CHAPTER **12**

ATYPICAL PYODERMA GANGRENOSUM OF THE LOWER EXTREMITY: A Case Presentation and Comprehensive Disease Overview

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Pyoderma Gangrenosum (PG) is a destructive, inflammatory skin disease first reported in 1916 as "phagedenisine geometrique" by Brocq. It was subsequently characterized as PG by Brunsting, Goeckerman and O'Leary in 1930 and again in 1982.[1,2] These authors have implicated streptococci and staphylococci as the causative agents because of the seemingly purulent nature of the disease.[3] Of interest is after nearly 74 years the precise etiology of this condition still remains unclear. Multiple authors have suggested a noninfectious dysregulation of the immune system as the primary etiology,[3] while others have hypothesized a possible genetic component.[2,3] Currently it is believed that PG's infectious involvement is secondary if present at all. Belonging to the dermatologic class of neutrophilic dermatoses, this pathologic condition should be considered in a differential diagnosis of chronic non-healing ulcerations recalcitrant to normal therapies.[1] Since the specific pathogenesis of this clinic entity remain undefined, its management for the most part is empirically based on clinicopathologic findings.[1-3]

Pyoderma Gangrenosum (PG) is a rare clinical entity with a reported incidence of 1 in 100,000 persons each year.[3] It has been reported to both be equal in distribution between the sexes,[2,4,5] with some authors suggesting a preference of women to men 2:1.[2,6-8] Predominately presenting between the ages of 25 and 50, PG has been reported in both infants[1,9] and children.[10]

The associated prevalence of underlying systemic disease ranges from 50-78% of affected patients with Inflammatory Bowel Disease as the leading co-morbidity at a reported incidence of 30%.[2,11,5] Systemic disease onset however may precede, coincide, or follow the presentation of a PG lesion.[2] Death from PG is rare, generally occurring from complications of the associated disease or as a result of its therapy.

There are four predominant variants of PG presently accepted in the literature, the most common being the ulcerative form (UPG). UPG has a prevalence to the lower extremity and trunk, with a reported incidence of 80% by Von den Driesch[2,8,1] and 75% by Bennett et al[2] to the legs. Other variants include Pustular PG (a.k.a. Atypical PG (APG)) that typically presents on the extensor surfaces of the upper extremity and trunk, Superficial Bullous PG (SBPG) generally presenting on the hands, neck and head, and Vegetative PG (a.k.a. Pyostomatitis Vegetans (VPG)) that presents in the oral cavity and genitals (all). Additional forms include Malignant PG (MPG), Superficial Granulomatous PG (SGPG) and Familial PG (FPG). The variant's specific associated underlying disease predilection will be covered later in the text.

CASE PRESENTATION:

A 53-year-old Caucasian female presented June 2003 with a chief complaint of redness, swelling, and exquisite pain on the medial portion of the left ankle and adjacent pretibial area. She related redness and pain beginning approximately one week prior at which time she sought medical assistance at the local urgent care center. She was diagnosed with cellulitis, given a short course of Augmentin® (Amoxicillin/Clavulanate) which she completed. The erythema increased and a central bluish-purple blister developed that erupted some time during the week and began to express a seropurulent yellow discharge. She related a fever of 100.1F the evening prior, but denies chills, nausea, vomiting, diarrhea or generalized malaise. She denied any significant trauma to the area at this time.

The patient was familiar to our service having previously undergone a subtalar joint fusion in 1997 for treatment of left posterior tibial tendon dysfunction and adult acquired flat foot syndrome healing without complication (Figure 1). At the time of her original surgery her past medical history was positive for a single episode of gout, rheumatoid arthritis (diagnosed in 1995), and Lupus (diagnosed in 1996). Her Rheumatologist was managing her medically on Plaquenil®, Voltaren® and Prednisone. She was also treated conservatively for a Morton's neuroma in the right foot with complete resolution.

Prior to presentation at our office for her current exacerbation, she had been managed by her primary care physician and had been hospitalized on multiple occasions for the same problem, beginning December 99', in a nationally known local tertiary care center where she underwent several "complete workups" for this problem. The patient's labs in December 99' were remarkable for an elevated platelet count of 498K/uL, C-reactive protein (CRP) of 4.1mg/dl, and erythrocyte sedimentation rate (ESR) of 83mm/hr. A CBC with differential was done and within normal limits. An anti-nuclear antibody (ANA) panel of 0.2 and rheumatoid factor (RF) of less than 20 were both considered negative. (Table 1) She did have a positive single light growth blood culture of coagulase negative staphylococcus. An arthrocentesis of her left ankle was unremarkable; cultures were negative. An MRI was performed showing a subcutaneous effusion medial and superior to the left medial malleolus with no bony involvement. She underwent IV antibiotic therapy with Vancomycin while hospitalized and was discharged on oral Dicloxacillin and advised to follow up with a rheumatologist.

She was seen for follow-up by a rheumatologist following discharge. He felt she had a cellulitis of unknown origin and suggested it was from the retained hardware with possible osteomyelitis despite the negative MRI study. A three phase bone scan that was interpreted as subacute inflammatory arthritis involving the left proximal foot without significant focal abnormality noted over the left ankle. Clinical correlation was suggested. Her dicloxacillin and NSAID therapies were discontinued. Although she was cleared of the concern of septic arthritis; he did feel the potential for osteomyelitis warranted treatment. A PICC line was established and a 6 week course of IV antibiotics was prescribed by infectious disease. In addition, the patient received an oral prednisone taper. The "cellulitis" has been recurrent with episodes of complete resolution followed with a reoccurrence every 5-7 months since its original appearance.

On her last hospitalization, in November 2002, she was started on prednisone (80mg QD) for a suspected vasculitis. She was referred to a dermatologist and a second rheumatologist for further consultation. A two week course of oral Levaquin® was prescribed along with local compressive dressings daily. At the time of her consultation with the dermatologist her "cellulitis" had resolved completely minimizing the value of the consult. The rheumatologist questioned her previous diagnosis of rheumatoid arthritis (RA), and lupus, however believed there was an undefined underlying connective tissue disease, and continued the patient on 60 mg daily oral Prednisone therapy for treatment of the connective tissue disorder for three and a half months. During this time her leg remained symptom free, and without flare-up. She was taken off of the steroids due to a combination of significant weight gain and systemic side effects including high blood pressure, headaches, and hirsutism from prolonged steroid use. In June of 2003 (2 months after discontinuing steroids) she presented with increased symptoms in the same area as the previous lesions.

