%). Systemic steroids were the most common treatment (43.5%). Other treatment approaches included adalimumab, infliximab, cyclosporine, oral doxycycline, topical tacrolimus, topical corticosteroids and intralesional steroids. Remission was achieved in 14 patients (60.9%), relapse was observed in 5 patients (21.74%), and no remission/relapse information was available for 4 patients (17.4%) who lost follow-up. The median duration of remission was 23 months (range: 3-96 months). Although systemic steroids are most commonly used in the treatment of pyoderma gangrenosum, it should be kept in mind that there are various treatment options ranging from systemic and topical anti-inflammatory therapies to biologic agents according to close follow-up of the patients and additional systemic diseases.

1. Introduction

Pyoderma gangrenosum (PG) is a non-toxic skin disease belonging to the group of neutrophilic dermatoses, which also includes Sweet syndrome and Behçet syndrome. The incidence of this disease is estimated to be approximately 0.63 per 100,000 people and the average age of onset is 59 years [1]. The pathogenesis of PG is unclear, but neutrophils are recognized to play an important role in the disease process [2]. After patients receive antigen priming, helper T (Th) 17/Th1 bias leads to the development of an autoinflammatory environment dominated by tumor necrosis factor-α (TNF-α), leukocyte-mediated IL level, and neutrophils. IL-1β, IL-1α, IL-8, IL-12, IL-15, IL-17, IL-23 and IL-36 [3, 4]. Most of PG is the classic form (approximately 85%), but other subtypes include bullous, vegetative, pustular, peristomal, and superficial granulomatous forms, and PG subtypes may differ from one form to another [5]. Diseases commonly associated with PG include inflammatory bowel disease, rheumatoid arthritis, hematological malignancies, and monoclonal immunoglobulin A (IgA) gamma disease [6] .

PG treatment is usually preventive and there is no universally accepted treatment, but corticosteroid treatment can be done. Oral cyclosporine is a widely used drug [7]. In recent years, drugs in the form of TNF-α inhibitors have begun to be used, and some recent studies have shown the effectiveness of TNF-α inhibitors in the treatment of PG [8].

This study aimed to evaluate the relationship between clinical features and response to treatment in patients diagnosed with PG treated in our hospital.

2. Material and Methods

This study included 23 patients diagnosed with PG who were treated and followed up at the Dermatology and Venereology Clinic of Ankara Health Sciences University Gülhane Training and Research Hospital between January 1, 2018 and April 1, 2023. Medical records were reviewed retrospectively. Information obtained about the patient's various demographic characteristics (age, gender, diseases in the body, etc.) and response to treatment characteristics (course of pain, dermatological findings, type and location, histopathological and diagnosis, treatment and treatment) are recorded. . SPSS 22.0 program was used to analyze the data and perform the descriptive analysis.

3. Results and Discussions

Of the 23 patients included in the study, 12 were female (52.2%) and 11 were male (47.8%). The mean age was 42.4±12.9 years (mean age in men: 44.64±13.7 years; mean age in women: 40.3±12.9 years). When the presenting complaints of the patients were analyzed, it was observed that pyoderma gangrenosum presented as ulcer in 13 patients (56.5%), plaque in 5 patients (21.7%), inflamed nodule in 4 patients (17.4%) and bullae in 1 patient (4.4%). The number of lesions varied between 1 and 17. The median disease duration was 52 months (range: 10-540 months). In four patients, PG lesions appeared in the postoperative period (after mammoplasty, varicose vein surgery). The lesions were present in 13 (56.5%) legs, 6 (26.1%) feet, 4 (17.4%) ankles, 3 (13%) inguinal, 2 (8.7%) breast, 2 (8.7%) gluteal, 2 (8.7%) genital, 2 (8.7%) trunk, and 1 (4.4%) shoulder lesions. There was a history of comorbid systemic disease in 14 patients (60.9%) (inflammatory bowel disease in 3 patients, anemia in 3 patients, Behçet's disease in 2 patients, rheumatoid arthritis in 2 patients, hidradenitis suppurativa in 2 patients, 1 patient with familial Mediterranean fever, 1 patient with ankylosing spondylitis, 1 patient with polychondritis, 1 patient with systemic lupus erythematosis overlap syndrome, 1 patient with venous insufficiency, 1 patient with osteomyelitis, 1 patient with hypertension, 1 patient with fulminant acne).

