Pyoderma Gangrenosum: A Retrospective Study of 25 Cases and Review of the Literature Findings

Nilay DUMAN,a Sibel ERSOY EVANS,b Ayşen KARADUMAN,b Gonca ELÇİN, Göz ERKİN ÖZAYGEN, b Nilgün ATAKAN, b Tülin AKAN b

aClinic of Dermatology, Afyonkarahisar State Hospital, Afyonkarahisar, bDepartment of Dermatology, Hacettepe University Faculty of Medicine, Ankara

Geïnterpreteerd: 25.11.2013
Kabul Tarihi/Accepted: 11.03.2014

This study was presented as a poster at 2009 XIX. Lütfü Tat Symposium, 11-15 November 2009, Ankara

This study was presented as a poster at 2009 XIX. Lütfü Tat Symposium, 11-15 November 2009, Ankara


Anahtar Kelimeler: Piyoderma gangrenozum; deri úlseri

ABSTRACT Objective: Pyoderma gangrenosum is a rare inflammatory disease of unknown etiology characterized by neutrophilic infiltration. Our aim was to evaluate the demographic and clinical features of patients with pyoderma gangrenosum and to review the literature findings about pyoderma gangrenosum. Material and Methods: Patients diagnosed with pyoderma gangrenosum between 1980-2009 years were retrospectively evaluated. Response was determined as complete improvement of the lesion with therapy. Results: The study included 25 patients (15 female, 10 male) with a mean age of 42 years. Mean disease duration was 2.7 years. The most common variant (84%) was ulcerative variant. 6 patients (24%) had a history of trauma that preceded the onset of lesions, and 10 patients (40%) had recurrent attacks. Multiple lesions (≥2) were observed in 12 patients (48%). Inflammatory bowel disease was present in 4 patients (16%). Other associated diseases included acute myeloid leukemia, vasculitis, aganglionic megacolon, incomplete Behçet’s disease, and Takayasu arteritis and diabetes mellitus. The most common lesion localization was the lower extremities (72%). Majority (88%) of the patients were treated with systemic immunosuppressive agents, the most common immunosuppressive agent used was systemic corticosteroids (n=18, 72%), and of those 88.8% (n=16) responded to the treatment. Conclusion: Pyoderma gangrenosum was primarily seen in adults with a slight female predominance, had a predilection for the lower extremities and ulcerative variant was the most common clinical type. Forty-four percent of patients had associated systemic disease of which the inflammatory bowel disease was the most common. Systemic corticosteroids were the mainstay of systemic therapy.

Key Words: Piyoderma gangrenosum; skin ulcer

Copyright © 2013 by Türkiye Klinikleri

Turkiye Klinikleri J Dermatol 2013;23(3):77-83
Pyoderma gangrenosum (PG) is a rare, chronic, often destructive, inflammatory skin disease.

PG was first described as ‘phagedeisme geometrique’ by Brocq in 1916. The term PG was first used by Brunsting et al in 1930 and an infectious agent was suspected as the causative agent. In fact it is neither pyoderma nor gangrenous and it is placed in the group of ‘non infectious neutrophilic dermatoses’.1

It is usually characterized by a painful nodule or pustule which breaks down to form a progressively enlarging ulcer with a raised, tender, undermined border. Although it was reported in all age groups, it is common in the 20-50-year age group with a slight female predominance.1 The pathogenesis of PG is not clear yet. Although the disease is idiopathic in 25-50% of patients, it can be associated with systemic diseases such as ulcerative colitis, Crohn’s disease, polyarthritis, hematological disease such as monoclonal gammopathy or hematologic malignancy.2 Laboratory or histopathologic findings of PG are not specific. Therefore it is a diagnosis of exclusion. Although the histopathologic findings are not specific histopathologic examination can help to differentiate PG from some of its mimickers.2

The aim of this study was to evaluate the demographic and clinical features of 25 patients with PG and to review the literature findings about PG.

MATERIAL AND METHODS

Patients diagnosed with PG between 1980 and 2009 were retrospectively evaluated. Data were collected from patient medical charts. Therapeutic response was determined as complete improvement of the lesion.

