

# Clinical Manifestations of Pyoderma Gangrenosum Associated with Inflammatory Bowel Disease

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## Abstract

**Background:** Pyoderma gangrenosum is an uncommon ulcerative cutaneous condition associated with inflammatory bowel disease. PG occurs rarely in IBD patients and there are insufficient data on the clinical manifestations of this disease with IBD.

**Objective:** To determine the incidence, clinical manifestations and treatment of PG in patients with IBD and the connection to IBD, its activity and extent.

**Methods:** All patients hospitalized with IBD at a university hospital during a 20 year period were evaluated for the occurrence of PG.

**Results:** Of 986 patients hospitalized for IBD 6 suffered from PG (0.6% incidence). Their average age was 37 with equal sex distribution and equal distribution of Crohn's disease and ulcerative colitis. PG appeared 6.5 years on average after diagnosis of IBD in all patients. The development of PG correlated with significant clinical exacerbation of IBD, the majority having active colitis at the onset of the PG. Extra-intestinal manifestations of IBD occurred in half the patients (sacroiliitis, peripheral arthritis and erythema nodosum). Pathergy was not elicited in any patients. Four patients had multiple skin lesions, frequently on the lower extremities. Diagnosis was made by skin biopsy in four patients. There was little correlation between amelioration of IBD and the skin lesions. Treatment consisted of high dose steroids and immunomodulatory drugs (cyclosporine, azathioprine and dapsone) in conjunction with topical treatment.

**Conclusions:** PG is a rare extra-intestinal manifestation of IBD that coincides with the exacerbation of the intestinal disease but does not always respond to treatment of the bowel disease.

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Pyoderma gangrenosum is an uncommon ulcerative cutaneous condition that is associated with inflammatory bowel disease [1-4]. Skin lesions appear as tender papules, papulopustules or vesicles that develop into painful ulcers with ragged, hanging purple edges and surrounding induration and erythema. The ulcer bases contain granulation or necrotic tissue often with purulent exudate. The pathogenesis of PG is uncertain and dysregulation of the immune system with defective immune responses has been suggested as a possible mechanism. This may be associated with imbalance of cytokines and an inflammatory response seen in active colitis of IBD [5]. Due to the low occurrence of PG in general, there is little information on the incidence, clinical manifestations and treatment of PG in patients with IBD [6,7]. In addition, the connection of PG to IBD, its activity and extent is uncertain. We therefore reviewed the records of all patients with IBD in a university hospital for the

occurrence of PG and the clinical characteristics of these patients with emphasis on its connection to activity of IBD.

## Patients and Methods

We reviewed the records of all hospitalized patients who had been diagnosed with inflammatory bowel disease at Hadassah University Hospital, Jerusalem, Israel during the 20 year period 1980-1999. A diagnosis of IBD was based on clinical symptoms and signs consistent with IBD and a tissue biopsy. Only patients with the above criteria were included in the study. All records were reviewed for the occurrence of PG. The records of patients having both diseases were reviewed carefully for the clinical manifestations of both diseases and the connection between them.

## Results

We found that 986 patients had a definite diagnosis of IBD based on clinical symptoms and signs and tissue biopsy. Of these, 503 suffered from Crohn's disease and 483 from ulcerative colitis. Their records were reviewed for the occurrence of PG and six such patients were found, with an incidence of 0.6%. Data on the clinical characteristics of the six patients are shown in Table 1. There were three males and three females and their average age at onset of PG was 37 years (range 23-72 years). Three patients suffered from Crohn's disease and three from ulcerative colitis. Four patients had a history of severe active bowel disease with multiple relapses and frequent hospitalizations due to flare-ups (patients 3-6). These patients were constantly on systemic steroids and needed additional immunosuppressive therapy. They also suffered from complications (bowel obstruction, pouchitis) and two needed a colectomy. The diagnosis of IBD preceded the onset of PG in all patients by 6.5 years on average (range 2-15 years). The appearance of PG correlated with significant clinical exacerbation of IBD in all patients except one. Four patients had active inflammatory lesions of the colon at the onset of PG. The other two patients with Crohn's disease had involvement of the terminal ileum. Half the patients had other extra-intestinal manifestations of IBD (sacroiliitis, peripheral arthritis and erythema nodosum). Treatment of IBD consisted of anti-inflammatory drugs (sulfasalazine and 5-ASA), steroids and immunosuppressive drugs. Prior to the onset of PG, patients were on minimal treatment and at the time of PG diagnosis only one patient was receiving immunosuppressive drugs (patient 4: methotrexate and azathioprine)

