REVIEW ARTICLE

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Etiology and Management of Pyoderma Gangrenosum

A Comprehensive Review

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Abstract

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by painful, necrotic ulceration. It typically affects patients in the third to sixth decades of life, with almost equal incidence in men and women. PG occurs most frequently on the lower extremities. Five clinical variants are currently recognized: classic, bullous, pustular, vegetative, and peristomal types. Half of PG cases are seen in association with systemic disease. Mimickers include infection, vascular insufficiency ulcers, systemic vasculitides, autoimmune disease, cancer, and exogenous tissue injury, among others. PG is often a diagnosis of exclusion, as there are no specific laboratory or histopathologic findings to confirm the diagnosis. PG

thus presents many clinical challenges: it is difficult to diagnose, is frequently misdiagnosed, and often requires a work-up for underlying systemic disease. Successful management of PG typically requires multiple modalities to reduce inflammation and optimize wound healing, in addition to treatment of any underlying diseases. Prednisone and cyclosporine have been mainstays of systemic treatment for PG, although increasing evidence supports the use of biologic therapies, such as tumor necrosis factor-α inhibitors, for refractory cases of PG. Here, we review the clinical presentation and pathophysiology of PG, as well as its associated conditions, diagnostic work-up, and management.

1. Definition and Clinical Presentation

Pyoderma gangrenosum (PG), first described by Brocq[1] and named by Brunsting et al.[2] in 1930, is a rare, ulcerating, neutrophilic dermatosis primarily affecting patients aged 25–54 years, without a clear gender predilection.[3,4] Epidemiologic data establishing disease incidence have yet to be published. A few single-center cohorts provide the best available estimates: one regional dermatology clinic saw 15 cases of PG out of 0.5 million patients over the course of 10 years.[4] At the Mayo Clinic in Rochester, MN, USA, 180 diagnoses of PG were made over 53 years.[5] In a survey study of 31 619 patients with chronic leg ulcers, PG represented 3% of cases.[6]

A PG lesion typically starts as a tender nodule, plaque, or sterile pustule that enlarges and erodes, over a course of days, into a sharply marginated ulcer with undermined, violaceous borders and a surrounding zone of erythema (figure 1); pain is a characteristic feature.[7] The skin and subcutis become necrotic, creating a friable wound bed often with a hemorrhagic or purulent exudate, sometimes extending as deep as muscle.[2] Cribiform or 'sieve-like' atrophic scars often form as the lesions heal. Lesions typically are multiple and recurrent,[8] and occur at areas of trauma in 25–50% of cases, a process known as pathergy (figure 2).[3]

PG lesions in adults most frequently affect the lower extremities; any anatomic site can be affected.[3,8] In children (approximately 4% of cases), PG typically involves the lower extremities, buttocks, and perineal region, as well as the head and neck.[9] PG may also involve extracutaneous sites such as the eye (scleritis and orbital inflammation[10]), the lungs (aseptic pulmonary nodules[11]), the spleen,[10] and the musculoskeletal system in the form of sterile pyoarthrosis[12] and neutrophilic myositis.[13]

There are currently five widely recognized subtypes of PG[4] (reviewed in table I): classic (ulcerative), bullous,[20] pustular,[16] vegetative,[14] and peristomal.[17-19] Cases of PG induced by drugs such as isotretinoin and sunitinib have been reported[21-24] but are generally not regarded as a distinct variant.

2. Pathophysiology

The pathophysiology of PG remains poorly understood, though is now believed to involve loss of innate immune regulation and altered neutrophil chemotaxis. Earlier hypotheses incorporated ideas of occult bacterial infection,[2] circulating autoantibodies,[3] or the Shwartzman reaction[25,26] (endotoxin-induced thrombosis with tissue necrosis). Decades of investigation have failed to support any of these initial hypotheses; however, a number of lines of evidence have strengthened the prevailing hypotheses of disease etiology, as outlined below.

2.1 Neutrophilic Dermatosis

The absence of evidence for infection, and the predominance of neutrophils in PG lesions, justifies its classification as a neutrophilic dermatosis, a spectrum that also includes Sweet syndrome (acute febrile neutrophilic dermatosis), bowel-bypass syndrome, dermatitis herpetiformis, erythema elevatum diutinum, subcorneal pustular dermatosis, and Behcet disease.[27] On biopsy, PG is characterized by the presence of inflammatory dermal infiltrates composed of mature neutrophils.[12] Although the neutrophils appear microscopically normal, a number of studies have demonstrated functional abnormality of these cells in PG. Abnormal neutrophil trafficking was described in one patient with PG with increased integrin CR3 and CR4 expression and dysregulated integrin signaling.[28] The importance of neutrophil dysregulation in the pathogenesis of PG is reinforced by the clinical response to anti-neutrophilic agents such as colchicine and dapsone, which disrupt neutrophil chemotaxis and phagocytosis.[29,30]

2.2 Autoinflammatory

Building upon the evidence for neutrophil dysfunction, a growing body of data favors the hypothesis that PG is a systemic autoinflammatory disease resulting from dysregulated innate immunity.[31] The association of PG with known autoinflammatory diseases such as Crohn disease and Behcet disease,[32] as well as the