Seventeen (73.9%) patients were treated as outpatients and 6 (26.1%) were hospitalized. Histopathologic examination was performed in 20 patients (24.4%) and nanspecific chronic inflammation findings were detected. Tissue/wound culture samples were obtained from 12 patients (52.2%). Growth was detected in 4 patients. The pathogens were S. aureus (2 patients), S. pyogenes (1 patient), E. coli (1 patient). Patients with growth were given agent-sensitive systemic antibiotherapy.

For pyoderma gangrenosum, three patients received adalimumab (80 mg/week, then 40 mg/week maintenance), 3 patients received infliximab (5-10 mg/kg/day 0.-2.-6. weeks, then every 8 weeks), systemic steroid (0.5-1 mg/kg methylprednisolone) in 10 patients, topical tacrolimus in 4 patients, topical steroid (0.05% clobetasol propionate) in 4 patients, intralesional steroid (5 mg/ml triamcinoloneacetonide) in 2 patients, cyclosporine (3-5 mg/kg/day) in 2 patients, oral doxycycline (200 mg/day) in 2 patients (Table 1). One patient was switched to infliximab due to cyclosporine side effects, but no treatment-related side effects were observed in the other patients.

Remission was achieved in 14 patients (60.9%), relapse was observed in 5 patients (21.7%), and no remission/relapse information was available for 4 patients (17.4%) who were lost to follow-up. The median duration of remission was 23 months (3-96 months). During the period analyzed, 1 patient who discontinued infliximab treatment due to the COVID-19 pandemic, 1 patient whose infliximab treatment was discontinued due to remission developed relapse after cat scratching, and 1 patient who received systemic steroid treatment with adalimumab treatment developed relapse while the steroid dose was reduced. One patient was in remission under adalimumab treatment and relapse was detected after inguinal hernia operation (Figure 1). One patient who received systemic steroid treatment developed relapse due to non-compliance with the treatment regimen. Pyoderma gangrenosum is a rare disease in the neutrophilic spectrum, characterized by rapid growth, pain and large lesions [9, 10]. It has been reported that women between the ages of 20-50 years are more affected by this disease than men [11]. In our study, it was observed that the majority of the patients were women. Pyoderma gangrenosum is observed more rarely in infants, children and the elderly. Among our patients, only adult patients were found and two of them developed PG at an advanced age. Although it has been reported that pyoderma gangrenosum frequently develops as a result of minor traumas and Köbner phenomenon, most of the cases do not have a history of trauma [12 ,13]. In our study, a history of trauma was found in only four of 23 cases and it is remarkable that PG developed postoperatively.

Figure 1. *Complete response with infliximab treatment in a 59-year-old patient who developed recurrence after inguinal hernia operation, in remission for 5 months.*

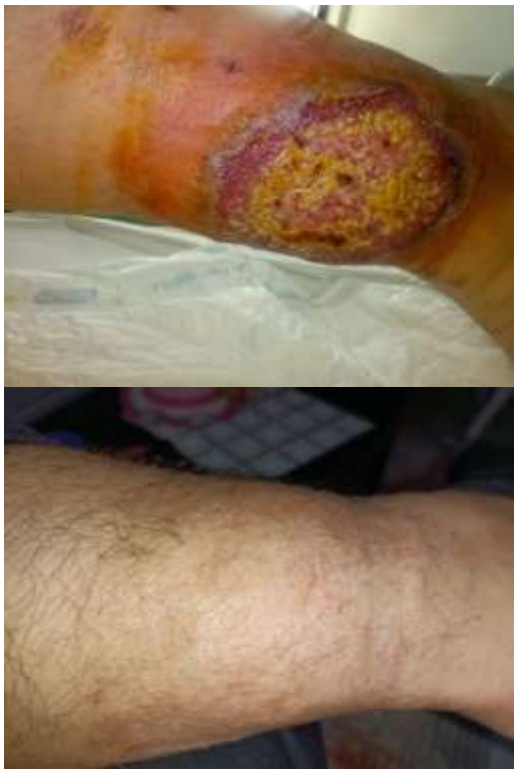

Figure 2. *39-year-old male patient with ulcerated lesion in the lower leg, complete healing with systemic steroid treatment, in remission for 4 years.*

