

SKIN ULCERS MISDIAGNOSED AS PYODERMA GANGRENOSUM

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ABSTRACT

Background Pyoderma gangrenosum is a diagnosis of exclusion, and the misdiagnosis of pyoderma gangrenosum can result in substantial complications in patients who have other causes of severe cutaneous ulceration.

Methods We reviewed the charts of 240 patients with a diagnosis of pyoderma gangrenosum who were evaluated at our institution from 1975 through 2000, including 157 consecutive patients treated for presumed pyoderma gangrenosum from 1984 through 1992. We also reviewed the English-language literature.

Results Ninety-five patients (49 from our institution and 46 described in the literature) had skin ulcers with a clinical resemblance to pyoderma gangrenosum. The final diagnoses were vascular occlusive or venous disease, vasculitis, cancer, primary infection, drug-induced or exogenous tissue injury, and other inflammatory disorders. Of the 95 patients studied, 64 had been treated for pyoderma gangrenosum for a median of 10 months (range, 3 to 180). These 64 included 15 of the 157 consecutive patients treated for pyoderma gangrenosum at our institution (10 percent). Of the ulcers in the 64 patients treated for pyoderma gangrenosum, it was clear that those in 23 patients (36 percent) did not respond to treatment directed at pyoderma gangrenosum, those in 8 (12 percent) were exacerbated by such treatment, and those in 15 (23 percent) improved with such treatment.

Conclusions The misdiagnosis of pyoderma gangrenosum is not uncommon and exposes patients to risks associated with its treatment. A thorough evaluation is required in all patients suspected of having pyoderma gangrenosum in order to rule out alternative diagnoses. (N Engl J Med 2002;347:1412-8.)

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THE misdiagnosis of pyoderma gangrenosum can have serious consequences. Cutaneous ulcerations in patients with suspected pyoderma gangrenosum often prove, on further workup, to have a different cause. Moreover, treatment directed at pyoderma gangrenosum — high-dose prednisone or other immunosuppressive medications — may be contraindicated in patients with any of several diseases that may produce ulceration resembling that of pyoderma gangrenosum, such as infectious or malignant processes.

Numerous case reports describe diseases that “mimic” or “masquerade as” pyoderma gangrenosum, but no large studies evaluating this phenomenon have

been conducted. This lack of data prompted us to review our experience and the literature to determine the frequency and consequences of misdiagnosis in patients with presumed pyoderma gangrenosum.

The objectives of our study were to determine the frequency of misdiagnosis of pyoderma gangrenosum at our tertiary referral center and to identify the causes of cutaneous ulceration and the usefulness of biopsy in patients who receive such misdiagnoses. For patients who had received treatment directed at pyoderma gangrenosum, we also attempted to ascertain the lag time between the initial diagnosis and the definitive diagnosis and the effect of treatment directed at pyoderma gangrenosum.

METHODS

Ascertainment of Cases

Medical charts of 240 patients were reviewed, including those of 157 consecutive patients treated at the Mayo Clinic in Rochester, Minnesota, for pyoderma gangrenosum and evaluated from 1984 through 1992 and those of 83 patients identified in a 25-year extraction (for 1975 through 2000) from the master index of diagnoses at the Mayo Clinic. We searched the index for patients with concomitant diagnoses of pyoderma gangrenosum and other vascular, malignant, infectious, exogenous, or inflammatory conditions that may produce cutaneous ulceration. The charts of these patients were reviewed in order to identify patients who were initially mistakenly given a diagnosis of pyoderma gangrenosum.

In addition, a Medline search of the English-language literature using the key words “pyoderma gangrenosum” produced 767 references. We reviewed the abstracts of all these articles and further reviewed the full text of articles that suggested a possible alternative cause of pyoderma gangrenosum-like ulceration. The review was expedited by the targeting of phrases such as “presenting as,” “masquerading,” “induced by,” “mimicking,” “simulating,” “caused by,” and “associated with.”