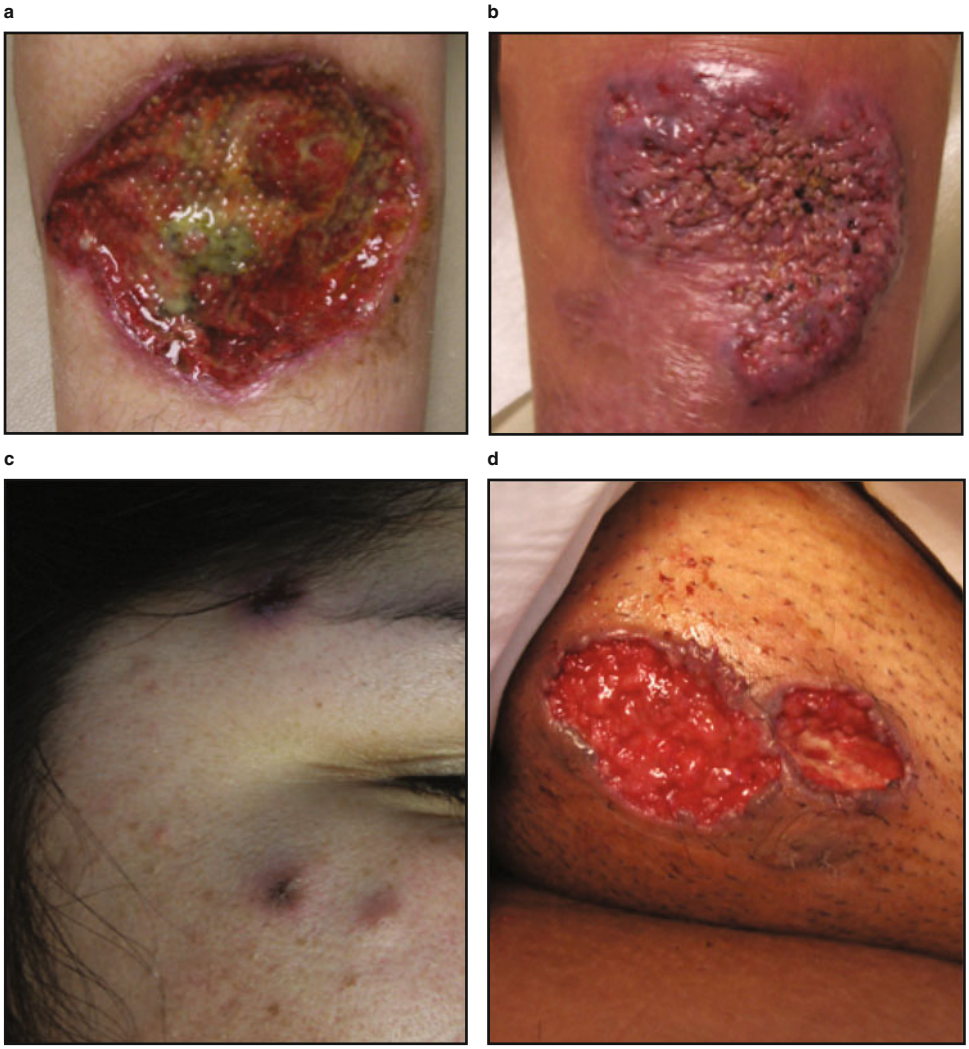

Fig. 1. Pyoderma gangrenosum (PG) lesions. (**a**) PG ulcer in a young female patient with IgA vasculitis. (**b**) Cribiform PG ulcer associated with inflammatory bowel disease and lymphoma. Early pustular (**c**) and late ulcerative (**d**) lesions of PG in a female patient with inflammatory bowel disease and overlap syndrome of hidradenitis suppurativa and PG.

elevation in markers of systemic inflammation such as erythrocyte sedimentation rate[33] even in idiopathic PG, argue in favor of PG as a systemic autoinflammatory process. This is further supported by the requirement for systemic therapy in many cases of PG, and the discordance in disease activity between PG and its associated systemic diseases.[32] Recently observed associations between PG and another cutaneous disorder, hidradenitis suppurativa, supports the notion that both are on a spectrum of autoinflammatory syndromes,[34,35] or perhaps a convergent skin manifestation shared by a number of systemic illnesses.