The patient's current medical history is positive for recurrent urinary tract infections, non-inflammatory generalized arthritis and a continuing questionable diagnosis of RA, SLE, and inflammatory bowel disease (IBD) two weeks prior to this visit. Her medications included Zolpidem, Propoxyphene, Hydrocodone, ketorolac, and hormone replacement therapy.

Our physical examination on June 16th 2003 revealed an area of significant erythema and inflammation which was exquisitely painful to light touch making examination essentially limited to our visual observation. (Figure 2) The erythema had nonspecific borders, encompassing primarily the medial aspect of the ankle and leg. The mild calor was disproportionate to the severity of the clinical picture. There was a mild joint effusion with

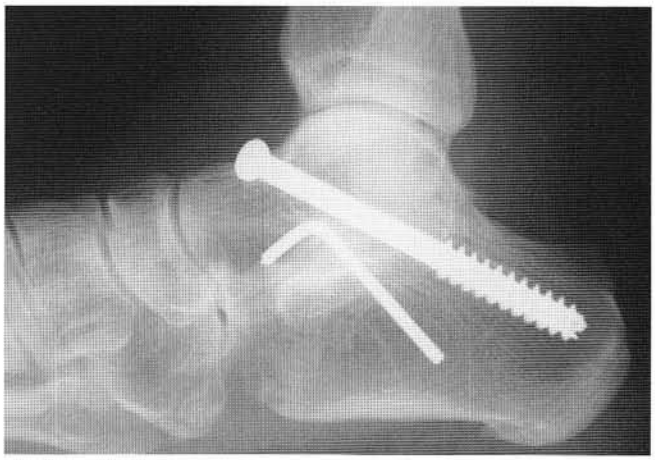

Figure 1. STJ fusion completed in 1997 for the treatment of Adult Acquired Flat Foot. Uneventful postoperative course.

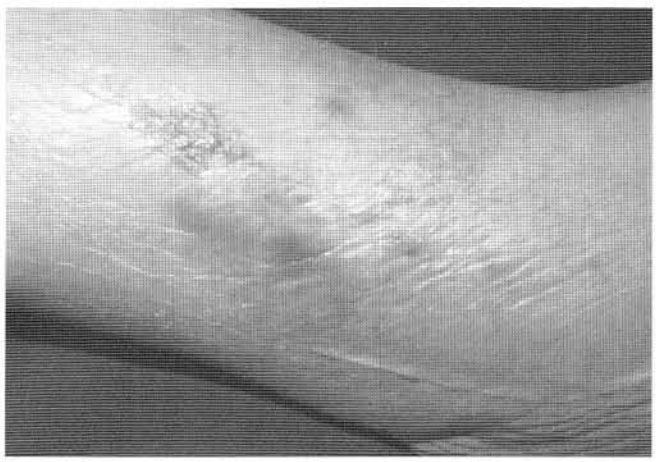

Figure 2. 6.16.03-Clinical presentation. Nonspecific erythematous border. Three 0.5cm bullae without observable drainage and a yellow opaque crust proximally.

Table 1

SUMMARY OF LABORATORY FINDINGS IN THIS PATIENT

Date	Test	Result	Normal Values
12.12.99	synovial fluid analysis	bloody, turbid %Neut = 80 no organisms on GS/C&S	clear, yellow 0-25%
12.13.99	WBC	10.65	4.0-11.0 k/uL
	PLT	419	150-400 K/uL
12.14.99	Haptoglobin	314	37-246 mg/dL
	LD	159	100-220 U/L
12.15.99	WBC	8.74	4.0-11.0 k/uL
	PLT	457	150-400K/uL
	%Neut	65.1	40-70%
	%Lymph	24.5	22-44%
	Albumin	3.5	3.5-5.0 g/dL
	CRP	5.2	0-1.0mg/dL
	Iron	20	30-140 ug/dL
	TIBC	301	210-415 ug/dL
	IronSat	7	11-46 %
	ANA	0.2 (negative)	<1.5 OD ratio
	RF	<20 (negative)	<20 IU/mL
	C3 complement	140	76-199 mg/dL
	C4 complement	15	16-64 mg/dL
12.18.99	CRP	2.8	0-2.0 mg/dL
	X-ray	(-) for osteo	
	MRI	(-) for osteo	
12.27.99	CRP	4.1	0-1.0 mg/dL
	ESR	83	0-30 mm/hr
12.30.99	triphase Tech-99 scan	(-) for osteo	
3.22.00	WBC	6.55	4-11.0k/uL
	%Neut	54.40%	40-70%
	CRP	3	0-1.0mg/dL
	ESR	57	0-30mm/hr
	C3 complement	96	76-199mg/dL
	C4 complement	14	16-64mg/dL
11.2001	ANA	1:640 positive, diffuse pattern	
	ESR	113	0-30mm/hr
	Anti SS-A	negative	
	Anti SS-B	negative	
	Anti double stranded DNA	negative	
1.2002	ESR	71	0-30mm/hr
	serum protein electrophoresis	polyclonal gammopathy	
10.28.02	WBC	9.5	4-11.0 k/uL
	CRP	10.1	0-1.0mg/dL
	ESR	95	0-30mm/hr
	ASO AB	22	<201 IU/mL

