Twenty Cases of Peristomal Pyoderma Gangrenosum

Diagnostic Implications and Management

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Hypothesis: Our experience with peristomal ulcers suggested that peristomal pyoderma gangrenosum (PPG) is an infrequent and usually unrecognized complication of inflammatory bowel disease. We hypothesized that a review of our experience with PPG would clarify the essentials of its diagnosis, evaluation, and treatment.

Design: A case series of 20 consecutive patients with PPG complicating inflammatory bowel disease were treated at our institution between 1986 and 1999. There were 15 women and 5 men. At the time of development of peristomal pyoderma, 10 of 20 patients had a diagnosis of Crohn disease (CD), while 9 had a diagnosis of ulcerative colitis (UC). One patient was diagnosed as having CD only after first developing PPG.

Main Outcome Measure: Healing of PPG.

Interventions: All patients had failed local enterostomal care prior to referral. Debridements and/or stomal revisions were uniformly unsuccessful. Biopsies, when performed, did not provide clinically important information. Treatment was directed toward inflammatory bowel disease, with variable clinical responses to corticosteroids, metronidazole, cyclosporine, sulfasalazine, and infliximab.

Results: Ultimately, 13 patients had a diagnosis of CD. Of these patients, 12 (92%) of 13 developed PPG coincident with recurrent disease. Two patients had a remote history of proctocolectomy for UC and subsequent evaluation revealed CD. One patient developed PPG adjacent to a urinary Kock pouch after cystectomy; ultimately, a diagnosis of CD was made. No patients were lost to follow-up, but in 1 case of UC, no evaluation for latent CD was carried out. The final diagnosis was CD in 13 (65%) of 20 and UC in 7 (35%) of 20 patients. All PPG ulcers healed completely, within an average of 11.4 months (median, 8 months; range, 1-41 months). Ulcer resolution was achieved with medical therapy alone in 14 (70%) of 20 cases. Resection of active gastrointestinal CD resulted in healing in 5 (83%) of 6 cases. One case healed 2 months after conservative therapy only.

Conclusions: This review of the largest reported series of PPG suggests the following: (1) PPG complicating inflammatory bowel disease is uncommon and often misdiagnosed by clinicians; (2) local wound care measures have little role in the healing of PPG; (3) PPG usually heralds active CD; (4) in patients with prior history of UC, PPG indicates CD until proven otherwise; (5) prolonged medical therapy (11 months), usually with immunosuppression, is required for healing of PPG; and (6) if feasible, surgical resection of all active CD leads to the healing of PPG ulcers.

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Pyoderma gangrenosum is an unusual debilitating skin condition that complicates about 2% of cases of inflammatory bowel disease (IBD). The ulcers typically occur on the lower extremities of patients with ulcerative colitis (UC). Although the histopathology of pyoderma gangrenosum is well described, the diagnosis is a clinical one. Skin lesions begin as pustules, break down, and rapidly coalesce to form superficial ulcers with necrotic undermined borders. The ulcers have a characteristic violaceous appearance (Figure 1) and severe pain is a consistent feature. First described in 1984 by McGarity et al, peristomal pyoderma gangrenosum (PPG) is much less common than lower-extremity pyoderma gangrenosum; to our knowledge, only 25 cases have been reported in the world literature. Whereas lower-extremity pyoderma gangrenosum usually occurs in patients with UC, PPG is usually seen in patients with Crohn disease (CD). It is difficult to determine the true incidence of PPG, as it is usually not recognized and infrequently reported. In the peristomal position, the ulcers may be confused with local trauma, infection, or...
PATIENTS AND METHODS

All patients at our enterostomal therapist clinic with chronic unexplained peristomal ulcers are cataloged and followed up to resolution by an enterostomal therapist nurse familiar with PPG (L.L.S.). Peristomal pyoderma gangrenosum was considered in all stoma patients with IBD and no obvious mechanical or infectious cause of peristomal ulceration. With failure of conservative measures and a high index of suspicion, all ulcers with features of pyoderma gangrenosum were referred to either a surgeon (R.C.T.) or a gastroenterologist (R.A.K.) with extensive experience with IBD. All patients were then reviewed by follow-up in person and/or medical record review for pertinent data. Treatments were analyzed for efficacy and duration of resolution. Demographic data are presented in the Table.