2.3 Genetic

Rare familial forms of PG have been reported.[36,37] The recently described PAPA syndrome (pyogenic sterile arthritis, PG, and acne, Online Mendelian Inheritance in Man [OMIM]: 604416) is an autosomal dominant autoinflammatory disorder initially mapped to chromosome 15q.[38,39] PAPA syndrome arises from mutations in the gene encoding proline/serine/threonine phosphatase-interacting protein 1 (*PSTPIP1*; also known as CD2 antigen-binding protein 1, *CD2BP1*) on chromosome 15q24–25.1.[40] PSTPIP1 protein binds to pyrin, a regulator of the cryopyrin inflammasome. Mutations in *PSTPIP1* may result in dysregulation of the cryopyrin inflammasome, activating interleukin (IL)-1β cytokine production and ensuing inflammation.[41] Although its relevance remains unclear for idiopathic PG cases, this discovery helps elucidate a potential pathway by which inflammation may be triggered in PG. PG has also been associated with other genetic diseases of immunity, including chronic granulomatous disease,[42]

leukocyte adhesion deficiency,[43] and complement C2 and C4 deficiency.[44]

2.4 Cytokines

Various cytokines essential for leukocyte signaling may have a role in PG. IL-8 is an important neutrophil chemokine that is over-expressed in PG. PG-like ulcers have been induced in human skin xenografts transfected with recombinant IL-8.[45] IL-16 also functions in neutrophil chemotaxis. Its gene maps to 15q25 and, like IL-1β, may be over-expressed in PAPA syndrome.[41] A few cases of PAPA syndrome have reported improvement in PG with the IL-1 inhibitor anakinra, highlighting the importance of IL-1 in the pathogenesis of PG in that syndrome.[46]

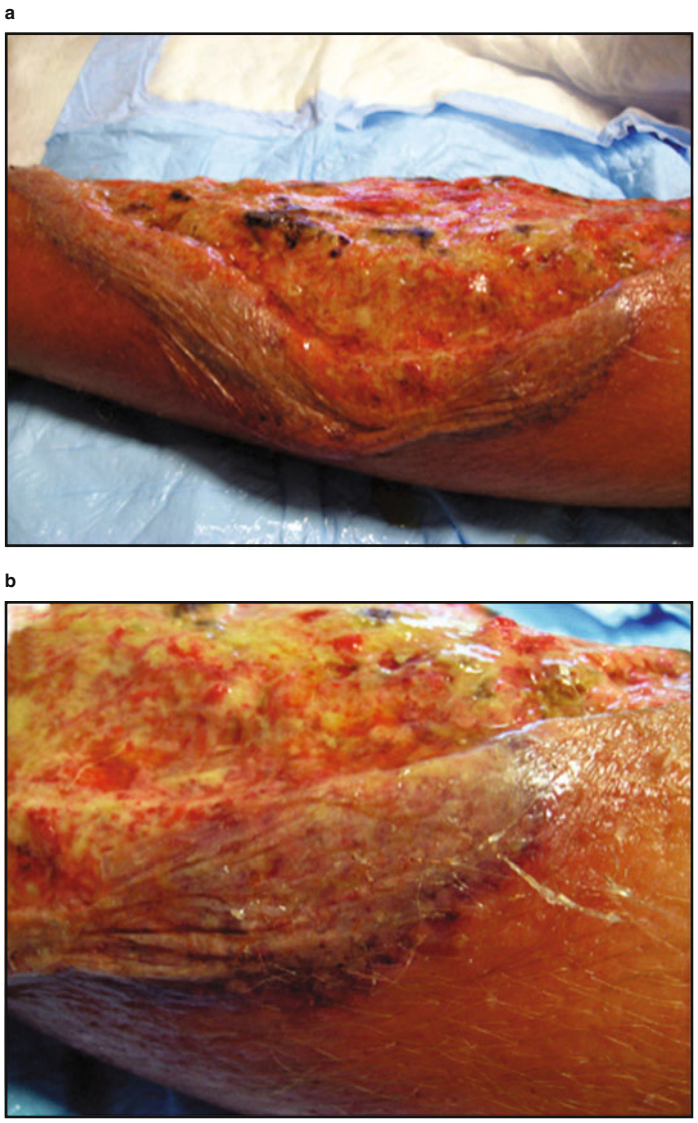

Fig. 2. (**a**) Extensive pyoderma gangrenosum ulcer of the leg associated with elective saphenous vein phlebectomy, exacerbated by repeated surgical wound debridement. (**b**) Close-up view demonstrates a violaceous, undermined border with surrounding erythema. Photograph courtesy of Michael Rosenblum, MD, PhD and Lindy P. Fox, MD.

3. Associated Conditions

Emerging evidence of the clinical efficacy of tumor necrosis factor (TNF) alpha inhibitor therapy for the treatment of PG strongly suggests a key role for this cytokine in this disease. PG is associated with underlying systemic diseases in approximately 50% of patients,[47,48] though association rates as high as 78% have been reported;[3] the remainder of cases are considered idiopathic. Inflammatory bowel disease (IBD), arthritis, and hematologic disorders are the most common disease associations. Although in most cases PG was diagnosed after the associated disease, it may also precede or be the presenting sign of an underlying disease. The courses of the two diseases are sometimes, but not necessarily, parallel.[3,32]