In pyoderma gangrenosum, the diagnosis is usually made with clinical features [14, 15]. Lesions start suddenly as painful nodules, pustules and/or papules. In patients with active lesions, the appearance of a hemorrhagic, suppurative and necrotic almost "swampy" appearance with indistinct, irregular, red-purple, hemorrhagic, suppurative and necrotic appearance surrounded by an erythematous halo should clinically suggest PG [10]. In our study, lesions were ulcerative type in most of the cases. In pyoderma gangrenosum, lesions are usually localized as a single lesion on the anterior surface of the tibia in the lower extremity. Atypical forms are more superficial and may be localized on the face, head-neck, breast, arm, hand and especially on the peristomal skin [9, 11, 16, 17]. Kim [18], Güngör [12] and Farrell [13] reported cases with PG localized atypically on the penis. In our study, PG was localized as a single lesion (56.5%) and in the lower extremities (82.6%) in most of the patients in accordance with the literature.

It has been reported that more than 50% of patients with pyoderma gangrenosum are associated with systemic diseases [11]. It may accompany rheumatologic and hematologic diseases, most commonly inflammatory bowel diseases [19], monoclonal gammopathies [9], hidradenitis suppurativa [20] and iatrogenic immunosuppression [21] or malignancies [19]. In our study, 65.2% of patients were accompanied by systemic diseases. Hasselmann et al. reported an association with inflammatory bowel disease with a rate of 33% [22]. In our study, inflammatory bowel disease was present in 13% of our patients. Waldman et al. reported a patient diagnosed with SLE 8 years after the development of PG [23]. In our study, SLE dermatomyositis overlap syndrome was present in one patient. While autoimmunity is blamed in SLE, humoral immunity, cell-mediated immunity and neutrophil dysfunction are more prominent in PG than autoimmunity, but the pathogenesis is not completely clear although the role of T cells has been emphasized in recent years [24]. The association of Hidradenitis suppurativa (HS) and PG is rarely reported in the literature. In the study of Weng et al. the association of HS and PG was reported in a series of 6 cases [20]. In our series, HS was associated with PG in two patients. In hidradenitis suppurativa, dysfunctional neutrophils and immune pathway dysfunction are involved in the pathogenesis [20]. It was thought that PG might have developed in the course of HS because of similar pathways. Coexistence of Behçet's disease and PG can be observed [25]. Two of our patients had a diagnosis of Behçet's disease.

High-dose systemic corticosteroids are the treatment of choice for pyoderma gangrenosum. Topical and intralesional corticosteroids can be used for mild pain. Immunosuppressants, intravenous immunoglobulins, and biologics are used in resistant patients [26–30]. The anti-inflammatory effects of corticosteroids are attributed to their transcriptional effects, particularly inhibition of NF-κB and subsequent reduction of many pro-inflammatory cytokines, chemokines and cell adhesion molecules [31] . Corticosteroid treatment (prednisolone dose of 0.5-1 mg/kg/day) provides cure in approximately 40-50% of patients [32]. The steroids we frequently use in our patients allow us to go into remission (Figure 2).

Cyclosporine is an antiviral drug used in the first-line treatment of PG. Cyclosporine is a calcineurin inhibitor that inhibits the synthesis of IL, especially IL-2, which is important for preventing T lymphocyte activation [33]. In a randomized controlled study, prednisolone (0.75 mg/kg/day, maximum 75 mg) and cyclosporine (4 mg/kg/day, maximum 400 mg) responses were compared in 121 PG patients and no difference was found and 47% of patients in both groups recovered in six months [7]. In our study, complete response was obtained in 2 patients who received cyclosporine treatment.