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11.4.02	WBC	12	4-11.0 k/uL
	PLT	530	150-400 K/uL
	ESR	84	0-30mm/hr
	%Neut	58%	40-70%
	%Lymph	32%	22-44%
	CRP	8.6	0-1.0 mg/dL
11.11.02	triphase Tech-99 scan	(-) for osteo	
4.10.03	Lipid profile	High cholesterol (205), high HDL (88)	
6.23.03	WBC	24.6	4-11.0 k/uL
	PLT	682	140-440 k/uL
	%Neut	78.2	40-70%
	%Lymph	16.2	20-30%
	ESR	77	0-30 mm/hr
	CRP	13.3	0-1.0 mg/dL
	X-ray	(-) osteo	
	GS/C&S	normal skin flora	
	teichoic acid Ab	negative	<1:2
6.24.03	WBC	14	4-11k/uL
	PLT	561	140-440k/uL
	Bleeding Time	2.5	2.0-5.0 min
	triphase Tech-99 scan	(-) osteo	
	RF	negative	
	ANA	negative	
	ASO screen	negative	
	serum protein electrophoresis	IgA= 331	70-400 mg/dL
		IgG= 1136	700-1600 mg/dL
		IgM=360	40-230 mg/dL
		Results = polyclonal gammopathy, IgM type	
6.27.03	WBC	12.8	4-11.0k/uL
	%Neut	64.8	40-70%
	%Lymph	28.2	22-44%
	ESR	68	0-30mm/hr
	CRP	3.2	0-1.0mg/dL

pitting edema around the ankle extending onto the dorsal aspect of the foot. The edema and erythema followed a linear course consistent with the saphenous nerve and vein with mild, small varicosities noted on both lower extremities. Centrally there were three 0.5cm bullae without observable drainage and a yellow opaque crust. There are no nodes or lymphangitis present. Patient was afebrile with a temperature of 37.2C.

A two week course of Levaquin® (750mg QD) was prescribed. Laboratory studies revealed an elevated CRP of 18.1mg/dl, ESR of 127mm/hr; however her WBC was 9.9K/uL without left shift. A gram stain of the exudate revealed the presence of rare WBC only; culture growth was negative. She was placed in a modified Jones compression dressing with Silvadene and will followup in two days. Our differential included cellulitis, venous stasis ulcer, ischemic ulcer, vasculitis, RSD or allergic reaction to retained hardware. It was felt that upon resolution of this presentation, fixation device removal would be performed.

She was seen for follow up 2 days later with some resolution of the erythema, but the three small bullas had coalesced into a large bulla measuring 2.5cm with continued seropurulent discharge. The base of the ulcer was essentially granular with a yellow crust on the periphery. Her severe hypersensitivity remained the same with an atrophic, waxy appearance to the surrounding skin consistent with RSD. Based on the patient's medical history, exquisite neuritic type pain, deep erythema, negative culture and Gram stain, and lack of significant WBC elevation, it was our impression that her problem was more of an inflammatory condition than infectious. She was continued on Silvadene dressings under compression for the edema and Levaquin prophylacticly. Additionally, she was given a prednisone taper and started on Indocin 25mg TID.

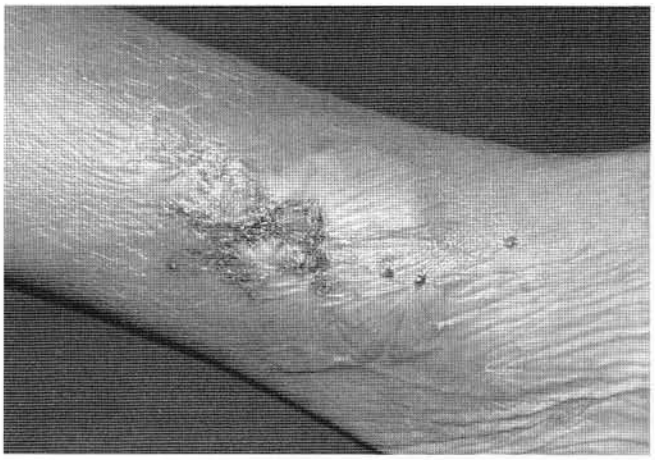

Figure 3. 7 days after initial presentation yielded increased erythema with a 4cm boggy bulla displaying irregular borders and peripheral yellow crusting. Gentle blunt débridement exposed a superficial ulcer with violet borders and fibropurulent base.

Five days later the patient related that the pain and erythema had decreased significantly within the first 48 hours after starting the prednisone taper, but increased as she completed the course of prednisone. Generally she was experiencing some GI upset, a metallic taste in her mouth, decrease appetite and general malaise. The erythema had increased from the previous visit with the bulla expanding in size to 4 cm with an irregular border and persistent seropurulent discharge with yellow peripheral crusting. (Figure 3) Gentile blunt débridement of the bulla exposed a superficial ulcer with violet borders and fibropurulent base measuring 4cm in diameter. The entire distal medial leg and foot continued to be exquisitely painful with a shiny taught appearance to the skin adjacent to the lesion. No lymphadenopathy or lymphangitis was present; she remained afebrile at 36.3C. She was admitted for cellulitis with possible underlying osteomyelitis due to the increased clinical picture severity and patients generalized symptoms of malaise.

Upon hospital admission a full blood workup including an ANA, ASO, RF, Lipid profile, CBC with differential, BMP, C-reactive protein, ESR, teichoic acid antibody study, and immunoglobulin electrophoresis to check for monoclonal gammopathy was ordered. Additionally a new wound swab was obtained for C&S and gram stain; conventional x-rays, Tc99MDP bone scan, and infectious disease (ID) consult were obtained. She was started on IV Vancomycin, and Zosyn per ID.

Her lab work was significant for a WBC of 24.6K/uL with neutrophil count of 78.2% and a lymphocyte count of 16.2%. Her platelet count was 682K/uL, ESR of 77mm/hr, and CRP 13.3 mg/dl. Her RF, ASO, and ANA were negative. The gram stain indicated no organisms or WBCs seen; the wound culture grew out normal skin flora of staphylococcus coagulase negative light growth. Lipid profile was significant for elevated cholesterol of 205mg/dl, and HDL of 88mg/dl. The teichoic acid antibody study was negative. The ID physician agreed with our assessment of the possible existence of an underlying vasculitis or granulomatous disease, and recommended a dermatology consult. Additionally, ID further supported our belief in a falsely elevated WBC due to recent steroid utilization. A normal bleeding time of 2.5 minutes was obtained that had been ordered as a precaution to her elevated platelet count.

A Tc99MDP scan revealed increased uptake in the medial ankle in the immediate and blood pool phases, with no increase in the delayed phase and was felt consistent with a cellulitis. The X-rays were negative for any signs of osteomyelitis or changes around the retained fixation. The immunoglobulin electrophoresis returned with multiple abnormalities; further analysis revealed a positive IG-M polyclonal gammopathy.