RESULTS

PATIENT POPULATION

Between 1986 and 1999, 20 patients with PPG were identified. There were 15 women (75%) and 5 men (25%). The female-male ratio was similar in PPG ulcers are usually present for quite some time before they are properly diagnosed and treated. After failure of conservative measures, the treatment is usually medical and the response is variable. No single therapy has been demonstrated to be efficacious in all cases. At our medical center, we have seen an increasing number of patients with this condition, probably due to the early recognition by our multidisciplinary team. We report a series of 20 consecutive cases of PPG and attempt to characterize the demographics, most effective treatment, and associated features of the disease.

TREATMENTS

Topical care included the use of exudate absorbant dressings (eg, Aquacel [Convatec, Princeton, NJ], calcium alginate, or callogen alginate), which allow for a more satisfactory wear time with collecting devices. We found no use for topical steroids or injection of steroids into the ulcerations. Effective treatment of PPG was either medical or surgical, both of which were directed toward active IBD. Medical treatment was classified as anti-inflammatory, antimicrobial, or immunosuppressant. It is difficult to determine the most effective treatment in each case, as most patients had trials of several medications during the course of the peristomal ulcer, and in many cases, several medications were used concurrently. Nevertheless, it is possible to identify the medication that was associated with healing in each case.

In the 7 patients with UC, prednisone (n=3) and metronidazole (n=3) each resulted in healing of PPG. In the cases of UC that required prednisone, the course was usually prolonged (average, 18 months), while ulcers that responded to metronidazole typically had a shorter duration (average, 3 months). Medical treatment resulted in complete healing in 6 (86%) of 7 cases of PPG complicating UC. The seventh case healed spontaneously after 2 months of wound care and observation alone.

Peristomal pyoderma gangrenosum in patients with CD was associated with active disease elsewhere (12 of 13 patients) and was typically harder to treat than those in UC. In patients with CD, the use of prednisone alone was never associated with healing of PPG (0 of 13). Metronidazole resulted in healing in 5 cases. Two patients...
with PPG refractory to treatment with antibiotics and corticosteroids were treated successfully with intravenous cyclosporine followed up by cyclosporine given by mouth. Two patients received 3 courses each of infliximab (a chimeric monoclonal anti–tumor necrosis factor α antibody). Infliximab was associated with control of ileal CD and healing of PPG in 1 case; however, the other patient’s ulcer did not respond to infliximab and ultimately healed with cyclosporine. One patient’s ulcer (patient 1, Table) healed immediately after completion proctectomy, but it recurred several months later with a flare-up of perineal disease. Eventually it healed with 4 months of sulfasalazine therapy.

Surgical treatment of the ulcer itself was not successful. Three of 5 patients (patients 3, 6, and 10, Table) who had a stomal revision developed PPG at the new ileostomy site, a phenomenon known as pathergy. The 2 patients who did not develop new ulcers as a result of stomal revision had definitive procedures to extirpate all active CD inflammation, healed in 11 months later with sulfasalazine. With PPG refractory to treatment with antibiotics and corticosteroids were treated successfully with intravenous cyclosporine followed up by cyclosporine given by mouth. Two patients received 3 courses each of infliximab (a chimeric monoclonal anti–tumor necrosis factor α antibody). Infliximab was associated with control of ileal CD and healing of PPG in 1 case; however, the other patient’s ulcer did not respond to infliximab and ultimately healed with cyclosporine. One patient’s ulcer (patient 1, Table) healed immediately after completion proctectomy, but it recurred several months later with a flare-up of perineal disease. Eventually it healed with 4 months of sulfasalazine therapy.

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Surgical resection of active CD was effective treatment of PPG. The ulcers of 5 of 6 patients (patients 1, 2, 10, 16, and 20, Table) (83%) healed after surgery an average of 1.8 months after resection. One ulcer in this group did not heal after completion proctectomy, but it was not possible to resect all active perineal CD (patient 17, Table). In this patient, the ulcer eventually healed during cyclosporine therapy. Ulcers recurred in 2 patients (patients 1 and 10, Table); in patient 1, recurrence was associated with a relapse of perineal disease.