To fully characterize the spectrum of associated diseases, a comprehensive search of the English literature on PG was performed on 23 December 2010 using PubMed with the keywords 'pyoderma gangrenosum.' In order to identify the most consistent and plausible disease associations, single-reported associations were excluded, with the final data set limited to case series, defined as (i) a report of two or more cases of an associated disease or (ii) an aggregated patient report including some individuals with a given associated disease and some unaffected. We have adapted the classification schema for grouping the most frequently observed diseases by type, as proposed by Bennett et al.[47] An overview of the results is provided in table II and an individual discussion of the most commonly associated conditions follows in sections 3.1–3.3. Also included in table II are less frequent and possibly coincidental associations, such as hidradenitis suppurativa, systemic lupus erythematosus, and HIV, whose prevalence in association with PG is likely similar to that seen in the general population.[34,47,66,82]

3.1 Inflammatory Bowel Disease

IBDs such as Crohn disease and ulcerative colitis (UC) are the systemic diseases most frequently reported in association with PG, with 214 reports found in our review. This association was seen in up to 41% of PG cases published in the past 3 decades.[62] However, in a population-based case series from the Mayo Clinic, Rochester, MN, USA, PG occurred in 0.48% of patients with UC and 0.33% of patients with Crohn disease,[3] suggesting over-representation of IBD in published PG case series.

Table I. Subtypes of pyoderma gangrenosum

Type	Clinical presentation and morphology	Notable features on histopathology	Typical location	Associated systemic disease	References
Ulcerative 'classic'	A single or a few small pustules without an inflammatory halo that rapidly ulcerate with inflamed, violaceous, undermined borders. Painful and often associated with systemic illness	Subcorneal collections of neutrophils; endothelial cell swelling; fibrin deposition in dermal vessel walls with thrombosis	Ulcers in sites of minor trauma are common. Most frequently on lower extremities	IBD; seronegative arthritis; RA; sacroiliitis; monoclonal gammopathy; malignancy	3
Vegetative	Usually a single superficial ulcer with rapid response to treatment. May form sinus tracts. Less aggressive than classic PG. Responds well to topical treatment	Pseudoepitheliomatous hyperplasia, dermal neutrophilic abscesses, sinus tracts, palisading granulomatous reaction	Typically on trunk, lacks the violaceous undermined border or pustular base seen in ulcerative PG	No systemic diseases	14
Bullous	Rapidly spreading, painful superficial bullae with inflamed blue-gray borders that break down to form ulcers. Less destructive than ulcerative type	Subepidermal bullae with intra-epidermal and dermal neutrophilic infiltrate	Affects face, upper more than lower extremities	Myeloproliferative disorders (most common): leukemia, myelodysplasia. Also IBD	14,15
Pustular	Rare, painful pustular lesion(s), often symmetric, with erythematous halo	Subcorneal pustules with perifollicular neutrophilic infiltrate, dense dermal neutrophilic infiltrates, subepidermal edema	Legs and upper trunk	IBD (most common); less common: jejunoileal bypass; PCV; hepatobiliary disease	16
Peristomal	Painful erythematous to violaceous papules that erode into ulcers with violaceous, undermined borders	Neutrophillic collections with granulation tissue and a mixed dermal inflammatory infiltrate	Occurs near stoma sites	IBD; enteric malignancies; monoclonal gammopathy; connective tissue disease	17-19

IBD = inflammatory bowel disease; **PCV** = polycythemia vera; **PG** = pyoderma gangrenosum; **RA** = rheumatoid arthritis.

A more recent prospective cohort study of 2402 French patients with IBD found PG in 0.75% of their patients, with no association between severity of IBD and presence of PG.[83] In the setting of IBD, the fluctuation of disease activity of PG may parallel that of IBD,[32] though frequently it does not.[8,84] However, the case for a related etiology is strengthened by reports of total proctocolectomy in a PG patient with UC leading to resolution of the PG. In one case series, PG lesions improved in all nine patients with UC following total proctocolectomy.[3]

3.2 Arthritis

PG is frequently associated with various arthritides, most commonly seronegative arthritis of a single, large joint,[85] though rheumatoid arthritis and ankylosing spondylitis are also common.[3,47] In our review, 83 cases were reported. An association as high as 37% was reported in one series.[3] The clinical severity of the arthritis is unrelated to PG activity.[4] While there is a significant subset of PG patients affected by both IBD and arthritis,[62,69] arthritis is more frequently seen in non-PG-associated IBD.

3.3 Hematologic Abnormalities, Paraproteinemias, and Malignancy

Hematologic abnormalities and hematologic malignancies (excluding paraproteinemias) were seen in 35 reports in our review, with 36 cases of paraproteinemia reported. Monoclonal gammopathy, most frequently IgA,[74] is the most common associated paraproteinemia with the reported association rate of 18%.[3] Though they usually remain clinically benign, these gammopathies occasionally progress to myeloma;[74] the likelihood of progression in PG-associated versus non-PG-associated monoclonal gammopathy has not been studied. Classic, ulcerative PG is the most common variant seen in monoclonal gammopathy, though bullous PG is seen in myeloma patients.[47] A variety of

Table II. Pyoderma gangrenosum disease associations[a]