After further consideration of the extensive list of differentials it was felt there was a high potential for PG as the causative etiology. She was started on Minocycline 100mg BID and 60mg prednisone QD. She responded well with a decrease in erythema within 24 hours. She remained afebrile throughout her hospital stay with the severity of the pain decreasing slightly; however she began presenting with increased neuritic symptoms consistent with the sural nerve distribution. She was started on Neurontin 300mg TID in an effort to provide symptomatic relief.

Her WBC decreased to 12.8K/uL, the ESR was 68mm/hr and CRP at 3.2 mg/dl. Based on the clinical presentation of her leg, positive IGM polyclonal gammopathy, suspected connective tissue disorders (IBD/RA/Lupus) and response to systemic steroid therapy, a diagnosis of Atypical Pyoderma Gangrenosum was made. She was discharged home on 60mg prednisone QD, Neurontin 300mg TID, and Darvocet N100 for pain. ID decided to discontinue her minocycline, and continue her on Vancomycin 1gm IV QD via PICC line, Levaquin 500mg PO QD for another two weeks as a precaution. She was to be followed by ID along with our service and to obtain a dermatology consult.

On July 2nd, two and a half weeks since admission to the hospital she was seen in the office with a significant decrease in the erythema. (Figure 4) The ulceration was stable in size with no active discharge. The borders remained irregular with some exfoliation and persistent yellow peripheral crusting. Her pain had significantly decreased and we were able now able to palpate her leg with minimal discomfort.

By July 9th her ulceration had completely resolved

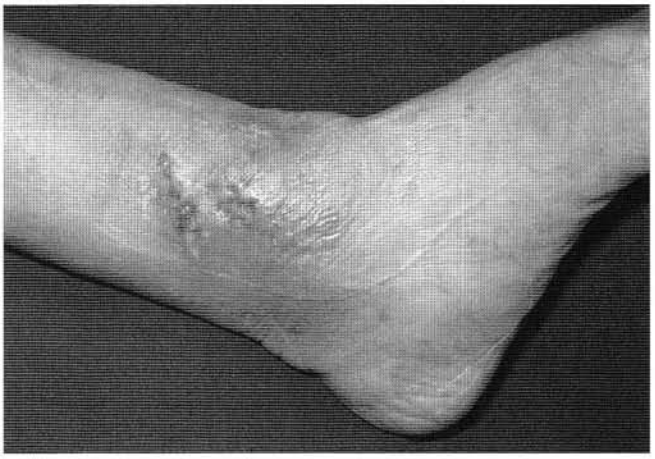

Figure 4. 7.2.03-Significantly decreased erythema. Ulceration had stabilized with no active discharge. Borders remained irregular with mild exfoliation and persistent yellow peripheral crusting.

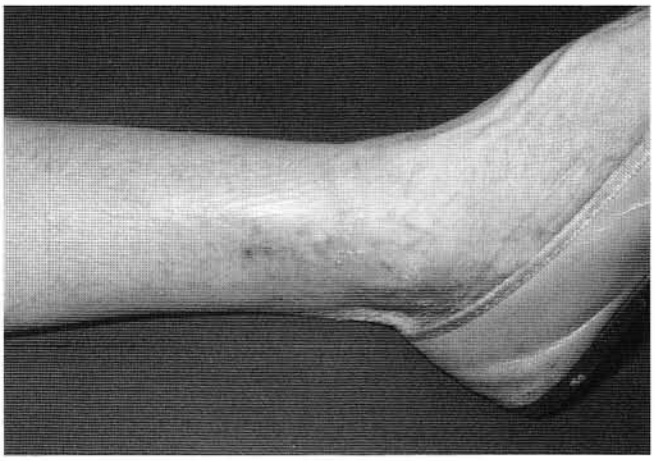

Figure 5. 7.9.03-Complete resolution of ulcer with characteristic depressed, hypo pigmented scar. Only a very mild erythema persisted.

and a depressed, hypo pigmented scar developed with only a very mild erythema persisting. (Figure 5) ID agreed with our diagnosis and discontinued all antibiotics. She was asymptomatic and pain free. The patient was anxious to taper off of the steroids due to her previous experience with sustained high doses. With near complete resolution of the lesion, a tapering of her prednisone was begun with intention of decreasing 10mg weekly as long as she remained asymptomatic. A vascular consult was also obtained for recurrent vasculitis and any further insight that might be offered.

The patient remained asymptomatic until August 20th when she presented with a severe reoccurrence of the ulceration to the same area after dropping a frying pan on her foot. The lesion measured 3.5cm with an irregular border and the same yellow seropurulent discharge. Additionally, she was beginning to develop the same symptoms on the contralateral limb with a 3mm bulla present centrally. Both were exquisitely painful and the patient was emotionally upset. The patient had also seen the vascular surgeon prior to her reoccurrence and had been told that she had venous stasis dermatitis, and to continue compression therapy. She was confident the above trauma had triggered the recurrence.

It was felt by our team that the clinical presentation was more consistent with APG. This was based on the initial clinical appearance of the lesion, its clinical course and response to therapy, the recent display of pathergy, and now its significant exacerbation with additional lesion appearance. The patient was placed on Dapsone 150mg QD, and the prednisone was increased to 40mg daily. Wound care would consist of Silvadene dressings under compression to be change daily.

As of September 2003, the patient has remained asymptomatic. Her lesions have healed and she has returned to work. She continues to take the dapsone and has tapered off of the prednisone. She is maintaining compression to the lower extremities with Jobst stocking.

DISCUSSION

Etiology

Nearly 75 years of clinical awareness of PG as a specific clinical entity exists, yet its precise etiology remains unclear. This is due in part to an inconsistent tendency of pyoderma gangrenosum to present concomitantly with underlying systemic disorders. 50% of patients with diagnosed PG do not have an underlying comorbid systemic condition. Of those who do have a confirmed comorbid condition, the range of conditions is quite impressive. (Table 2) The most consistent of these are the Inflammatory Bowel diseases with ulcerative colitis leading the list.[3] Other common pathologic conditions include Crohn disease, rheumatoid arthritis, leukemia and myeloproliferative disorders.[2,3,12] Several theories have been proposed as to the actual etiology of this rare ulcerative disease, all of which are suggestive of either a vascular or immunologic etiology.

