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 immunosupression, 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).1 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.1,2 Skin lesions begin as pustules, break down, and rapidly coalesce to form superficial ulcers with necrotic undermined borders.3 The ulcers have a characteristic violaceous appearance (Figure 1) and severe pain is a consistent feature.4 First described in 1984 by McGarity et al,3 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.4 Whereas lower-extremity pyoderma gangrenosum usually occurs in patients with UC, PPG is usually seen in patients with Crohn disease (CD).7 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

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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 stomal 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 patients with CD and those with UC (CD, 10:3; UC, 5:2). The average age was 48 years (range, 21-77 years). The average ages in patients with CD and UC were 47 and 58 years, respectively. At presentation, 10 patients were diagnosed as having CD. However, after appropriate workup, the final diagnosis was CD in 13 (65%). Two of these patients (patients 7 and 19, Table) presented with a history of total proctocolectomy and ileostomy for UC, but flexible ileoscopy and biopsy revealed active CD. Another patient had a urinary Kock pouch and developed PPG. Crohn disease was diagnosed by ileoscopy. Another patient (patient 6, Table) with a history of UC was strongly suspected of having CD but refused ileoscopy. Thus, 7 patients (35%) had UC. In the patients with UC, the time from operation to development of PPG averaged 12 years (median, 5 years). In 12 (92%) of the 13 patients with CD, PPG was associated with active CD, either alimentary or perineal. In 3 of these patients, PPG was the initial sign of CD (patients 7, 13, and 16, Table).

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 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 ostomy site, a phenomenon known as pathergy.1,4,5,10 The 2 patients who did not develop new ulcers as a result of stomal revision had definitive procedures to extirpate all active disease at the time of ostomy revision (patients 16 and 20, Table). In 1 patient (patients 6, Table), an elective ileostomy revision caused PPG that lasted for 2 years.

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. Ulcersrecurred 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 (mean, 7.5 months; range, 1 to 41 months). The average time to healing in patients with UC was 9.6 months (mean, 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.

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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C. Edward Hartford, MD, Denver, Colo: The report by Sheldon et al brings to our attention an annoying, difficult-to-treat, and infrequently occurring complication of IBD, that of pyoderma gangrenosum in the peristomal position. With the strong reputation of the Virginia Mason Clinic and the vast experience of Drs Kozarek and Thirlby in the field of IBD, we can be assured that the segregation of disease into UC and CD is accurate. Therefore, I want to concentrate my remarks on the diagnosis of these peristomal ulcers and challenge the authors on the statement that neither biopsy nor culture is needed and that one can merely look at these lesions and make the diagnosis of pyoderma gangrenosum. I do not believe that this entity has been properly characterized. Pyoderma gangrenosum in its classic presentation is a destructive, noninfectious ulcerative process associated with a massive neutrophilic infiltration of the dermis, which undermines and destroys the epidermis. There is often pain and a systemic response. Usually there is a dramatic ameliorating response to high-dose steroids. The ulcers may become undulant, however. The authors point out that if all active IBD can be resected, the peristomal ulcers invariably heal or improve, and apparently control of the IBD controls these ulcers.

However, in this study, among those patients with CD, the peristomal ulcers did not respond to steroids, whereas 5 of these patients had healing with the use of metronidazole. Three patients with UC also responded to metronidazole. The use of any microbial agents in the IBD is based on the assumption that enteral flora may play a role in the origin of symptoms and/or complications. Pyoderma gangrenosum is not related to an infectious process.

In 1990 an article titled “Refractory Parastomal Ulcers” from the Virginia Mason Clinic was published in the *Journal of Clinical Gastroenterology*. There were 5 cases of pyoderma gangrenosum presented and 2 sets of color photographs. I believe 1 set was shown here today. One example was of a pyoderma and I was of an ulcerated dermatitis related to a face plate. Both examples looked the same to me. Granted that these lesions and the one shown today are far from the acute phase. However, all of these factors bring into question the diagnosis and a long list of differential diagnoses, including a cutaneous manifestation of CD, bacterial or fungal infections, one of several dermatoses. The list can be very long.

Therefore, is what we are calling pyoderma gangrenosum in the peristomal location really a variant of the more classic pyoderma gangrenosum? Is it a cutaneous manifestation of CD, or is it some other entity? To convince me of the diagnosis, there needs to be a clinical pathological characterization of this entity to include histologic data, confirmation of lack of a bacterial and fungal component, and, possibly, immunologic confirmation of a relationship to pyoderma gangrenosum. Do the authors have such data?