Disease	Frequency of reported association	Articles and cases	Calculated percentage association[b] and other features	Reference
Inflammatory bowel disease	Common	25 articles (214 patients): 144 patients with UC 68 patients with CD 2 patients with indeterminate colitis 48 patients with peristomal PG	118 IBD cases of 398 PG patients = 29.6% (excludes cases of peristomal PG)	
		Of 18 PG patients, 3 with UC (17%)		49
		2 UC patients who developed peristomal PG		50
		Of 580 CD patients, 9 with PG (1.5%). Of 370 UC patients, 8 with PG (2.2%)		51
		Of 289 UC patients with ileal pouch-anal anastomosis, 6 with PG (2%)		52
		Of 352 IBD patients (234 UC, 118 CD), 8 with PG 6 UC patients with PG (2.5%), 2 CD patients with PG (1.7%)	Higher incidence of PG in patients with IBD-associated arthritis	53
		Of 7 PG patients, 3 with CD (43%)		54
		Of 17 peristomal PG patients, 14 with UC, 2 with CD, 1 with indeterminate colitis		55
		Of 404 IBD patients (212 UC and 192 CD), 3 UC patients with PG (1.4%) and 1 CD patient with PG (0.5%)	Retrospective chart review of inpatients	56
		4 peristomal PG patients, all with CD	Diagnosis of peristomal PG was based on clinical appearance alone in 83% of cases. This paper also reviewed 20 previously published cases: of these, 11 CD, 9 UC	17
		Of 5 cases of PG, 4 patients had UC (80%)	First published characterization of PG	2
		Of 138 cases of CD, one with PG (0.7%)		57
		Of 62 PG patients, 31 (50%) had chronic UC	4 of these patients had small intestine involvement raising the question of CD. 25 of the 31 UC patients had colitis prior to onset of PG lesions	58
		Of 415 patients with UC, 7 with PG (2%)	No association with extent or severity of UC	59
		2 UC patients who presented with PG at time of UC exacerbation		16
		Of 15 PG patients, 4 had IBD (27%): 1 with UC (7%) and 3 with CD (20%)		60
		Of 15 PG patients, 2 with UC (13%)	In both cases PG developed while UC was active	61

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Table II. Contd

Disease	Frequency of reported association	Articles and cases	Calculated percentage association[b] and other features	Reference
		Of 85 patients with PG, 31 had IBD (36%) of which 17 had UC (20%) and 14 CD (16%)	IBD pre-existing at time of PG diagnosis in 29 patients	3
		Of 22 PG patients, 9 with IBD (41%): 7 UC, 2 CD		62
		5 cases peristomal PG: 2 UC, 3 CD		63
		Of 44 PG patients, 6 with IBD (14%): 3 UC (7%), 3 CD (7%)		48
		Of 86 PG patients, 19 with IBD (22%): 10 UC (12%, of which 1 atypical PG), 9 CD (10%)	64 typical PG, 22 atypical/bullous PG	47
		20 patients with peristomal PG complicating IBD: 10 CD and 10 UC	All but 1 case of CD diagnosed prior to appearance of PG lesions	19
		Of 21 PG patients, 5 with IBD (24%) of which 4 UC (19%) and 1 CD (5%)		64
		2 IBD (1 UC, 1 indeterminate colitis)	IBD did not worsen with flares of PG	65
		18 PG patients, 2 (11%) with IBD (1 UC, 1 CD)		66
Arthritis	Less common	13 articles (83 patients): 35 patients with RA 47 patients with seronegative arthritis 1 seropositive IBD-associated arthritis	77 arthritis cases of 348 total PG patients = 22%	
		Of 18 PG patients, 4 with seronegative arthritis		49
		Of 36 RA patients with leg ulcers, 2 with PG		67
		Of 86 PG patients, 10 with RA (12%, one in atypical PG) and 6 with seronegative arthritis, non-osteoarthritis (7%, 3 typical and 3 atypical PG)		47
		2 patients with RA who developed PG with features of leukocytoclastic vasculitis		68
		Of 18 PG patients, 1 with RA		66
		Of 15 PG patients, 3 with arthritis (all seropositive RA)	Of CD cases: 1 colitis, 1 ileocolitis, 1 regional enteritis	60
		Of 15 PG patients, 8 total with arthritis (53%): 6 with erosive seronegative polyarthritis, 2 with RA		69
		Of 21 PG patients, 1 with RA		64
		Of 85 PG patients, 29 (34%) had arthritis: 4 had RA, 13 seronegative IBD-associated arthritis, 9 seronegative non-IBD-associated arthritis, 3 with ankylosing spondylitis	3 patients with osteoarthritis in this article excluded	3