The concept of pathergy, or the tendency to form new lesions in sites of minor or severe trauma, is thought to represents an exaggerated immune response. It is unknown whether it is of vascular or immunologic origin. Those that believe this disease to be of immunologic origins site PG's response to cyclosporine, an immunosuppressive drug, as an indicator suggesting a disturbance in immune cell function.[3,12] Further supporting the dysregulated immune theory is PG's association with a number of autoimmune diseases. However, there remains insufficient evidence to support these claims.[12,13]

Another proposed mechanism associated with altered

Table 2

ASSOCIATED SYSTEMIC CONDITIONS[12,2]

Ulcerative colitis = 50%
Crohn's disease
Hepatic disease = Active chronic hepatitis
Primary biliary cirrhosis
Sclerosing cholangitis
Carcinoid
Diverticulitis
Myeloproliferative disorders
Rheumatic = Polyarthritis
Rheumatoid arthritis
Ankylosing spondylitis
Wegener's granulomatosis
Behcet's syndrome
Paraproteinemia (multiple myeloma)
Drug reactions
Delayed altered hypersensitivity
Takayasu arteritis
Suppurativa hiradenitis
Cryoglobulinemia
Autoimmune anemia

immunologic response is akin to that of the Schwartzman reaction. It is hypothesized that the PG lesions are comparable to skin graft rejection reactions in which a combination of intravascular coagulation and altered immunoglobulins lead to the necrotic ulcerations.[14] Additionally, it has been shown that by increasing levels of IL-8 expression on human fibroblasts in mice with a combined immunodeficiency syndrome having undergone human skin grafting, massive infiltration of neutrophils resulted. This infiltration led to ulceration which both clinically and histologically resembled pyoderma gangrenosum.[3,15,16,17]

Immunofluorescence testing has offered no additional conclusions with only 10% of patients diagnosed with pyoderma gangrenosum displaying an IgA type monoclonal gammopathy. Though also suggestive of an immunologic etiology[12] further testing also substantiates a vascular etiology in which 50% of patients show perivascular deposition of C3 and IgM, both are general indicators of a non-specific vasculopathy[12] adding yet another variable to the equation.

Though the basis of the close relationship between GI disease such as ulcerative colitis and Crohn's disease to pyoderma gangrenosum is unknown, a vascular etiology is again suggested based only on the inflammatory nature of these disorders without any research to support it.[14] A second hypothesis as to a possible vascular basis is venous hypertension. Samitz et al propose that extravasation of an "unknown circulating agent" through venule walls leads to sequestration of the "unknown agent" in the interstitial layers of the skin, causing necrosis and ulceration.[14]

Khandpur et al offer a more complex, mixed etiology defining pyoderma gangrenosum as a syndrome of acute vascular insufficiency to the skin secondary to lympho-toxicity. They concluded that immune complex deposition leads to vascular infarcts and subsequent ulceration. Their theory is supported by the typical findings of immune reactant deposition on immunofluorescence testing and visible features of vasculitis on light microscopy.[13]

Some authors have elucidated to a possible autosomal recessive mode of inheritance.[13] Though literature in the area of familial predisposition is extremely limited, a case of pyoderma gangrenosum in siblings with unaffected parents has been presented. The authors suggested a probable etiology of genetic surface glycoprotein deficiency of the leukocytes resulting in impaired chemotaxis, phagocytosis and aggregation.[13,18,19] In spite of numerous articles and papers offering various hypotheses, none of them have sufficient clinical evidence to substantiate their theories leaving the exact etiology of pyoderma gangrenosum a continued enigma.

Clinical Manifestations

On initial presentation the lesions of UPG, the most common form of the disease, appear as moderately painful papulopustular lesion(s) or folliculitis which eventually ulcerate, giving rise to a dark, dusky lesion characteristic of the disease. The mature lesion typically exhibits marked edema with a raised undermined red to purple border surrounded by a strikingly erythematous halo as the ulceration advances.[3,20] The base of the lesion is typically boggy and necrotic with multiple scattered sterile abscesses producing a purulent and/or hemorrhagic exudate.[3] UPG can present as a solitary expanding lesion or multiple smaller lesions that typically coalesce into a larger lesion with irregular borders. In rare cases, the disease begins in the subcutaneous tissue as a tremendously painful panniculitis which eventually produces purulent bullae and ulcerate, spreading circumferentially to again produce the characteristic lesion.[3]

The data regarding distribution of UPG between the sexes is inconclusive. It has been reported to both be equal in distribution,[2,4,5] and to favor women to men 2:1.[2,6,7,8] Predominately presenting between the ages of 25 and 50, PG has been reported in both infants[1,2,6,7,8,9] and children.[10] UPG has a prevalence to the lower extremity and trunk,[20,21]

though they can present anywhere on the body, with approximately 57% of patients presenting with more than one lesion.[21] The oral cavity, larynx, pharynx, vulva, cervix and eyes occasionally exhibit massive ulcerative involvement.[3] If the lungs become involved they may produce pulmonary infiltrates that are culture-negative.[2,10]

The clinical progression of pyoderma gangrenosum typically follows two general patterns.[3] 1: An aggressive and rapid onset of quickly spreading ulcerations with the patient potentially showing signs of toxicity including significant pain, fever, highly inflammatory ulcers with extensive necrosis and exudate, and multiple hemorrhagic blisters. 2: An indolent slowly progressing disease characterized by considerable granulation tissue at the wound base with a hyperkeratotic rim and crusting at the wound margins. Both forms may demonstrate spontaneous regression resulting in a classic thin, atrophic, stellate hypo-pigmented scar like those seen in Atrophie Blanche.[3]

All variants of PG may exhibit the phenomenon of pathergy. Simply defined, it is the development or exacerbation of new or existing lesions following minor trauma or aggravation.[3,12,21,22] Pathergy is reportedly present in 20-30% of PG patients .[3] However, the possibility of its presence has lead most authors to an aggressively minimalist approach to ulcer débridement, some stating that an existing PG lesion is an absolute contraindication to surgery.[2,3,14]