Abstraction of Data

The charts and cases from the literature were reviewed by two of the investigators with the use of a formal abstraction tool. The information abstracted from the charts and cases included demographic information about the patients (age, sex, location of ulcer, and duration of ulcer), relevant medical history (inflammatory bowel disease, arthritis, monoclonal gammopathy, underlying cancer, coagulopathy, or connective-tissue disease), the initial diagnosis, the microscopical description and diagnoses rendered by a pathologist on the initial and subsequent biopsies of the ulcer, the final diagnosis, the interval between the initial clinical diagnosis and the final diagnosis, treatments prescribed before the final diagnosis, and the final treatment and outcome. If there was insufficient information concerning these variables, the patient was excluded from the analysis.

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Case Definition

Cases that clinically resembled pyoderma gangrenosum but were found to be due to an alternative cause were included in the analysis. Cases in the subgroup of patients who received treatment directed at pyoderma gangrenosum before receiving an alternative final diagnosis were classified as "misdiagnosed."

RESULTS

Ulcers Resembling Pyoderma Gangrenosum

Ulceration resembling pyoderma gangrenosum had alternative causes in 95 patients (49 from our institution and 46 described in the literature). The cause of ulceration fell into one of six disease categories (Table 1): vascular occlusive or venous disease (in 28 patients) (Fig. 1), vasculitis (in 21 patients), a malignant process involving the skin (in 16 patients), primary infection (in 14 patients), drug-induced or exogenous tissue injury (in 13 patients), and other inflammatory disorders (in 3 patients). Eighty-six patients had skin biopsies. The initial or repeated biopsy demonstrated diagnostic histologic findings of the alternative diagnosis in 46 of the cases in which biopsies were performed (53 percent) (Table 2).

Ulcers Misdiagnosed as Pyoderma Gangrenosum

A total of 64 of the 95 patients (67 percent) had received treatment directed at pyoderma gangrenosum before the establishment of an alternative diagnosis. Included among the 64 were 15 of the 157 consecutive patients treated for pyoderma gangrenosum between 1984 and 1992 at our institution (10 percent), among whom the mean duration of follow-up was 42 months. The median lag time between the initial diagnosis of pyoderma gangrenosum and a final diagnosis among these 64 patients was 10 months overall and varied among the disease categories (vascular occlusive or venous disease, 12 months; vasculitis, 15 months; cancer, 12 months; infection, 5 months; and exogenous tissue injury, 5 months).

Disorders classically associated with pyoderma gangrenosum — seropositive or seronegative rheumatoid arthritis, inflammatory bowel disease, paraproteinemia, and myeloproliferative disorders — were present in 31 patients overall (33 percent) and in 25 of the 64 patients who received a misdiagnosis of pyoderma gangrenosum (39 percent).

Of the 64 patients who had received treatment for pyoderma gangrenosum, it was clear that 23 (36 percent) had ulcers that were refractory to standard treatment directed at pyoderma gangrenosum (high-dose prednisone [≥ 1 mg per kilogram of body weight], with or without a corticosteroid-sparing agent [e.g., azathioprine, cyclosporine, or cyclophosphamide]), 8 (12 percent) had an exacerbation of the condition simulating pyoderma gangrenosum (infection or lymphoma), and 15 (23 percent) had a further delay in

diagnosis (because of temporary improvement of vasculitis, antiphospholipid-antibody syndrome, or lymphoma) while they were receiving treatment for presumed pyoderma gangrenosum.

DISCUSSION

We identified six broad disease categories that may simulate pyoderma gangrenosum. Vascular occlusive or venous disease, vasculitis, cancer, infection, exogenous tissue injury, and other inflammatory disorders should be specifically ruled out before a diagnosis of pyoderma gangrenosum is made.

