

Crohn's Disease Presenting with Pyoderma Gangrenosum and Treated with Infliximab

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P pyoderma gangrenosum is one of the more uncommon extraintestinal manifestations of Crohn's disease and, more broadly, inflammatory bowel disease (IBD). Despite its coincidence with active inflammation, the presence of pyoderma gangrenosum and its severity are poor predictors as to the extent of gastrointestinal involvement. Furthermore, little is known with respect to its pathophysiology. However, treatment of systemic inflammatory disorders (eg, rheumatoid arthritis) and dermatologic disorders (eg, psoriasis) with tumor necrosis factor- α (TNF- α) inhibitors (eg, infliximab) has had promising results; TNF- α inhibitors may help to elucidate a clearer connection between Crohn's disease and pyoderma gangrenosum.

We report a case of a 29-year-old man presenting with fever, intractable diarrhea, and intermittent nausea and vomiting as well as a 2-week history of multiple, irregular, and violaceous lesions with purulent necrotic bases consistent with pyoderma gangrenosum. Colonoscopic evaluation revealed multiple, fistulizing, perianal lesions and nodular ulcerated mucosa throughout the extent of the colon consistent with Crohn's disease. Following treatment with infliximab, the patient's Crohn's disease and cutaneous ulcers improved markedly. We suggest that TNF- α suppression, in addition to its possible efficacy in treating fistulizing Crohn's disease, may prove beneficial in alleviating cutaneous symptoms by a similar mechanism.

CASE PRESENTATION

Initial Presentation and History

A 29-year-old man presented to the emergency department with a 1-week history of subjective fevers and frequent, small volume, watery, nonbloody bowel movements, and recently developed nonsanguinous emesis of undigested food. The patient denied any concomitant abdominal pain, melena, or hematochezia.

Four months prior to presentation, the patient noted the eruption of multiple erythematous lesions located in the lower extremities and the proximal dor-

sum of both feet. At that time, the patient also developed a painful, cystic, perianal lesion that was subsequently lanced and treated with antibiotics. The patient's medical history was notable only for the presentation above. The patient was taking no medications and denied any drug allergy. Family history was remarkable for a distant history of rectal ulcers in the patient's father that were excised without any recurrence or symptoms. Social history was noncontributory.

On examination, the patient was febrile to 38.2°C (100.8°F). He also was tachycardic, tachypneic, and had moderately elevated blood pressure. The patient's eyes were free of injection. The oropharynx was free of ulcers, but some evidence of gingival hyperemia and erosion was noted. Abdominal examination revealed an obese, nontender abdomen with hyperactive bowel sounds. Examination of the perianal area demonstrated multiple, tender, ulcerated lesions in various states of healing with scant purulent drainage, one of which formed a fistula. Stool was positive for occult blood. The lower extremities were characterized by multiple purulent ulcers predominantly located in both pretibial areas, ranging in size from 1 to 10 cm, with dusky, undermined, tender margins (**Figure 1**).

Laboratory Evaluation

Laboratory evaluation revealed a moderate leukocytosis with a left shift, a microcytic anemia, hyponatremia,

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Figure 1. Purulent ulceration of the case patient's lower extremity at presentation.

Table. Laboratory Values for the Case Patient Before and After Treatment with Infliximab

Test	Values at Admission	Values After Therapy	Normal Values
Electrolytes			
Sodium (mEq/L)	129	137	135–145
Serum potassium (mEq/L)	3.8	3.7	3.6–5.1
Chloride (mEq/L)	91	98	98–110
Bicarbonate (mEq/L)	26	26	20–30
Transaminases and liver function			
AST (IU/L)	11	27	10–42
Alkaline phosphatase (IU/L)	39	90	40–130
ALT (IU/L)	7	40	5–40
Total bilirubin (mg/dL)	0.6	0.4	0.2–1.1
Albumin (g/dL)	1.5	3.7	3.5–5.0
Complete blood count			
Leukocytes ($\times 10^3/\text{mm}^3$)	16.3	8.3	3.5–11.0
Band forms (%)	28	0	0
Hemoglobin (g/dL)	7.5	15	13.5–16.0
Hematocrit (%)	24	45.8	40–54
Platelets ($\times 10^3/\text{mm}^3$)	609	424	150–400
MCV (fL)	71.4	84	80–98
ESR (mm/h)	110	14	0–15
p-ANCA	< 1:40	Not tested	< 1:20
c-ANCA	< 1:20	Not tested	< 1:20

ALT = alanine transaminase; ANCA = antineutrophil cytoplasmic antibody; AST = aspartate transaminase; ESR = erythrocyte sedimentation rate; MCV = mean corpuscular volume.