Clinical Variants

The most typical variant, Ulcerative PG, described above accounts for the vast majority of all cases reported in the literature. There are, however, several atypical variants. Hemorrhagic bullous pyoderma gangrenosum differs from the traditional ulcerative disease in that it is characterized by rapidly arising dark bullous plaque-like lesions.[2,23,24] The lesion eventually ulcerates but remains more superficial than typical UPG lesions. These atypical lesions very closely resemble the violaceous plaques associated with Sweet's syndrome or acute febrile neutrophilic dermatosis potentially making a clinical diagnosis difficult.[2] This rare variant is frequently associated with leukemias and myeloproliferative disorders; therefore, any suspected malignancy should be a primary concern when evaluating a patient who presents with the bullous form of this disease.[2,23,24] A confirmed diagnosis of bullous pyoderma bears a poor prognosis and usually progresses on a parallel course with the underlying hematologic disorder. Koester, et al reported an 82.6% mortality rate in the presence of underlying systemic disease with death occurring at an average of 7 months from time of diagnosis. With further supposition he believed that the possibility of neutrophilic infiltration of organ systems potentially contributed to the elevated mortality rate.[23,24]

A second variant is Superficial Granulomatous PG (SGPG). It is generally characterized by its non-aggressive nature and its tendency to follow a chronic, limited course.[25] Initially appearing as an abscess-like lesion, it develops into a violaceous superficial ulceration with a strong predilection for the trunk, back and buttocks. The ulcers show a relatively clean base and vegetative wound margins. SGPG lacks any strong association with systemic disease; however, it does exhibit pathergy and usually appears at sites of previous surgery or other traumatic stimuli.[25] This form of pyoderma carries a more favorable prognosis than other forms and generally responds well to more conservative treatment options, as was the case with our patient.

Malignant PG (MPG) differs from the traditional form in that it presents as multiple small ulcerations of the scalp, face and neck which slowly spread to encompass the trunk and extremities as well. The ulcers are rather typical in appearance, being necrotic in nature but are small, 2-4 cm in diameter, with smooth, not irregular wound edges and are accompanied by erythematous papulopustular lesions.[26] This variant affects younger adults, ages 15-45, and lacks any correlation with systemic disease. It can however induce temporary neurological dysfunction, for example sensorimotor loss and cranial nerve palsies. Histologically, pseudo-acantholytic changes are indicative of this malignant form.[26] With prompt initiation of systemic treatment, complete remission is possible.

The Vesiculopustular variant of PG (VPG) is closely associated with inflammatory bowel disease. It typically presents as painful, small pustular lesions with an erythematous inflammatory border arising on otherwise normal skin. It has a predilection for the extensor surfaces of the arms and upper trunk.[10] The lesions usually recede with proper treatment of the underlying GI disease.

Lastly, PG may arise as a vegetative form, or pyostomatitis vegetans. This variant affects adults only and usually involves the oral mucosa and trunk only.[10] The lesions begin as superficial necrotic ulcers and gradually progress to an exophytic vegetative lesion. A notable feature of this syndrome, unlike in typical ulcerative pyoderma, is that the wound edges do not have an undermined inflammatory border.[10]

Histopathology

Within the PG lesion there are generally three distinctly different histological areas. Centrally, a necrotizing

suppurative inflammation is present surrounded peripherally by a region of lymphocytic and perivascular infiltrates. Transitionally, vessel involvement may be absent, but in fully developed lesions may present as focal vasculitis or fibrinoid necrosis.[12,20] In the vesiculopustular variant, associated with ulcerative colitis or hepatobiliary disease, the central nidus is often composed of a necrotizing pustular folliculitis. In contrast, the superficial granulomatous lesion is comprised of pseudoepithelioma-tous hyperplasia with suppurative dermal inflammation marked by the presence of eosinophils and plasma cells.[12,25] APG is distinguished by a diffuse neutrophilic dermatitis without primary vasculitis.[2]

Histological findings in pyoderma gangrenosum are considered essentially nonspecific, aiding only as a function of exclusion toward a definitive diagnosis. Most authors describe an intense neutrophilic infiltrate with potential predilection for follicular structures. The principal invading cell associated with the pathology of this disorder is the neutrophil leading to the classification of PG as a neutrophilic dermatosis.[3] In differentiating pyoderma gangrenosum from other neutrophilic dermatoses, such as Sweet's syndrome, PG typically presents with a deeper more extensive infiltrate, the presence of pustular vasculitis with involvement of the reticular dermis and subcutaneous tissue. Biopsy is reported to be of minimal aid to the practitioner in reaching the final diagnosis of pyoderma gangrenosum.

Diagnosing pyoderma gangrenosum

Pyoderma gangrenosum is a diagnosis of exclusion after similar lesions caused by infection, trauma, diabetes, malignancy, vasculitis and collagen vascular diseases have been ruled out. Several differential diagnoses must be considered when evaluating a patient for possible PG.[1,2,3,10] (Table 3)

Laboratory testing for pyoderma gangrenosum also plays an exclusionary role. The initial evaluation should focus on identifying the presence or absence of secondary infection via gram stain and routine cultures. If a chronic infectious process is suspected (i.e. chronic osteomyelitis) plain film radiographs, triphasic or WBC labeled bone scan and MRI should be considered. Leukocytosis and an elevated erythrocyte sedimentation rate are consistently present; however, they are neither specific nor diagnostic of pyoderma gangrenosum. In addition, C-reactive protein may be elevated, anemia and iron deficiency may or may not be identified and the presence of hypo- or hyper-globulinemia may occur.[3] Suggested diagnostic tests include an exclusionary 2-section biopsy for histological evaluation and culture as well as studies to confirm the

Table 3

DIFFERENTIAL DIAGNOSES[21,20,19,8]