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Table II. Contd

Disease	Frequency of reported association	Articles and cases	Calculated percentage association[b] and other features	Reference
		Of 22 PG patients, 9 with arthritis (41%): 2 RA, 4 seronegative IBD-associated, 1 seropositive IBD-associated, 2 seronegative (non-IBD-associated)		62
		2 patients with RA who then developed PG		70
		Of 44 PG patients, 5 with RA (11%)		48
		Of 25 PG patients, 1 with RA (4%)	All of these patients had superficial granulomatous, 'vegetative' PG	14
Hematologic malignancy and other hematologic abnormality (excluding MG)	Less common (most frequent association with bullous PG)	11 articles (35 patients): 5 patients with acute leukemia 8 patients with chronic leukemia 3 patients with lymphoma 3 patients with PCV 2 patients with myeloma 10 patients with myelodysplastic syndromes 2 patients with myelofibrosis/myeloid metaplasia 2 others	19 hematologic malignancy/abnormality (excluding MG) of 341 total PG cases = 5.6%	
		Of 18 PG patients, 1 with PCV and 1 with CML		49
		Of 86 PG cases, 7 with hematologic abnormality: 1 IgA myeloma, 1 Hodgkin lymphoma, 1 myeloma, 4 myelodysplasia	Myeloma was in the setting of POEMS syndrome	47
		Of 4 PG patients, 1 myelodysplastic sydrome, 1 AML, 1 CLL, 1 PCV evolving into AML (all died within 2 years of PG development)	2 with concurrent disease, 2 who developed PG 5 years after hematologic disease. Also reviewed 138 previously published PG patients from 4 reviews, of whom 10 had an underlying malignancy	71
		Of 3 PG patients, 1 with CML, 1 with AML, 1 with refractory anemia with excess of blasts (myelodysplastic syndrome)	All with atypical/bullous PG	72
		Of 6 PG patients, 4 with myelodysplasia, 1 with acute leukemic transformation of myelofibrosis, and 1 with *de novo* AML	All with atypical/bullous PG	73
		Of 21 PG patients, 1 with CLL, 1 with autoimmune anemia, 1 with B-cell lymphoma		64
		Of 62 PG patients, 1 with myeloid metaplasia		58
		3 patients with bullous PG as presenting sign of leukemia (1 acute leukemia, 2 chronic)	PG features seen on biopsy	20
		Of 85 PG patients, 1 with acute myelomonocytic leukemia, 1 with PCV		3

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Table II. Contd

Disease	Frequency of reported association	Articles and cases	Calculated percentage association[b] and other features	Reference
		Of 44 PG patients, 1 with CML, 1 with plasmacytoma, 1 with CLL, 1 with mycosis fungoides		48
		Of 25 PG patients, 1 with CLL	All of these patients had superficial granulomatous, 'vegetative' PG	14
Monoclonal gammopathy	Less common	8 articles (36 patients)	36 MG of 358 total PG cases = 10.1%	
		Of 15 PG patients, 3 (20%) with 'IgA myeloma' meeting current clinical criteria for MG	2 cases of IgG gammopathy (kappa), 1 case of IgG gammopathy (lambda)	69
		Of 86 PG cases, 6 (7%) with MG	4 cases of typical PG and 2 cases of atypical/bullous PG	47
		Of 18 PG patients, 2 with MG (11%)		66
		Of 63 PG patients, of whom 8 (13%) had MG, all except one had IgA gammopathy	7 patients had a benign course, one developed multiple myeloma. In seven patients, PG preceded MG. MG did not affect clinical features, course, or therapy of PG	74
		Of 85 PG patients, 9 (11%) had MG (7 with IgA, 1 with IgM, 1 with IgG, no light chain majority – 4 with kappa chains and 5 with A). At time of publication, only one had gone on to develop multiple myeloma	In all patients, the MG was detected either concurrently with or after the diagnosis of PG	3
		Of 22 cases of PG, 4 (18%) found to have IgA gammopathy	3 kappa light chain, one lambda. Of note, in general MG population, only 10% are IgA[75]	62
		Of 44 PG patients, 3 (7%) with benign paraproteinemia		48
		Of 25 PG patients, 1 with IgA paraproteinemia	All of these patients had superficial granulomatous, 'vegetative' PG	14
Hidradenitis suppurativa	Rare	3 articles (16 patients)	5 HS cases out of 106 total PG patients = 4.7%	
		11 patients with HS presenting with PG lesions a median of 2.5 yrs post-HS development	All patients required multiple therapeutic agents because their diseases were often poorly responsive to standard therapies	34
		Of 85 PG patients, 4 with HS		3
		Of 21 PG patients, 1 with HS		64
PAPA syndrome	Rare genetic disorder	2 articles (15 patients)	N/A	
		Family with 5 members affected over 3 generations	All shared E250Q mutation on the *CD2BP1* gene on chromosome 15	76
		Family with 10 members affected, autosomal dominant pattern	Original paper describing PAPA syndrome	38