In 1930, Brunsting et al.⁴² of the Mayo Clinic described five patients with rapidly progressive, painful, suppurative cutaneous ulcers with edematous, boggy, blue, undermined, and necrotic borders, which they called "pyoderma gangrenosum." This condition falls in the spectrum of the neutrophilic dermatoses, inflammatory disorders that have in common a tendency for pathergy (induction of the inflammatory process after skin trauma) and the presence of noninfectious neutrophilic infiltrates of the skin. Pyoderma gangrenosum is associated with a number of specific diseases, including inflammatory bowel disease, paraproteinemia, arthritis, and myeloproliferative diseases. The pathogenesis of pyoderma gangrenosum is poorly understood, but neutrophil dysfunction (defects in chemotaxis or hyperreactivity)⁴³ and overexpression of interleukin-8⁴⁴ and interleukin-16^{45,46} have been reported. These observations suggest that pyoderma gangrenosum represents an overreactive inflammatory response to traumatic, inflammatory, or neoplastic processes in susceptible persons.

Biopsy of an early lesion of pyoderma gangrenosum often demonstrates a dermal neutrophilic abscess. Later-stage lesions show epidermal necrosis and ulceration, superficial dermal edema, and a dense, mixed dermal infiltrate that may extend to the panniculus. Histologic examination of the advancing, inflamed border reveals dense perivascular lymphocytic inflammation, which may at times be associated with vascular destruction. None of these histologic features is pathognomonic.

No laboratory finding is diagnostic of pyoderma gangrenosum, but patients often have a neutrophilic leukocytosis and an elevated erythrocyte sedimentation rate. Because of the protean nature of these findings, laboratory investigation should focus on identifying associated diseases and excluding diseases that may simulate pyoderma gangrenosum (Table 3).

We found a frequency of misdiagnosis of pyoderma gangrenosum of approximately 10 percent. However, because of referral bias, this estimate most likely exceeds the actual frequency, because many patients with apparently refractory or difficult cases of ulceration resembling pyoderma gangrenosum are referred to ac-

TABLE 1. ULCERS RESEMBLING PYODERMA GANGRENSUM.

CAUSE OF CUTANEOUS ULCERATION	NO. OF PATIENTS WITH MISDIAGNOSIS/ TOTAL NO.*	NO. OF NEW CASES IDENTIFIED†	NO. OF PREVIOUSLY REPORTED CASES	REFERENCES
Vascular occlusive or venous disease	23/28			
Antiphospholipid-antibody syndrome	11/15	7	8	Schlesinger and Farber, ¹ Schmid et al., ²
Livedoid vasculopathy	4/4	4		Babe et al., ³ Freedman et al., ⁴ Chacek et al., ⁵ Grob and Bonerandi, ⁶ Selva et al. ⁷
Venous stasis ulceration	6/6	6		
Small-vessel occlusive arterial disease	1/1	1		
Type I cryoglobulinemia	1/1		1	White et al. ⁸
Klippel-Trénaunay-Weber syndrome	0/1		1	Scheinman ⁹
Vasculitis	13/21			
Wegener's granulomatosis	6/8	4	4	Micali et al., ¹⁰ Handfield-Jones et al., ¹¹
Polyarteritis nodosa	4/7	7		Thomas et al. ¹²
Cryoglobulinemic (mixed) vasculitis	3/3	2	1	Smith et al. ¹³
Takayasu's arteritis	0/2		2	Perniciaro et al., ¹⁴ Frances et al. ¹⁵
Leukocytoclastic vasculitis plus secondary infection	0/1	1		
Cutaneous involvement of malignant process	9/16			
Lymphoma				
Angiocentric T-cell lymphoma	3/5	4	1	Thomas et al. ¹⁶
Anaplastic large-cell T-cell lymphoma	2/3	1	2	Camisa et al. ¹⁷
Mycosis fungoides bullosa	0/1		1	Ho et al. ¹⁸
Unspecified lymphomas	2/3		3	Kitahama et al., ¹⁹ Vose et al. ²⁰
Leukemia cutis	1/2		2	Helm et al., ²¹ Torok et al. ²²
Langerhans'-cell histiocytosis	1/2	1	1	Norris et al. ²³
Primary cutaneous infection	11/14			
Deep fungal infection				
Sporotrichosis	5/5	1	4	Stroud, ²⁴ Liao et al., ²⁵ Spiers et al., ²⁶ Leshner et al. ²⁷
Aspergillosis	1/1		1	Harmon et al. ²⁸
Cryptococcosis	1/1		1	Massa and Doyle ²⁹
Zygomycosis	0/2	1	1	Liao et al. ³⁰
<i>Penicillium marneffei</i> infection	0/1		1	Chiewchanvit et al. ³¹
Herpes simplex virus type 2	2/2		2	Brown and Callen, ³² Wahba and Cohen ³³
Cutaneous tuberculosis	1/1		1	Matsui et al. ³⁴
Amebiasis cutis	1/1		1	Sunarwan ³⁵
Drug-induced or exogenous tissue injury	8/13			
Munchausen's syndrome or factitial disorder	5/5	3	2	Parent et al., ³⁶ Barrett and Buckley ³⁷
Hydroxyurea-induced ulceration	1/1	1		
Contact vulvitis	1/1	1		
Injection-drug abuse with secondary infection	1/1	1		
Bromoderma	0/1		1	David et al. ³⁸
Loxoscelism (bite of a brown recluse spider)	0/3		3	Rees et al., ³⁹ Hoover et al. ⁴⁰
Drug-induced lupus	0/1		1	Peterson ⁴¹
Other inflammatory disorders	0/3			
Cutaneous Crohn's disease	0/2	2		
Ulcerative necrobiosis lipoidica	0/1	1		
Total	64/95	49	46	