- Infection:
  - Bacterial infection (i.e. Syphilitic gumma, Necrotizing fasciitis)
  - Mycobacterial infection
  - Deep fungal infection (i.e. North American Blastomycosis)
  - Parasitic infection (i.e. cutaneous amebiasis)
  - Viral infection (i.e. chronic ulcerative herpes simplex)
  - Tuberculosis Gumma
  - Anthrax
- Vascular Diseases:
  - Venous insufficiency
  - Arterial insufficiency
  - Thrombophlebitis with gangrene
  - Antiphospholipid antibody-associated occlusive disease
- Vasculitis associated syndromes:
  - Systemic Lupus Erythematosus
  - Atrophie Blanche
  - Behçet disease
  - Wegener granulomatosis
  - Rheumatoid arthritis
  - Polyarteritis nodosa
  - Collagen vascular disease (i.e. RA, SLE)
  - Necrotizing Vasculitis
  - Hypersensitivity vasculitis (i.e. leukocytoclastic vasculitis)
- Malignancy:
  - Cutaneous T-cell lymphoma
  - Squamous cell carcinoma
  - Basal cell carcinoma
  - Kaposi's Sarcoma
  - Melanoma
  - Angiosarcoma
  - Metastatic carcinoma
  - Verrucous carcinoma
- Endocrinologic Diseases:
  - Diabetic foot ulcer
  - Ulcerative necrobiosis lipoidica diabeticorum
- Hologenoderma:
  - Bromoderma
  - Iododerma
- Other:
  - Insect Bites (i.e. Brown Recluse spider)
  - Aphthous stomatitis
  - Sweets Syndrome (Acute febrile neutrophilic dermatosis)
  - Factitial ulceration
  - Drug Reaction (i.e. barbiturate overdose)
  - Sickle cell disease
  - Psychosomatic disease
  - Churg-Strauss Syndrome (a.k.a. Allergic Granulomatosis)
  - Acute febrile neutrophilic dermatosis
  - Post-op gangrene
  - Ecthyma gangrenosum
  - Pemphigus Vegetans

diagnosis of a concomitant systemic disease, for example, GI evaluation, CBC and bone marrow, preps for RA, ANA, SLE, serum protein electrophoresis, cryoglobulins, VDRL, serum bromide/iodide and evaluations for delayed-type hypersensitivities.[14,20] Minimum recommended laboratory testing of a suspected new onset PG patient including other diagnostic modalities are presented as a guideline. (Table 4)

Table 4

DIAGNOSTIC TESTING FOR PYODERMA GANGRENOSUM

CBC
CMP
ANA
RF
Hepatitis profile
Rapid plasma reagent
Serum protein electrophoresis
Urinalysis
VDRL
Antineutrophil cytoplasmic Ab test
CXR
Complete GI evaluation (upper and lower GI)
Biopsy for microbiologic and histologic examination
CRP
ESR
X-rays
MRI / bone scan (if indicated)
Bone marrow aspiration
Serum bromide / iodide
Total iron

Treatment

The management of pyoderma gangrenosum is challenging, often involving the combination of several topical and systemic therapeutic modalities. The combination of disease rarity and general lack of an understanding of its true pathogenesis causes increased difficulty when attempting to provide the most effective treatment options. The prognosis for a patient diagnosed with pyoderma gangrenosum is entirely dependent on prompt recognition of the entity and initiation of treatment. Treatment begins with a comprehensive therapy regiment for the underlying associated systemic disease when applicable.[3,27]

Local wound care may be effective in mild, early stage pyoderma gangrenosum in conjunction with topical therapy. Wet-to-dry dressings, bio occlusive semipermeable dressings, rest and elevation serve to promote reepithelialization and improve symptoms. Proper wound care also serves to enhance and prolong the function of topical medications, for instance, potent topical steroids. In regard to lesion débridement one must remember PG's tendency for pathergy. Removal of only the loose peripheral sloughing skin is recommended over aggressive sharp débridement wound therapies.

Topical applications of corticosteroids have been shown to dramatically improve early stage lesions but are deemed ineffective in advanced or recurrent lesions.[2,3,28] Intralesional injections of corticosteroids or cyclosporine has proven not only to hasten healing but to actually halt the progression of even advanced ulcers when used as an adjunct to systemic therapies.[2,3,28,29] Tacrolimus, formerly F-506, has shown promising results in clinical trial as a topical therapy not reliant on concomitant systemic treatment.[3] Other topical options include hyperbaric oxygen, nicotine patch, and sodium cromoglycate, all of which have not been well-studied. A summary of topical treatment modalities is provided. (Table 5)

Systemic corticosteroid therapy is generally required in cases of severe disease remaining one of the most successful methods studied.[3,28,29] The administration of corticosteroids halts the advancement of existing ulcerations while preventing the development of new lesions.[3] Initially, high doses of prednisone are recommended, 100-200 mg daily, with a slow gradual taper employed to discontinuation after the lesion has completely resolved. It is imperative that the cessation of steroid utilization occur gradually, and under diligent supervision, for if withdrawn to quickly can lead to reoccurrence with potential severe exacerbation. The adverse effects of long-term usage of systemic corticosteroids may be avoided by also administering steroid-sparing agents know to have an antiinflammatory effect.[3,28]

Dapsone and other sulfa drugs, like prednisone, are very widely utilized in the treatment of pyoderma gangrenosum.[28,30] They are not relied upon for their antimicrobial action but rather utilized because of their effects in altering neutrophilic function and their actions as anti-inflammatory agents.[26] Dapsone has proven successful as a solitary agent in mild disease in dosages of up to 400 mg/day. In aggressive, severe cases, dapsone may augment the function of tapered or pulsed corticosteroids and intralesional steroids as well.[28,30]

Recalcitrant or severe disease has been successfully treated with immunosuppressive medications, most notably cyclosporin, an immunosuppressive agent.[31,32-34] Still, immunosuppressive agents are most effective when combined with corticosteroid therapy.[3,28,29,32,34] A complete list of successfully employed systemic treatment options for pyoderma gangrenosum is provided. (Table 6)

Surgical intervention as a treatment for pyoderma gangrenosum is an area of contention. Most authors agree

that any débridement or attempt at skin grafting brings a significant risk for promoting exacerbation or new ulcerations due to PG's associated pathergy, discussed earlier.[3,28] If surgical intervention is required due to an underlying systemic illness, the most widely accepted strategy includes delaying any non-emergent surgery until the course of ulceration has remised. This preferential delay also applies to the patient still being treated with anti-inflammatory and/or immunosuppressive agents.[3,28,29,35] Others believe the effects of pathergy can be avoided with aggressive, yet careful débridement and allogenic skin grafting employing careful plastic closure techniques thereby minimizing any additional puncture trauma to the skin.[35]

CONCLUSION

PG as a disease entity remains one of many pathologic manifestations without a defined etiology, or diagnostic criteria. Its diagnosis is based on its clinical appearance and course of presentation. The presence of underlying systemic comorbidity can aid the practitioner by cluing him in the right realm of differential diagnoses, however with the lack of this co-association in as many as 50% of the patients it again falls on clinical suspicion and exclusion.