Clinical manifestations of PG in the IBD patients are shown in Table 2. The majority had multiple skin lesions (four of six patients), most appearing on the lower extremities. One patient had a single

PG = pyoderma gangrenosum  
IBD = inflammatory bowel disease

**Table 1.** Clinical characteristics of patients with pyoderma gangrenosum associated with inflammatory bowel disease

Patient no.	Gender	Age of onset of PG (yrs)	Type of IBD	Severity of IBD and complications	Time of onset of PG relative to diagnosis of IBD (yrs)	Onset of PG related to IBD exacerbation	Extent of intestinal disease at onset of PG	Extra-intestinal involvement of IBD	Treatment of IBD
1	M	25	Crohn's	Minimal disease activity	5	Not related	Terminal ileum	None	p.o. sulfasalazine
2	F	42	UC	Recurrent exacerbations	15	Related	Distal colon	Sacroiliitis	p.o. 5-ASA steroid enema
3	F	72	Crohn's	Recurrent exacerbations, bowel obstruction	2	Related	Sigmoid colon	None	i.v./p.o. steroids
4	M	31	Crohn's	Recurrent exacerbations	5	Related	Terminal ileum	Peripheral arthritis, encephalopathy	i.v./p.o. steroids p.o. methotrexate p.o. azathioprine
5	M	33	UC	Recurrent exacerbations, total colectomy, pouchitis	2	Related	Diffuse colon	None	p.o. sulfasalazine i.v./p.o. steroids
6	F	23	UC	Recurrent exacerbations, total colectomy	10	Related	Diffuse colon	Erythema nodosum	p.o. 5-ASA i.v./p.o. steroids p.o. azathioprine

UC = ulcerative colitis, p.o. = per os, i.v. = intravenous

**Table 2.** Clinical manifestations and treatment of pyoderma gangrenosum

Patient no.	No. of skin lesions	Sites of skin lesions	Diagnosis	Correlation between improvement of IBD and PG	Treatment of PG
1	Single	Distal leg	Biopsy	Not related	i.v. high dose steroids followed by p.o. steroids p.o. cyclosporin Topical bacitracine
2	Single	Dorsum of hand	Biopsy	Related	p.o. steroids Topical bacitracine
3	Multiple	Feet	Biopsy	Related	p.o. steroids
4	Multiple	Palms Abdomen Distal legs	Biopsy	Not related	p.o. steroids p.o. azathioprine p.o. cyclosporine
5	Multiple	Distal legs	Clinical	Not related	p.o. steroids p.o. dapsone Topical bacitracine Skin graft
6	Multiple	Distal legs	Clinical	Not related	i.v. high dose steroids followed by p.o. steroids

lesion on the dorsum of the right hand (patient 2) and another had multiple lesions including the palms of both hands and several lesions on the abdomen. Diagnosis of the skin lesions was made by skin biopsy in four patients. The diagnosis of PG in the other two patients was made on clinical grounds of a skin lesion consistent with PG. A definite history of trauma preceding the development of PG, a phenomenon known as pathergy, was not elicited in any of the patients.