*Data are the numbers of patients with the given final diagnosis who were initially treated for pyoderma gangrenosum, over the total numbers of patients with the given final diagnosis and ulcers simulating pyoderma gangrenosum.

†Data are numbers of cases identified at the Mayo Clinic between 1975 and 2000.

ademic centers such as ours, whereas those who have cases that are easily treated are unlikely to be referred.

More than half the patients from this study who had biopsies had histopathological evidence of an alternative diagnosis on the initial or repeated biopsy. Although the rate of pathergy in patients with pyoderma gangrenosum is unknown, we propose that the need to rule out an alternative disease should override the fear of exacerbating the condition by performing a biopsy.

A substantial number of the patients we analyzed who were treated for pyoderma gangrenosum had ulcers that were refractory to treatment. These cases emphasize the need to reconsider the diagnosis of pyoderma gangrenosum when the condition fails to respond to standard treatment. Some patients had progression of the condition simulating pyoderma gangrenosum or had temporary improvement in the condition while they were receiving treatment for presumed pyoderma gangrenosum. Five patients died



Figure 1. Ulceration Resembling Pyoderma Gangrenosum but Due to Antiphospholipid-Antibody Syndrome.

A 27-year-old woman presented with a nine-year history of systemic lupus erythematosus and debilitating leg ulcers. The ulcers were refractory to treatment with 80 mg of prednisone daily, cyclophosphamide, and dapsone. A circulating anticardiolipin antibody was identified. Definitive treatment consisted of a two-week course of low-dose tissue plasminogen activator, followed by maintenance therapy with aspirin. The ulcers healed completely and did not recur during 10 years of follow-up.

from overwhelming infection, and four died from progression of disease. The contribution of treatment directed at pyoderma gangrenosum to exacerbated illness or death in these cases cannot be determined.

Treatment directed at pyoderma gangrenosum can itself produce substantial complications, or it may adversely affect other causes of ulceration — for example, by promoting the progression of infection or lymphoma. It may also result in temporary improvement of disorders such as vasculitis, antiphospholipid-antibody syndrome, and lymphoma and thereby delay the diagnosis of these disorders.

Venous stasis ulcers are the most common cause of ulceration of the legs, are classically located on the medial aspects of the legs, and are markedly less painful than pyoderma gangrenosum. It is usually not dif-

ficult to distinguish clinically between stasis ulcers and pyoderma gangrenosum unless there is a complicating factor such as secondary bacterial infection, arterial insufficiency, or irritant or allergic contact dermatitis.