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Table II. Contd

Disease	Frequency of reported association	Articles and cases	Calculated percentage association[b] and other features	Reference
Pulmonary disease	Rare/questionable	2 articles (9 patients)	N/A (sample size insufficient)	
		Of 85 PG patients, 4 had pulmonary disease	Asthma, COPD	3
		Of 62 PG patients, 5 had history of 'inflammatory pulmonary disease' but no pathologic diagnosis made		58
Systemic lupus erythematosus	Rare	5 articles (7 patients)	N/A (sample size insufficient)	
		Of 18 PG patients, 1 with SLE		66
		2 patients with PG as initial presentation of SLE		77
		Of 18 PG patients, 1 with SLE		49
		Of 150 SLE patients, 2 with PG		78
		Of 85 PG patients, 1 with SLE		3
Thyroid disease	Rare/questionable	2 articles (7 patients)	N/A (sample size insufficient)	
		2 patients who developed PG ulcers as initial manifestation of Graves disease	One patient had a history of pustular palmoplantar psoriasis and family history of IBD	79
		Of 85 PG patients, 5 had thyroid disease (6%)	Of these, 4 had Hashimoto disease and one had Graves disease	3
Solid organ malignancy	Rare/questionable	2 articles (5 patients)	N/A (sample size insufficient)	
		Of 44 PG patients, 1 with glioblastoma multiforme		48
		Of 85 PG patients, 4 had solid malignancies: 2 with adenoCA of colon, one with bladder carcinoma, one with prostate cancer	All but one patient had metastatic cancer at time of presentation for PG	3
Autoimmune hepatitis	Rare	2 articles (4 patients)	N/A (sample size insufficient)	
		Of 85 PG patients, 2 had hepatitis		3
		2 patients, one who simultaneously presented with AIH and PG, the other who presented with PG lesions after 4 years of AIH		80
Sarcoidosis	Rare	2 articles (3 patients)	N/A (sample size insufficient)	
		2 patients with pulmonary sarcoidosis who then developed PG		5
		Of 7 PG patients, 1 with sarcoidosis		54

a Additional associated diseases rarely reported in case series: Sjogren syndrome (1 case)[64], Behcet disease (1 case)[81], Takayasu arteritis (1 case)[64], mixed connective tissue disease (2 cases)[81], acne conglobata (2 cases)[3], HIV (2 cases)[82], cryoglobulinemia (2 cases).[48,64]

b Calculated using only case series of PG patients in which the cohort includes some with associated disease and some without, in order to estimate percentage of PG cases affected with the disease.

AIH = autoimmune hepatitis; **AML** = acute myeloid leukemia; **CD** = Crohn disease; **CLL** = chronic lymphoid leukemia; **CML** = chronic myeloid leukemia; **COPD** = chronic obstructive pulmonary disease; **HS** = hidradenitis suppurativa; **IBD** = inflammatory bowel disease; **MG** = monoclonal gammopathy; **N/A** = not applicable; **PAPA** = pyogenic sterile arthritis, PG, and acne; **PCV** = polycythemia vera; **PG** = pyoderma gangrenosum; **POEMS** = polyneuropathy, organomegaly, endocrinopathy, myeloma and associated skin changes; **RA** = rheumatoid arthritis; **SLE** = systemic lupus erythematosus; **UC** = ulcerative colitis.

other hematologic abnormalities have been reported in association with PG, including polycythemia vera,[3,86] agnogenic myeloid metaplasia,[87,88] and essential thrombocythemia.[89] Two interesting cases of leukemoid reaction (white blood cells >50 000/uL) with fever and elevated neutrophil precursors as the initial presentation of severe PG were recently reported for the first time; all infectious cultures were negative and the patients failed to respond to initial antibiotic therapy.[90]

Hematologic malignancy is seen in up to 7% of PG cases, with acute myeloid leukemia (AML) being the most common subtype.[71] Most cases of leukemia were preceded by a hematologic abnormality such as myelodysplastic syndrome. While 30% of all paraneoplastic PG is of the previously described bullous subtype,[20] in leukemia, two-thirds of PG is bullous. PG lesion development portends a poor prognosis in AML, with a 1-year mortality rate as high as 75%[71,91] versus 67% in all AML patients.[92] This clinical observation underscores the need for an expeditious and thorough work-up for hematologic malignancy in any patient presenting with bullous PG lesions. Similarly, development of PG in the setting of myelodysplastic or myeloproliferative syndrome may herald impending malignant transformation.[71] Improvement of bullous PG has been reported with the treatment of the underlying malignancy.[73,93] This may be explained by the presence of a leukemic cell infiltrate in the skin seen in some bullous PG lesions associated with leukemia.[94,95]

4. Diagnosis

PG remains a clinical diagnosis; it lacks specific serologic or histologic markers. Although no clinical criteria have been formally adopted, one proposed set requires the fulfillment of two major criteria: (i) rapid progression (margin expansion of 1–2 cm per day, or 50% increase in ulcer size within 1 month) of a painful, necrolytic, cutaneous ulcer with an irregular, violaceous, and undermined border; and (ii) exclusion of other causes of cutaneous ulceration; and at least two minor criteria, including (a) a history suggestive of pathergy or a clinical finding of cribiform scarring, (b) systemic diseases associated with PG, (c) histopathologic findings (sterile dermal neutrophilia ± mixed inflammation ± lymphocytic vasculitis), and (d) treatment response (rapid response to systemic corticosteroid treatment).[7]