**TIME TO HEAL**

Time to heal the ulcer was based on the initial patient recollection of the ulcer and the eventual resolution was based on an indication by an enterostomal therapist that greater than 90% epithelialization had occurred. Photo documentation was used in most cases to monitor progression (Figure 2 and Figure 3). The average time for healing of all cases of PPG was 11.4 months (median, 7.5 months; range, 1 to 41 months). The average time to healing in patients with UC was 9.6 months (median, 4 months; range, 2-27 months). In patients with CD, the average time was 12.4 months (median, 8 months; range, 1-41 months). However, in those patients in whom it was possible to remove all active CD inflammation, healing occurred within 1.8 months on average. The ulcer of the patient with PPG but inactive CD healed after only 1 month of treatment with metronidazole (patient 12, Table).

**COMMENT**

Peristomal pyoderma gangrenosum is being seen with increasing frequency at our medical center, likely due to an increased awareness of the condition. Patients are usu-
ally seen after initial care by primary care physicians, dermatologists, surgeons, and gastroenterologists. Peristomal pyoderma gangrenosum should be considered in all patients with IBD who have peristomal ulcerations. Patients with peristomal ulcers that have no obvious precipitating cause and/or are refractory to local wound care should probably be referred to a center with physicians experienced with IBD and ostomy problems for further evaluation. The diagnosis of PPG is a clinical one, based on the history and appearance of the ulcer. We do not believe that biopsies and/or cultures are warranted, as they cannot confirm the diagnosis and do not provide any clinically useful information. Familiarity with the appearance and behavior of pyoderma gangrenosum is all that is needed to make the diagnosis.

Similar to previously published reports, our experience demonstrated that women are more likely to have the condition and that most patients with PPG have CD. The notion that PPG heralds active IBD was recognized soon after its initial description in 1984. In our series, active CD was present in most patients. Previous studies have demonstrated the efficacy of surgical resection in healing lower-extremity pyoderma gangrenosum complicating IBD. We believe that surgical resection of all active inflammatory foci of IBD, either intestinal or perineal, in patients with PPG should be performed if possible. Complete resection is often not possible, especially in cases of severe rectal or perineal inflammation associated with CD. These patients are difficult to treat and are frequently very frustrated. Typically, the ulcers in these patients are severe and parallel the activity in the rectum and/or perineum. If complete resection is not possible, medical therapy with an immunosuppressant is usually necessary and will result in a prolonged course prior to healing. Antimicrobials with activity in CD (eg, metronidazole or ciprofloxacin) may be tried prior to and/or in addition to immunosuppressants. However, our experience suggests that cyclosporine may be the most effective medication in patients with CD. Recent data indicate that thalidomide may be effective in refractory CD. Ongoing trials at our medical center are under way to evaluate this drug in refractory PPG. Even with combined therapy, the average time to healing of PPG in our series was about 1 year.

Patients with an ileostomy after proctocolectomy for presumed UC who develop PPG should be assumed to have CD until proven otherwise. Pathology specimens from a previous colectomy should be reviewed and flexible ileoscopy and biopsy should be performed. Two of our patients initially thought to have UC actually had CD; a third was strongly suspected of having CD, but refused workup. In patients in whom the diagnosis of UC is confirmed, PPG appears to behave differently, presumably because there is no active bowel disease. Peristomal pyoderma gangrenosum in UC responds to less aggressive medical therapy and healing tends to occur more quickly than in patients with CD. Whereas steroids had no apparent effect in our patients with CD, healing of PPG occurred consistently during prednisone administration in patients with UC. Similarly, use of metronidazole alone was associated with healing in several patients with UC. In all patients, it is imperative to emphasize that prolonged treatment is required to effect healing, averaging 1 year in the present series.

This study, to our knowledge the largest reported study of PPG, suggests that this condition may be more common than clinically appreciated. Because of the phenomenon of pathergy, stomal revisions and biopsies should not be performed. These ulcers usually reflect recurrence of active intestinal or perineal CD. In patients with UC, a workup to rule out CD is warranted. If there is no evidence for CD, less aggressive treatment with corticosteroids and/or ciprofloxacin or metronidazole may be effective. However, it must be emphasized that the time to healing of the ulcerations is long. Patients with CD usually have large, progressive ulcers that require aggressive treatment. Surgical resection of active intestinal disease is usually warranted in concert with combination medical therapy (eg, metronidazole plus immunosuppressants). Our anecdotal experience suggests that cyclosporine may be the agent of choice.