Antiphospholipid-antibody syndrome can produce exquisitely tender vascular occlusive ulcers that may clinically resemble pyoderma gangrenosum. Our study revealed that this syndrome is a highly problematic simulator of pyoderma gangrenosum because of the low specificity of histologic findings in patients with the syndrome and its frequent response to systemic corticosteroids. Indeed, less than one third of cases showed histologic evidence of a coagulopathy. Moreover, approximately 60 percent of patients had improvement with systemic corticosteroids — which

TABLE 2. FREQUENCY OF DIAGNOSTIC FINDINGS ON INITIAL OR REPEATED BIOPSY.

CAUSE OF ULCERATION	NO. OF PATIENTS WITH A BIOPSY	NO. OF PATIENTS WITH DIAGNOSTIC PATHOLOGY ON BIOPSY (%)
Vascular occlusive disease	23	8 (35)
Vasculitis	19	13 (68)
Cancer	16	13 (81)
Infection	14	9 (64)
Drug-induced exogenous tissue injury	11	0
Other inflammatory disorder	3	3 (100)
Overall*	86	46 (53)

*Nine patients from this study did not undergo biopsy.

accounted for the greater lag time before a final diagnosis in patients with antiphospholipid-antibody syndrome as compared with those with other causes of ulceration. In the absence of a lupus anticoagulant, ulceration resembling pyoderma gangrenosum is very unusual in patients with systemic lupus erythemato-

sis. In a prospective study involving patients with systemic lupus erythematosus, 3 of the 33 patients who were positive for lupus anticoagulant had ulceration resembling pyoderma gangrenosum during a mean follow-up of 13.8 years (range, 5 to 22). In contrast, none of the 37 patients with systemic lupus erythematosus who were negative for lupus anticoagulant had such ulceration during a mean follow-up of 15.7 years (range, 7 to 25).⁴⁷

Livedoid vasculopathy is a rare segmental, thrombo-occlusive disorder of postcapillary venules that results in exquisitely tender, slow-healing, purpuric ulcers that principally affect the legs. It is characterized histologically by superficial, pauci-immune perivascular inflammation, thrombosis, and intramural hyaline deposition.^{48,49} Acute inflammation due to secondary infection of ulcers related to livedoid vasculopathy may cause the condition to be confused with pyoderma gangrenosum, even on histologic analysis, as it did in two of the four cases of livedoid vasculopathy in our study.

Cutaneous ulceration is a common manifestation of several vasculitides. We found that, in the vasculitis

TABLE 3. APPROACH TO THE PATIENT WITH SUSPECTED PYODERMA GANGRENOSUM.

Important historical data
Markedly painful ulcer
Rapid progression of ulceration
Type of skin lesion preceding the ulcer (papule, pustule, or vesicle)
Minor trauma (pathergy) preceding development of the ulcer
Symptoms of an associated disease (e.g., inflammatory bowel disease or arthritis)
Drug history (e.g., bromides, iodide, hydroxyurea, or granulocyte-macrophage colony-stimulating factor)
Characteristic features of ulcer on physical examination
Tenderness
Necrosis
Irregular violaceous border
Undermined, rolled edges
Skin biopsy
Aim: to rule out diagnoses that mimic pyoderma gangrenosum
Protocol:
Elliptical incisional biopsy preferable to punch biopsy; include inflamed border and ulcer edge at a depth that includes subcutaneous fat
Specimen from inflamed border — routine histology (hematoxylin-and-eosin staining) and special staining (Gram's, methenamine silver, and Fite) to detect microorganisms
Specimen from edge of ulcer — culture in appropriate culture media (to detect bacteria, fungi, and atypical mycobacteria)
Laboratory investigations
Aims: to identify associated diseases and to rule out diagnoses that mimic pyoderma gangrenosum
Investigations to consider:
Complete blood count
Erythrocyte sedimentation rate
Blood chemistry (liver- and kidney-function tests)
Protein electrophoresis
Chest radiography
Colonoscopy
Coagulation panel (including antiphospholipid-antibody screening)
Antineutrophilic cytoplasmic antibodies
Cryoglobulins
Venous- and arterial-function studies
Close, continuous follow-up
Monitor response to and side effects of therapy
If no response to treatment, reconsider diagnosis and repeat biopsy

category, Wegener's granulomatosis was the most frequent cause of pyoderma gangrenosum-like ulceration. Lesions resembling pyoderma gangrenosum and involving the head and neck — called “malignant pyoderma” by Perry et al.⁵⁰ — are characterized by a more aggressive clinical course than that of common, nonfacial pyoderma gangrenosum. Subsequently, Gibson et al.⁵¹ showed that many cases of malignant pyoderma are actually a manifestation of Wegener's granulomatosis.