Doxycycline is a tetracycline group antibiotic. Doxycycline reduces proinflammatory cytokines such as interleukin (IL) 1β, IL-6 and TNF- α. It is widely used in dermatology in many diseases such as acne, rosacea, bullous pemphigoid and perforating dermatosis due to its anti-inflammatory properties and good safety profile [34]. There are studies showing that tetracyclines are beneficial in the treatment of PG [35]. Anuset et al. treated 23 of 42 PG patients with doxycycline 200 mg/day as monotherapy or in combination with topical steroid or topical tacrolimus, 15 patients with systemic steroid as monotherapy or in combination, and 4 patients were followed up with other treatment modalities (colchicine, dapsone, topical steroid only). Doxycycline and systemic corticosteroid treatment responses were found to be comparable and the recurrence rate was lower in the doxycycline group [35]. In our study, complete response was obtained in 2 patients who received doxycycline treatment.

Tacrolimus is an immunomodulator that acts by inhibiting T lymphocyte activation [7]. It inhibits T lymphocyte activation by inhibiting interleukin 2 (IL-2) gene expression. It has also been shown to inhibit gene transcription of IL-3, IL-4, interferon-α, TNF-α, and granulocyte-macrophage colony-stimulating factor. Additionally, tacrolimus blocks mast cell, neutrophil, basophil and cytotoxic T cell degranulation. The specific mechanism by which tacrolimus improves PG remains unclear. However, since PG is characterized by central neutrophil and peripheral lymphocyte infiltration, tacrolimus can effectively treat PG by inhibiting the accumulation and activation of lymphocytes and neutrophils [36]. In a study comparing 24 patients with peristomal PG, 11 patients were treated with topical tacrolimus 0.3% monotherapy and 13 patients were treated with topical clobetasol propionate 0.05%. Seven patients in the tacrolimus group improved in an average of 5.1 weeks, and five patients in the clobetasol propionate group improved in an average of 6.5 weeks. Topical tacrolimus is better for patients with lesions larger than 2 cm in diameter. Response and treatment duration were better in the tacrolimus group than in the steroid group [37]. This study recommends adding tacrolimus to the treatment to increase the effectiveness of the treatment.

Tumor necrosis factor-α is an important pro-inflammatory pleiotropic cytokine that regulates IL1-β, IL-6 and IL-8. Tumor necrosis factor is a potent chemokine that acts as a chemoattractant and works synergistically with TNF-α to promote and maintain a proinflammatory state. Expression of TNF-α and its receptors is increased in the PG region of the skin [38]. Growing evidence supports the use of TNF-α inhibitors, particularly infliximab and adalimumab, as first-line therapy. In fact, a partial analysis showed that the response to TNF-α inhibitors was 67% (238/356 patients) and the overall response was 87% [8] . To date, infliximab remains the only anti-TNF-α agent shown to be effective in classic PG, as demonstrated in a randomized, double-blind study [39] . Recently, a phase III, open-label, multicenter study was conducted in 22 Japanese patients to evaluate the efficacy and safety of adalimumab in refractory PG. At the end of 26 weeks of treatment, 55% of participants fully recovered [40]. In this study, patients treated with TNF-α inhibitors had a good response, although relapses occurred due to various factors (treatment, trauma).

Surgical treatment is highly controversial in PG, and most of the autonomists think that PG is a "pathergy" reaction and trauma may exacerbate the lesions. Therefore, surgical aggressive approaches should be avoided in PG.

Recurrence can be an important problem in the follow-up after PG treatment. Mlika et al. reported a recurrence rate of 46% [9]. In our study, recurrence was found in 5 cases (21.7%).

In conclusion, although PG is rare, it is a disease that may accompany various systemic diseases, most commonly with ulcers and should be

considered in the differential diagnosis. Although systemic steroids are the most common treatment given to patients, it should be kept in mind that there are various treatment options ranging from systemic and topical anti-inflammatory therapies to biological agents according to close follow-up of the patients and additional systemic diseases.

4. Conclusions

In conclusion, although PG is rare, it is a disease that may accompany various systemic diseases, most commonly with ulcers and should be considered in the differential diagnosis. Although systemic steroids are the most common treatment given to patients, it should be kept in mind that there are various treatment options ranging from systemic and topical anti-inflammatory therapies to biological agents according to close follow-up of the patients and additional systemic diseases.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
- **Acknowledgement:** The authors would like to thank Dr. Zeynep Rümeysa Çelik for her contribution to the study.
- **Author contributions:** The authors declare that they have equal right on this paper.
- **Funding information:** The authors declare that there is no funding to be acknowledged.
- **Data availability statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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