William Turner, MD, Jackson, Miss: I am intrigued by the location of these ulcers and particularly by the possibility that this process is related to perianal CD. I wonder if the authors might comment on why they think these ulcers are occurring in a peristomal position in the group of patients they describe as compared with some remote site such as the lower extremity.

Fabrizio Michelassi, MD, Chicago, Ill: As the authors have suggested, pyoderma gangrenosum is one of the more dramatic manifestations of IBD, and when it occurs around ileostomies and colostomies, it is usually characterized by multiple and connecting ulcers. For the patient this is a very difficult problem: frequently these ulcers are painful and they always interfere with obtaining and maintaining a waterproof seal with the appliance. As a consequence, the quality of life of these patients is dramatically altered.

Local therapy is frequently unsuccessful and therapy should be aimed at active disease. If the choice of therapy is surgical, should we consider the presence of pyoderma gangrenosum a contraindication to bowel-sparing procedures owing to the possible need of complete extirpation, if possible, of the entire active disease?

Don M. Morris, MD, Albuquerque, NM: What happened to these patients long-term? Once the ulcers were healed, did they stay healed?

Dr Thirlby: I would like to thank the discussants for their questions and especially Dr Hartford for his conversations over the last 3 days. We have been bickering about the role of diagnostic testing in these patients at every break: ie, do these patients need biopsies? Do these patients need cultures? Any self-respecting surgeon would say that they should perform a biopsy on lesions with an unclear diagnosis. We initially did that. We have biopsy specimens for about half of our patients. The biopsy specimens all show nonspecific inflammation consistent with pyoderma gangrenosum. There are no pathognomonic histologic characteristics of pyoderma. There may be excessive neutrophilic infiltration. There may not be. Cancer is not in the differential diagnosis. Cancer may develop at an ileostomy after a proctocolectomy, but that is really a cancer of the ileum. It is not cancer of the peristomal skin. Cultures classically are sterile, and that is what has been our experience. While it is frustrating to stand here and tell you, “You have to believe me, I am intrigued by...”
these patients have pyoderma," trust me, that's what I am telling you. The biopsies do not provide clinically useful information. They are not that expensive, so “why not?"? They don’t help and, in fact, they may hurt. Pathergy is a very impressive event in these patients. Most patients with extremitry pyoderma will have antecedent trivial trauma—a little scratch, even a needlestick—trivial trauma that will precipitate this florid inflammatory process. There are reports of biopsies of peristomal pyoderma accelerating this disease. Respecting Dr Hartford’s opinion, I do not believe biopsies are essential or indicated in most cases.

The differential diagnosis rarely includes infection. While these patients may have yeast overgrowth, it is usually obvious with inspection.

What about the appearance? I would like to combine a couple of questions. Dr Turner asked why these lesions occur at the peristomal site as opposed to elsewhere. I think it is owing to pathergy. These patients probably have suffered trivial trauma to the skin; whether it be from the wafer, their appliance, or from leakage, a trivial breakdown has occurred in the skin and the pyoderma begins. So the peristomal location is a reflection of pathergy, which is why it occurs where it does. These patients, for the most part, are seen first by our enterostomal therapist. The patients know their stomas; the ET nurses know the stomas. They can tell if it is local trauma, ie, a poor-fitting appliance or leakage, that is the problem. There is also a characteristic location. An ulcer due to local trauma typically occurs inferior to the stoma where the leakage occurs. 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 surgery. I believe that bowel-sparing surgery would be completely appropriate. Dr Fazio has reported that when he reoperates 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 reaction 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 pancreatitis and his primary care physician stopped treatment with cyclosporine because of the association with pancreatitis; his pyoderma recurred. At the present time, all 20 patients are healed.

### IN OTHER AMA JOURNALS

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

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**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 hemostatic function.

**Objective:** To evaluate associations between fasting insulin levels and hemostatic factors in subjects with normal and impaired glucose homeostasis.

**Design:** Cross-sectional analysis conducted between January 1991 and June 1995.

**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, fibrinogen, and plasma viscosity. We stratified analyses by sex and glucose tolerance status and adjusted hemostatic factor levels for obesity, lipid levels, and traditional cardiovascular disease risk factors.

**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 factors, were higher comparing subjects with insulin tolerance 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 mediated in part by enhanced potential for acute thrombosis. (2000;283:221-228) www.jama.com

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