Data about the literature about PG was obtained by searching the PubMed database using the key words ‘pyoderma gangrenosum’. Statistical analysis was performed using SPSS v.15.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean±standard deviation and categorical variables were presented as percentages.

RESULTS

The study included 25 patients (15 female, 10 male) with a mean age of 42 years (range: 1.5-73). Mean disease duration was 2.7 years (range: 7 days-24 years). In 2 patients the lesions occurred during pregnancy, 6 patients (24%) had a history of trauma that preceded the onset of lesions, and 10 patients (40%) had recurrent attacks. The most common variant was ulcerative variant characterized by ulceration with a purulent base and undermined borders surrounded by a halo of centrifugally enlarging erythema. Multiple lesions (≥2) were observed in 12 patients (48%). Inflammatory bowel disease was present in 4 patients (16%). Other associated diseases included acute myeloid leukemia, C-ANCA (anti-neutrophil cytoplasmic antibody) positive vasculitis, aganglionic megacolon, incomplete Behçet’s disease, and Takayasu arteritis and diabetes mellitus. All the patients with an associated systemic disease had ulcerative variant. The most common lesion localization was the lower extremities (72%), followed by the trunk (36%), upper extremity (12%) and face and scalp (8%) (Table 1).

Laboratory testing revealed an elevated white blood cell count in 48% of the patients, elevated sedimentation rate in 56%, and elevated C-reactive protein (CRP) levels in 44%. Biopsy was performed in 21 patients (84%) which was consistent with PG. In the remainder, diagnosis was made by typical clinical findings. Complete remission was observed in 18 patients (72%). Majority (88%) of the patients were treated with systemic immunosuppressive agents, the rest was given only local wound care (Table 2). The most common immunosuppressive agent used was systemic corticosteroids (n=18, 72%), and of those 88.8% (n=16) responded to the treatment.

DISCUSSION

PG is a rare noninfectious neutrophilic ulcerating skin disease. Classic PG lesion starts as a superficial hemorrhagic pustule that rapidly progresses to form a painful ulcer with undermined, elevated violaceous borders, peripheral zone of erythema...
and purulent discharge (Figure 1). The ulcers may be single or multiple (Figure 2) and mostly localize to lower legs although any area of the body including the breast, genitals may be affected (Figure 3, 4).3,4

The ulcers may occur de novo or after a trauma which is called as ‘pathergy’ and have either acute onset and rapid spread or more indolent course with slower spread.5,6 They usually heal from the margins with atrophic cribriform scars (Figure 5). In our study, most of the lesions occurred de novo whereas 24% patients had a history of trauma preceding the lesions. The most common lesion localization was the lower extremities (72%). And our results were in consistence with the literature findings.

PG lesions can be recurrent. In a report of 21 cases, the recurrence rate was reported as 46%.7

In our study, similarly 10 patients (40%) had recurrent attacks. There are 5 major clinical variant of PG. The classical ulcerative form comprises approximately 85% of all cases.8 In our study similar to literature findings, the most common variant (84%) was ulcerative variant.

The other clinical variants of PG are bullous, vegetative, pustular and peristomal PG.8 Bullous PG is characterized by rapidly evolving painful vesicules and enlarging bullae with central necrosis. It is usually associated with hematological malignancies and myeloproliferative disorders. Bullous PG has similar clinical features with Sweet’s syndrome and overlap cases were reported.1,9 It usually has poorer prognosis than the classical ulcerative form especially when associated

and purulent discharge (Figure 1). The ulcers may be single or multiple (Figure 2) and mostly localize to lower legs although any area of the body in-
with hematological malignancies and lesions may be seen in atypical locations such as arms, face or more widespread.\textsuperscript{1,9}

Vegetative PG is also called as ‘superficial granulomatous pyoderma’, usually characterized by a limited superficial ulcer on trunk without undermined borders especially at sides of surgical incisions or other traumatic area. The base of the ulcer is clean and usually not tender and heals without scarring.\textsuperscript{10} It usually runs a chronic but nonaggressive course. Many patients do not have an associated systemic disease.\textsuperscript{11} In our study, none of the patients with vegetative variant had an associated systemic disease.