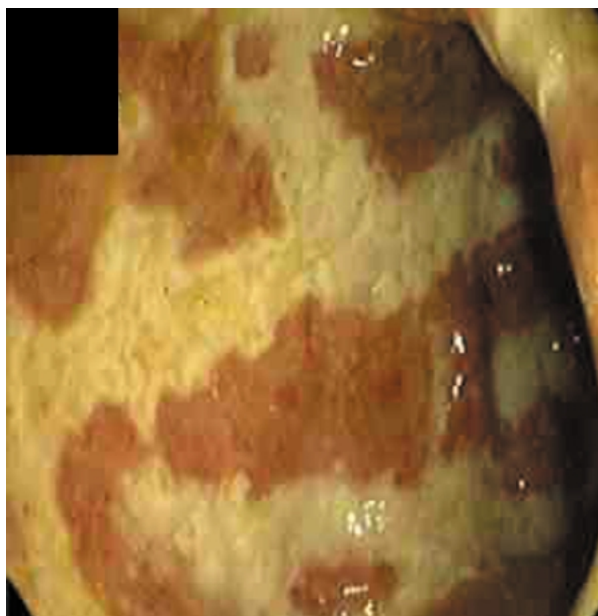


Figure 2. View of the case patient's sigmoid colon at presentation.

and normal coagulation profile (**Table**). Erythrocyte sedimentation rate was markedly elevated at 110 mm/h, and hepatitis serologies were negative. Another blood specimen was sent at the time of admission for p-antineutrophil cytoplasmic antibody (ANCA), which returned mildly positive (titers of 1:40) for the atypical p-ANCA pattern characteristically seen in primary sclerosing cholangitis and IBD.

Diagnostic Studies

In light of the patient's leukocytosis and with possible superinfection of his lesions, polymicrobial antibiotic coverage was initiated consisting of piperacillin/tazobactam, tobramycin, and doxycycline after a consultation with a dermatologist.

Biopsy of a right ankle lesion demonstrated a diffuse neutrophilic infiltrate extending into the subcutis with an interstitial mixed infiltrate of lymphocytes and histiocytes. This result, in conjunction with the absence of vasculitis and negative periodic acid-Schiff, Gram, and acid-fast bacilli stains, confirmed the lesion to be consistent with pyoderma gangrenosum.

The patient then underwent colonoscopy that demonstrated discontinuous areas of nonbleeding, erythematous, nodular, and ulcerated mucosa throughout the colon, sparing the terminal ileum (**Figure 2**). Biopsies of the transverse and descending colon as well as the rectum revealed severe active inflammatory changes

marked by a chronic inflammatory cell infiltration of the lamina propria, neutrophilic infiltration, epithelialitis, cryptitis, and crypt abscess formation. Furthermore, there was focal thickening of the muscularis mucosa, dense lymphoid infiltration, and focal thrombus formation in the superficial submucosal vessels. Biopsies of the cecum and ascending colon showed variable architectural distortion consistent with the chronic changes of Crohn's disease.

Treatment and Follow-up

The patient was started on a course of ciprofloxacin and metronidazole for enteric antimicrobial coverage as well as 60 mg/d of oral prednisone. Shortly thereafter, he received his first graduated infusion of infliximab, totaling 600 mg. At the time of the patient's second infliximab infusion (week 2), the patient's cutaneous ulcers were healed with the exception of some residual erythema of the lesion on his right malleolus (Figure 3). He received his third infusion of infliximab at week 6. The patient noted a substantial reduction in the frequency of bowel movements and episodes of abdominal pain at subsequent follow-up and remained stable 1 year after his initial presentation. Follow-up laboratory evaluation reflected this clinical improvement as evidenced by resolution of the anemia with iron supplementation, normal leukocyte count, and improvement in erythrocyte sedimentation rate (Table).

DISCUSSION

Crohn's disease is a sporadic idiopathic inflammatory condition that may affect any portion of the digestive tract and frequently results in discontinuous transmural inflammation. This inflammation may ultimately result in fistula formation and its various complications, including obstruction, abscess formation, and malignancy. One rare but significant complication includes the development of pyoderma gangrenosum, which is classified as one of the noninfectious neutrophilic dermatoses. These disorders are characterized by neutrophilic infiltration of vessel walls that may lead to vessel wall destruction (vasculitis) as with Reiter's syndrome, psoriasis, and polyarteritis nodosa; or, less commonly, without vessel wall invasion as with pyoderma gangrenosum, Sweet's syndrome, and Behçet's disease. Pyoderma gangrenosum is often associated with IBD, but it may also be seen in a variety of other diseases, notably rheumatoid arthritis, osteoarthritis, leukemias, and myelofibrosis. In addition, pyoderma gangrenosum has been reported in chronic active hepatitis, myeloma, primary biliary cirrhosis, systemic lupus erythematosus,



Figure 3. The case patient after his second infusion of infliximab. Only residual erythema and minimal scarring persist.