There was little correlation between amelioration of IBD and the skin lesions. Improvement of the intestinal inflammatory

disease by steroid therapy alleviated the skin lesions in only two patients (patients 2 and 3; Table 2). In the other patients, additional treatment was needed including high dose steroids (patients 1 and 6) and immunomodulatory drugs such as cyclosporine, azathioprine and dapsone. Most patients were treated in addition with topical bacitracine ointment. Patient 5 responded poorly to steroid therapy and because of significant damage to the skin required several skin grafts. Additional treatment with dapsone led to healing of the lesions.

## Discussion

Pyoderma gangrenosum is an uncommon ulcerative cutaneous condition that was first described by Brunsting et al. in 1930 [8]. It is associated with a systemic disease in 50% of patients with PG and may precede, coincide or follow the onset of PG [9–12]. The most common associated systemic disease is inflam-

matory bowel disease, occurring in 27% of the patients [9]. Other systemic diseases include arthritis, paraproteinemia and hematologic malignancies. However, PG is an extremely rare disease, occurring in less than 1% of patients with IBD with an equal ratio of patients with Crohn's disease and ulcerative colitis [1]. In our series the incidence of PG in IBD was 0.6% with an equal distribution between Crohn's disease and ulcerative colitis. This is similar to other series that demonstrated an incidence of less than 1% [1,6].

Clinical manifestations of PG were typical in our series of patients. The most commonly affected area of the body was the

lower extremities [9], seen in the majority of our patients. Multiple lesions occurred in 60%. The diagnosis of PG is a diagnosis of exclusion usually based on clinical features consistent with PG and histologic examination. The histopathologic features of PG are not specific, however they are important to rule out other causes of ulceration such as vasculitis. Indeed, there is significant controversy regarding the histopathology of PG. Reports vary between neutrophilic infiltration with necrosis [10,13] that may initiate as folliculitis [14] or lymphocytic infiltrate [15]. In the majority of our patients the diagnosis was based on clinical features and a biopsy that was typically described as epidermal ulceration and necrosis with neutrophil infiltration.

The association between IBD and PG is well established, however the exact connection regarding the activity of both diseases and indeed the pathophysiology that may allude to a mechanistic explanation for the connection are lacking [5]. IBD is regarded as an inflammatory process that derives from an imbalance in the immune system. PG is also regarded as an inflammatory process with ill-defined pathogenesis. Therefore, it is logical that active bowel disease will coincide with the onset of PG. Indeed, the onset of PG is usually correlated with activity of the bowel disease, especially active colitis [3,6]. We noted that this occurred in nearly all our patients. Two patients with Crohn's disease who did not have active colitis had terminal ileitis, not specifically reported as associated with PG. Most of our patients had severe bowel disease including complications, and half had other extra-intestinal manifestations of IBD. Moreover, treatment prior to onset of PG was minimal. This is consistent with a correlation between disease activity and the onset of PG. We did not find that amelioration of the bowel disease correlated with amelioration of the skin lesions. Indeed, most patients needed extra immunomodulating therapy before improvement in the lesions was seen.

Treatment of PG consists of local therapy in conjunction with systemic anti-inflammatory therapy that may also be beneficial for active bowel disease. No treatment is uniformly effective [16–18] and no treatment has been subjected to controlled trials. All the patients in our series were initially treated with corticosteroids with the addition of high dose steroid pulse therapy or immunomodulating drugs if there was no response. Immunomodulatory drugs that are considered beneficial include dapsone and clofazimine, as are immunosuppressive drugs like azathioprine, cyclophosphamide and cyclosporine [19–21]. It was recently shown that infliximab, an anti-tumor necrosis factor-alpha monoclonal antibody for the treatment of Crohn's disease, is effective for treating PG [22]. Topical agents include antibacterial agents and topical or injected steroids.

In conclusion, PG is a rare cutaneous ulcerating lesion that occurs in less than 1% of patients with IBD. It coincides with the exacerbation of the intestinal disease, in particular the colon, however it may not respond to treatment of the bowel disease. Treatment consists of anti-inflammatory therapy in conjunction with topical treatment.

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