Pustular PG is characterized by painful sterile pustules with a surrounding erythema, usually associated with inflammatory bowel disease. Frank ulceration usually is not seen.

Pyostomatitis vegetans was first described as oral counterpart of vegetative PG by McCarthy in 1949 but today it is accepted in the spectrum of chronic pustular dermatoses as the oral pustular PG.\textsuperscript{1,12} It is characterized by miliary pustules that ruptures and leads to erosions and ulcerations and it is the hallmark of inflammatory bowel disease.

Peristomal PG is characterized by ulcers in peristomal area in patients with inflammatory bowel disease after enterostomy or colostomy. It has been postulated that local skin trauma leads to
the formation of ulcers in the region of the stoma.\textsuperscript{1,13}

The etiopathogenesis of PG is still unknown. Numerous defects of immune system, including humoral immunity, cell-mediated immunity, neutrophil chemotaxis and phagocytosis, lymphokine production abnormalities have been reported.\textsuperscript{14,15} In a histopathologic and immunologic study of 65 cases, immunoglobulin and complement deposition was shown along the endothelium in 55\% of cases indicating a vasculitic etiology.\textsuperscript{16} Disseminated PG has been found to be associated with vascular endothelial growth factor and hypoxia in one study.\textsuperscript{17} Interleukin-8, a potent chemotactic polypeptide for neutrophils was found to be increased in the serum and lesional fibroblasts in PG.\textsuperscript{18,19}

In their study, Bister et al. found that matrix metalloproteinases (MMP-9 and -10) and TNF-α were increased in the stroma of PG and they suggested that these molecules cause degradation of the matrices needed for migration in healing process and retard epithelial repair and may be therapeutic targets for PG. Also in the same study MMP-1 and -26 that are high in the normally healing cutaneous wounds were found decreased in PG.\textsuperscript{20}

In more than half of the cases of PG there is an associated systemic illness such as ulcerative colitis, Crohn’s disease, rheumatoid arthritis, seronegative polyarthritis, hematological malignancies (acute leukemia, chronic myeloid leukemia, hairy cell leukemia, myelofibrosis) or monoclonal gammopathy, particularly of IgA type.\textsuperscript{1} Peristomal lesions, pustular variants including pyoderma gangrenosum vegetans are usually associated with inflammatory bowel disease whereas bullous lesions are usually associated with hematological malignancies.

There are also rare clinical associations such as autoimmune hepatitis, sarcoidosis, systemic lupus erythematosus, hepatitis C infection, systemic sclerosis, Behçet’s disease, thyroid disease, internal cancer, Takayasu arteritis, diabetes mellitus, pregnancy, hidradenitis suppurativa and Wegener granulomatosis. Additionally, PG cases were reported after treatment with isotretinoin, adalimumab, tyrosine kinase inhibitor sunitinib, propylthiouracil and granulocyte colony stimulating factor.\textsuperscript{11,21-24} In our study, 44\% percent of patients had associated systemic disease of which the inflammatory bowel disease was the most common. The other associated diseases included seronegative arthritis, acute myeloid leukemia, C-ANCA (antineutrophil cytoplasmic antibody) positive vasculitis, aganglionic megacolon, incomplete Behçet’s disease, Takayasu arteritis and diabetes mellitus.

PG can occur in an autosomal dominant condition known as PAPA syndrome that is characterized by a triad of pyogenic sterile arthritis, pyoderma gangrenosum and acne.\textsuperscript{23}

Histopathologic findings of PG are nonspecific and changes with the age of the lesion, biopsy site and clinical variant. In classical ulcerative PG, the earliest lesions show sterile perifollicular and perivascular neutrophil rich infiltration occasionally with abscess formation. In older lesions there is necrosis of the superficial dermis and epidermis forming an ulcer with mixed inflammatory cell infiltrate at the base of the ulcer.\textsuperscript{22,25} The most controversial histopathologic finding is the presence of vasculitis. In a report of 44 cases a lymphocytic and/or leukocytoclastic vasculitis was present at the erythematous border of PG in 73\% of cases. Histocytes, giant cells, palisading granulomatous reaction and pseudoepitheliomatous hyperplasia are seen in vegetative, subcorneal pustules with subepidermal edema and dense dermal neutrophilia are seen in pustular variant and subepidermal bullae with dermal neutrophilia is seen in bullous PG.\textsuperscript{22,25}