Wegener's granulomatosis, sarcoidosis, HIV infection, thyroid disease, and diabetes.¹

Dermatoses Associated with IBD

The prevalence of pyoderma gangrenosum in IBD is estimated to be from 2% to 5%.^{2,3} Among patients with pyoderma gangrenosum, approximately 50% have endoscopic evidence of active inflammation.⁴ In addition to pyoderma gangrenosum, other dermatoses accompany Crohn's disease with higher frequency than in the general population. Erythema nodosum is estimated to occur in up to 15% of patients with IBD^{5,6} and often parallels the extent of intestinal disease activity, with the amelioration of the cutaneous findings coinciding with clinical remission of the Crohn's disease. By comparison, the extent of pyoderma gangrenosum correlates less strongly with intestinal involvement than erythema nodosum.² In another study, psoriasis was present in 9.6% of Crohn's patients compared with 2.2% in healthy control subjects. This disparity was also observed when comparing relatives of patients with Crohn's disease with disease-free relatives.⁷ Less frequently observed in IBD is necrotizing cutaneous vasculitis as well as epidermolysis bullosa acquisita, which is observed more specifically in Crohn's disease.⁸

Treatment of Crohn's Disease Dermatoses with TNF- α Inhibitors

Given the increased prevalence of such cutaneous inflammatory disease in conjunction with IBD, it would be reasonable to extrapolate that both pathologic processes are likely the product of an activated inflammatory cascade or response to specific mediators. In particular, promising therapy of infliximab in the treatment of Crohn's disease with monoclonal antibodies to TNF- α

as well as new evidence of the role of TNF- α in cutaneous inflammation suggest that the dermatologic and intestinal manifestations of Crohn's disease may be variable expressions of a common pathway.

Increasing evidence for the efficacy of using TNF- α inhibitors such as infliximab has demonstrated promise to those patients refractory to conventional first-line anti-inflammatory therapies such as aminosalicylates and steroids and to those patients in which such therapy is contraindicated. Studies of patients with refractory Crohn's disease treated with infliximab have demonstrated marked clinical improvement in over 80% of participants.^{9,10} With respect to fistulizing Crohn's disease, as is pertinent to this case, significantly higher rates of fistula closure were observed in patients treated with infliximab than those patients treated with more conventional therapies (eg, steroids, aminosalicylates) and immunosuppressive therapy (eg, azathioprine and 6-mercaptopurine).¹¹⁻¹⁴

The potential efficacy of TNF- α modulation in Crohn's disease is supported by the observations that the levels of TNF- α activity are increased in the colonic mucosa with active disease, and the levels of TNF- α themselves are elevated in the stools of Crohn's disease patients proportionally to disease activity.¹⁵ In a study of patients with either active ulcerative colitis or Crohn's disease, levels of the cytokines TNF- α , IL-1 β , and sIL-2R were significantly elevated when compared with normal controls; significant correlation was found between the levels of the 3 cytokines and disease activity indices.¹⁶ This evidence is supported by observations that TNF- α and interferon- γ are produced at significantly higher levels in T-cell cultures in Crohn's disease versus healthy controls.¹⁷

A similar paradigm applies to many dermatoses that occur with greater frequency in patients with IBD, such as psoriasis, erythema nodosum, and pyoderma gangrenosum. TNF- α constitutes one of the major quantifiable cytokines produced by the skin and has role in the acute inflammatory reaction to lipopolysaccharide,¹⁸ inflammatory response to surgical manipulation,¹⁹ neutrophil recruitment, and activation of other mediators in the inflammatory cascade. Levels of TNF- α were elevated in active psoriasis lesions,²⁰ while evidence suggests that TNF- α levels correlate with the extent of disease activity in erythema nodosum.²¹

The benefit of decreasing cutaneous disease severity with infliximab is evidenced by recent case reports. In one such report, a patient with refractory Crohn's disease with psoriasis demonstrated modest clinical improvement in her psoriasis after a single infusion of infliximab.²² A report of 2 patients with Crohn's disease and pyoderma

gangrenosum and a third patient with Crohn's disease and psoriasis showed clinical improvement of their fistulae and their dermatoses with infliximab.²³

CONCLUSION

The paucity of experience with infliximab with pyoderma gangrenosum precludes conclusively recommending TNF- α monoclonal antibodies as first-line therapy at this time. With accumulation of cases of Crohn's disease with concomitant cutaneous manifestations, the long-term effectiveness of TNF- α inhibitors will be better understood. Promising results of infliximab and further implication of TNF- α in inflammatory cutaneous conditions may help to elucidate a clearer connection between Crohn's disease and pyoderma gangrenosum. We suggest that, in addition to the known efficacy of TNF- α suppression for fistulizing Crohn's disease, such treatment might prove beneficial in alleviating cutaneous symptoms by a similar mechanism and recommend further investigation in elucidating a common pathway.

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