Treatment is another missing piece of the puzzle. The most definite protocol for successful treatment is defined when caused by a treatable underlying condition. The treatment of PG itself both systemically and locally is based on high dose steroids and/or immunosuppressive agents. Glucocorticoid therapy remains the gold standard of therapy, with Cyclosporine becoming increasingly more popular. However even these drugs are not considered effective 100% of the time, leaving the treatment if unsuccessful to trial and error.

Our treatment course would seem to us typical of a patient with this disease having undergone nearly 4 years of combined therapy without a definitive diagnosis. One can appreciate the difficulty the previously treating physicians would have had in attaining an appropriate diagnosis based on the subclinical presentation they were faced with. We believe the reason she had not expressed the full extent of the disease prior to the June 2003 presentation was her preexisting oral antiinflammatory therapies for RA/SLE. This would also explain her ability to abate and heal the partial eruptions without focused appropriate treatment. It was shortly after her discontinuation of the Plaquenil®,

Table 5

LOCAL THERAPY FOR PG[3,27,29]

Modality	Dose	Time to Healing	Notes
Intralesional corticosteroids	triamcinolone acetonide 6-40mg/ml	3-8 weeks	skin atrophy if concentration >10mg/mL, more successful in small ulcers, must avoid introducing infection
Topical corticosteroids	betamethasone 17-valerate lotion 0.1%	–	little literature exists, ineffective in most patients
Topical 5-aminosalicylic acid	10% cream daily	5 weeks	suppresses leukocyte motility and cytotoxicity
Topical sodium cromoglycate	2% aqueous solution	3 weeks	
Intralesional cyclosporine	35 mg, twice weekly	12 weeks	adverse effect = pain
Tacrolimus	(FK506)	–	inhibits transcription of pro-inflammatory cytokine genes in T-cells
Granulocyte macrophage colony stimulating factor		–	may act by correcting the local defect in chemotaxis and mediator release
Nicotine			
Hyperbaric oxygen	80+ treatments		promotes healing, relives pain, permits successful skin grafting
Topical nitrogen mustard	20% aqueous solution	12 weeks	

Table 6

SYSTEMIC TREATMENT OPTIONS[1-35]

Glucocorticoid-DOC	Prednisone 1-3 mg/kg/day PO. Decrease to approximately 75% of initial dose, or to minimum level controlling disease process.	Taper as condition resolves. Withdraw of therapy to quickly generally results in a reoccurrence, and possible severe exacerbation. May require low dose maintenance therapy to control disease processes.
	Methylprednisolone 1 gm/day IV X 5days (Pulsed Supraphamacologic doses)	To be considered in severe cases quickly gain control of the disease process. Patient then either placed on oral steroid therapy or preferably to a non-steroid medication
Immunosuppressive Agents	Cyclosporine A 5-10 mg/kg/day PO/IV	Considered by some to be the primary DOC for treatment of PG when using this class of drug. Most advantageous after/ or in combination with glucocorticoid therapy. Tapered in same manner as steroids.
	Thalidomide (Thalomid) 100-300mg/d PO	Steroid sparing function.
	Azathioprine (Imuran) 1-2mg/kg/day PO (50-200mg)	Allopurinol increases effects. Steroid sparing function.
	Methotrexate 10-25mg PO/IM/IV q wk	Steroid sparing function
	Mycophenolate mofetil 1-2g/day PO	Steroid sparing function
	Tacrolimus (Prograf) 0.05mg/kg/dayIV or 0.15-0.30mg/kg/day PO divided BID	Do not administer simultaneously with cyclosporine; tonic clonic seizures may occur
Antimicrobials	Dapsone 100-300mg/day PO	Steroid sparing function
	Sulfasalazine (Azulfidine) 2g/d PO divided QID	Steroid sparing function
	Clofazimine (Lamprene) 100mg/d PO	Dapsone may inhibit anti-inflammatory effects of clofazimine
	Minocycline 100mg/day PO BID	Steroid sparing
Others	Plasmaphoresis	
	Skin graft	Autogenous graft not recommended due to pathergy

Voltaren® and prednisone that there was a full presentation of the disease process. However, even with the complete clinical picture some of the treating physicians remained skeptical of our diagnosis until clinical cure was achieved utilizing her current appropriate therapy.

One should be suspicious of this clinical entity and other atypical ulcerative disorders when the clinical presentation does not follow a "normal" clinical course for a specific clinical entity. For example, venous stasis ulcers are usually preceded by a well know and easily recognized venous insufficiency with chronic pitting edema and typical pigmentation changes. Our patient had no such findings or complaints. In addition, she healed uneventfully from her original foot surgery with no issues of prolonged edema as a post operative complication.

Arterial ulcers are typically exquisitely painful,

punched out lesions with a classic presentation that is not suppurative in nature. Typically located on the medial pretibial area this was a consideration early in the patient's presentation. Our patient's diagnosis became clearer as we further investigated and researched potential etiologies. Diligence and persistent search yielded the diagnosis of PG. With the exception of one consultant, all other individuals involved in her care agreed that this was not a typical problem, and that there appears to be an underlying atypical connective tissue disorder component as conventional treatment of ulcers had proven unsuccessful. Her predictable and rapid clinical response to the treatment of PG, once initiated, was impressive and convincing that our suspected diagnosis was correct. Her family history, particularly the similar lesion appearing on her sister, added additional weight against a typical venous or arterial ulcerative disorder. While a biopsy may have been of some additional value, we chose not to perform one based on the inconclusive findings reported in the literature and our concern of causing additional trauma to the area potentiating a pathergy response.

We also considered more likely etiologies including insect bites, factitial ulceration, and metal reaction from the retained fixation devices. However, the history, physical examination, and clinical course were not consistent with any of these potential diagnoses.

Finally, chronic lesions of any type must always be suspect for malignancy. A number of malignant skin lesions should be considered in the differential including squamous cell carcinoma, malignant melanoma, and Kaposi's sarcoma. A biopsy would be appropriate and essential to confirming a diagnosis and providing appropriate treatment recommendations.

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