As the laboratory or histopathologic findings of PG are nonspecific, the diagnosis of it is a diagnosis of exclusion of other possible causes. The first step in the diagnostic evaluation is to rule out other causes with similar skin lesions and the second step is to determine the presence of possible associated disorders. When a lesion was suspected as PG, the first step is to take a detailed medical history, to perform a good physical and dermatological examination to for diagnostic clinical clues of PG and as-
sociated signs and symptoms of a possible underlying systemic disease. Ulcers with early pustules, crater like holes, purulent discharge, undermined borders located on the legs and peristomal areas and association with inflammatory bowel disease were suggested by Hadi and Lebwohl as diagnostic clinical clues. Next, a biopsy especially including the erythematous elevated border of the lesion may be done. Elliptical incisional biopsy at a depth including the subcutaneous fat is preferable to punch biopsy. Histopathological findings can not be the sole way to diagnose PG, therefore a clinicopathological correlation is necessary.

As the lesions can be aggravated with trauma, surgical debridement must be avoided. The cultures for bacteria including acid-fast bacilli, fungi and parasites should be taken from the exudate and/or from tissue specimens. If the histopathological findings support the diagnosis of PG, basic laboratory examination must include complete blood count, liver and kidney function tests, postero-anterior chest X-ray, peripheral smear, erythrocyte sedimentation rate, CRP, stool occult blood test (3 times), serum protein electrophoresis, serum-urine immunoelectrophoresis, serum rheumatoid factor and ANCA profile. If any of those findings suggest a systemic diseases further evaluations are required.

There is no specific effective therapy for PG. The aim of treatment is to decrease the inflammation in the skin lesion, to decrease the pain and to promote healing. The treatment agents are selected according to the patient age, clinical status, underlying systemic diseases, and the lesional characteristics. Topical wound care is essential for all types. If there is an associated systemic disease, effective management of underlying disease results in improvement of clinical lesions of PG. If the infection is detected, oral antimicrobial agents are added to the therapy regimen.

When the lesions are small and localized, topical treatments and intralesional injections may be used. The most commonly used topical therapies are topical steroids (esp. Clobetasol), calcineurin inhibitors (pimecrolimus, tacrolimus) and intralesional triamcinolone acetonide (5 mg/mL) injected in the erythematous elevated border.

In more disseminated cases or recalcitrant cases or cases unresponsive to topical therapies systemic agents are used. Systemic corticosteroids (1-2 mg/kg/day prednisone or pulse methylprednisolone, 1g/day for 5 consecutive days) are the mainstay of systemic treatment Cyclosporine is the second choice if the lesions are either resistant to steroid therapy or there are side effects of longterm steroid therapy. In our study, most of the patients needed systemic therapy agents. In consistence with literature knowledge, systemic corticosteroids were the mainstay of systemic therapy, although in recalcitrant cases cyclosporine was effectively used.

Azathioprine, methotrexate, cyclophosphamide, dapsone, sulfasalazine, mycophenolate mofetil, thalidomide, colchicine, clofazimine, intravenous immunoglobulin, plasmapheresis and newer therapies such as tacrolimus, adalimumab and infliximab are effective in some, but not all cases. The role of hyperbaric oxygen is controversial, it has been reported to be helpful in some cases.

In conclusion, in our study PG was primarily seen in adults with a slight female predominance, had a predilection for the lower extremities and ulcerative variant was the most common clinical type. Forty-four percent of patients had associated systemic disease of which the inflammatory bowel disease was the most common. Most of the patients needed systemic therapy agents. Most of the patients (72%) had complete remissions with immunosuppressive therapy, recurrences were observed in 40%.
REFERENCES