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ostomal therapist. The patients know their stomas; the ET nurses
These patients, for the most part, are seen first by our enter-
reflection of pathergy, which is why it occurs where it does.

Skin and the pyoderma begins. So the peristomal location is a
ance, or from leakage, a trivial breakdown has occurred in the
trauma to the skin; whether it be from the wafer, their appli-
fitting appliance or leakage, that is the problem. There is also
characteristic location. An ulcer due to local trauma typi-
Peristomal pyoderma gangrenosum ulcers are often cephalad
or superior to the stoma, away from typical sites of leakage. I
think a good enterostomal therapist and a good patient can tell
you if an ulcer is caused by local trauma or if this is something
that they don’t understand, and thus is likely PPG.

Dr Michelassi asked about the role of bowel-sparing sur-
egy. I believe that bowel-sparing surgery would be com-
pletely appropriate. Dr Fazio has reported that when he reop-
erates on patients after stricturoplasties, he can’t tell where he
did the stricturoplasty. This has been my experience as well.
The theory is that after stricturoplasty, the inflammatory reac-
tion around that bowel resolves as the obstruction resolves. I
suspect, therefore, that the PPG would resolve, albeit slower
than after resection.

Dr Morris asked about the long-term results. In our study,
the ulcer recurred in 3 patients. One case occurred recently in a
young man taking cyclosporine. He developed gallstone pan-
creatitis and his primary care physician stopped treatment with
cyclosporine because of the association with pancreatitis; his pyo-
derma recurred. At the present time, all 20 patients are healed.

IN OTHER AMA JOURNALS

Hyperinsulinemia, Hyperglycemia, and Impaired Hemostasis: The Framingham Offspring Study

Context: Increased risk for cardiovascular disease in persons with glucose intolerance (impaired glucose tolerance and type 2 diabetes mellitus) is not fully explained by concomitant elevations in traditional atherosclerosis risk factors. Hyperinsulinemia associated with glucose intolerance may increase risk directly, or its effect could be mediated through impaired he-

Objective: To evaluate associations between fasting insulin levels and hemostatic factors in subjects with normal and im-
paired glucose homeostasis.


Setting: The population-based Framingham Offspring Study.

Subjects: A total of 1331 men and 1631 women aged 26 to 82 years, without diagnosed diabetes or cardiovascular disease and classified as having normal glucose tolerance (80.2%) or glucose intolerance (impaired glucose tolerance and impaired fasting glucose combined, 15.2%; previously undiagnosed diabetes, 4.7%) using an oral glucose tolerance test.

Main Outcome Measures: Trends across quintiles of fasting insulin in levels of plasminogen activator inhibitor 1 (PAI-1) antigen, tissue-type plasminogen activator (tPA) antigen, von Willebrand factor (vWF) antigen, factor VII antigen, fibrino-
gen, and plasma viscosity. We stratified analyses by sex and glucose tolerance status and adjusted hemostatic factor levels for

Results: Mean levels of all hemostatic factors (except for fibrinogen in men) increased across fasting insulin quintiles among

Subjects with normal glucose tolerance (P<.001 for trend). Levels of PAI-1 and tPA antigens, but not other hemostatic fac-
tors, were higher comparing subjects with glucose intolerance with those with normal glucose tolerance (P<.001). Among
subjects with glucose intolerance, levels of PAI-1 and tPA antigen in men and women (P<.01 for trend) and vWF antigen in
men (P<.05 for trend) increased significantly across insulin quintiles, but levels of factor VII antigen, fibrinogen, and plasma
viscosity did not increase.

Conclusions: Elevated levels of fasting insulin are associated with impaired fibrinolysis and hypercoagulability in subjects
with normal glucose tolerance. Hyperinsulinemia is associated primarily with impaired fibrinolysis in subjects with glucose
intolerance. Excess risk for cardiovascular disease associated with hyperinsulinemia and glucose intolerance may be medi-
ated in part by enhanced potential for acute thrombosis. (2000;283:221-228) www.jama.com

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