Patients with systemic or cutaneous polyarteritis nodosa may present with cutaneous ulcers that can progress rapidly and simulate pyoderma gangrenosum. Patients with polyarteritis nodosa may also have livedo reticularis in association with cutaneous nodules. The histopathology of polyarteritis nodosa is distinctive (medium- and small-vessel arteritis), but because of the segmental nature of vascular involvement, multiple biopsies may be required in order to establish the diagnosis. Cryoglobulinemic vasculitis may occur in type II (monoclonal plus polyclonal) or type III (polyclonal) cryoglobulinemia, revealing leukocytoclastic vasculitis on histopathological analysis.

Lymphoma cutis, leukemia cutis, and Langerhans' cell histiocytosis were the malignant diseases that simulated pyoderma gangrenosum in our series. On the basis of histopathological features alone, such malignant diseases would appear to be the easiest to rule out. However, in some cases, a biopsy was not performed during the initial workup, or the initial biopsy results were nonspecific or were interpreted as consistent with a diagnosis of pyoderma gangrenosum. Thus, it is often necessary to obtain repeated biopsies when following patients suspected of having pyoderma gangrenosum. Six of the nine patients with diseases in this category who had been treated for presumed pyoderma gangrenosum died of progression of their disease or overwhelming infection. A few patients had temporary improvement of their ulcers with treatment directed at pyoderma gangrenosum (prednisone), which may have delayed the diagnosis of lymphoma.

In the category of primary cutaneous infection, deep fungal infection was the most frequent cause of pyoderma gangrenosum-like ulceration. In several of the cases, there was profound dermal neutrophilia, supporting a diagnosis of pyoderma gangrenosum. In a few of these cases, after tissue culture proved to be positive, special staining was performed retrospectively on the stored tissue and revealed the offending microorganism. In three of our cases, the perineum or perianal region was the site of involvement. Although pyoderma gangrenosum may rarely affect this region in adults, it appears to affect it more commonly in children.⁵²⁻⁵⁴

An important question regarding the patients giv-

en a final diagnosis of primary cutaneous infection is whether infection was indeed the primary cause of ulceration, because infection could occur as a complication of pyoderma gangrenosum, as a result of a compromised skin barrier and immunosuppression. However, after targeted antimicrobial therapy was started and treatment directed at pyoderma gangrenosum was discontinued, the ulcers healed in 8 of 11 patients with such infections who were being treated for pyoderma gangrenosum. The three other patients died from complications related to their illness.

Not surprisingly, biopsy was not helpful in ruling out exogenous causes of ulceration, because these tissue injuries are not characterized by specific histopathological findings. Self-induced ulceration (Munchausen's syndrome and factitial ulceration) was the most common diagnosis in this category.

In conclusion, our data indicate that the misdiagnosis of pyoderma gangrenosum is not uncommon (as high as 10 percent) and that it exposes patients to substantial risks associated with its treatment (exacerbation or delay in diagnosis of an alternative disease process in 36 percent of patients erroneously treated for pyoderma gangrenosum). A thorough workup (including biopsy) is required in all patients suspected of having pyoderma gangrenosum in order to rule out diagnoses that mimic pyoderma gangrenosum. Close long-term follow-up and reappraisal of the diagnosis (with repeated biopsy if indicated) are recommended for all patients with suspected pyoderma gangrenosum, even patients with a response to treatment or with coexisting conditions typically associated with pyoderma gangrenosum.

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