PG is also a diagnosis of exclusion: it is crucial to rule out other etiologies of ulcers, especially infectious causes.[96] The differential diagnosis is broad (reviewed in table III). Misdiagnosis of PG as another condition is frequent and may be harmful to patients. Well demarcated ulcers may be presumed to represent factitial dermatitis, potentially causing delay in treatment or psychological distress.[97] PG may also be mistaken for infection and subjected to wound debridement, which can provoke pathergy and exacerbate disease, or result in limb amputation.[98,99] A recent study suggests that as many as 10% of PG cases are actually misdiagnoses. Actual diagnoses,

Table III. Common differential diagnoses of pyoderma gangrenosum

Vascular/neuropathic	Vascular occlusive disease (including livedoid vasculopathy, Dowling-Degos disease, ulcers of sickle cell disease, antiphospholipid antibody syndrome)
	Arterial or venous insufficiency
	Diabetic/trophic ulcer
Cancer	SCC
	BCC
	Cutaneous T-cell lymphoma
	Leukemia cutis
Exogenous tissue injury	Arthropod bite
	Factitial ulcers
	Drug-induced tissue injury
	Halogenodermas
	Calciphylaxis
Systemic vasculitis	Behcet disease
	Polyarteritis
	ANCA-associated vasculitides
	Cryoglobulinemic vasculitis
Skin manifestations of autoimmune or connective tissue disorders	Cutaneous Crohn disease
Neutrophilic dermatoses	Sweet syndrome
	Subcorneal pustular dermatosis
	Bullous lupus erythematosus
Bacterial	Impetigo
	Ecthyma
	Necrotizing fasciitis
	Anthrax
	Tuberculosis
	Atypical mycobacteria
	Buruli ulcer
	Syphilitic gumma
Viral	Chronic HSV
Protozoal	Leishmaniasis
	Amebiasis cutis
Fungal	Blastomycosis
	Histoplasmosis
	Sporotrichosis
	Cryptococcosis
	Aspergillosis
	Penicilliosis
	Zygomycosis

ANCA = antineutrophil cytoplasmic antibodies; **BCC** = basal cell carcinoma; **HSV** = herpes simplex virus; **PG** = pyoderma gangrenosum; **SCC** = squamous cell carcinoma.

delayed on average by 10 months, included vascular disease (occlusive or venous insufficiency), vasculitis, malignancies, infections, drug-induced or exogenous tissue injury, and manifestations of other autoimmune diseases.[33]

Maintaining a high index of suspicion for PG is crucial to making the diagnosis. The diagnosis of PG should be considered in patients whose wounds are painful, rapidly expanding, non-healing and unresponsive to antibiotics, or worsening with surgical debridement. Vigilant monitoring for PG is also appropriate in any patient with a frequently associated systemic disease, such as IBD, arthritis, or hematologic disorder, presenting with new skin lesions.

The minimum evaluation should include a complete history, physical examination, and skin biopsies. A thorough patient history should clarify the progression of lesions, pathergy, recent exposures, and results of prior interventions attempted. A complete physical examination is necessary to reveal lesion morphology, define all areas of involvement, and assess for evidence of concurrent systemic disease. Skin biopsies are essential both for histologic examination with routine hematoxylin and eosin and special stains for infectious organisms, as well as for culture of bacteria, viruses, fungi, and atypical mycobacteria. Direct immunofluorescence studies may be helpful to exclude autoimmune skin disease or vasculitis (though findings are neither sensitive nor specific for PG).[100] Direct immunofluorescence studies show IgM, C3, and fibrin deposits in blood vessels of the papillary and reticular dermis in a majority of PG biopsy specimens.[100,101]

In obtaining a biopsy specimen, a deep elliptical incisional biopsy is preferable over a punch biopsy, with the specimen including a portion of the lesion's edge and encompassing the subcutis.[33,100] Concern for inducing pathergy should not preclude the initial biopsy as it is essential to exclude other diagnoses, especially infection. Although nonspecific, the histopathology of PG is useful for exclusion of other conditions. The initial lesion, prior to ulceration, shows a deep suppurative, often folliculocentric inflammation with dense neutrophilic infiltrates, and a leukocytoclastic vasculitis is often present.[100] The undermined border of an ulcer shows a mixed, neutrophil-predominant, inflammatory infiltrate and the base of the lesion typically shows evidence of necrosis and hemorrhage. In a specimen taken from erythema surrounding a PG ulcer, necrosis of thrombosis of dermal or pannicular blood vessels may be seen, with a lymphocyte-predominant infiltrate.[7] Edema and lymphocytic vasculitis may also be present.

5. Work-Up

Experts recommend that a reasonable search for associated conditions is warranted in the evaluation of every case of PG,[4,32,47] though data are lacking on the predictive value of these tests. It is imperative to exclude infection or malignancy as part of the initial diagnostic work-up, especially if the patient will undergo systemic immunosuppression. No formal guidelines exist, but the emerging consensus for a work-up is presented here. Routine laboratory tests such as complete blood count with differential, electrolytes, urinalysis, and liver function tests may be helpful as an initial screen for hematologic disorders, liver or kidney dysfunction related to a variety of possible associated conditions, and hepatitis. Additional studies are helpful in excluding systemic disorders: anti-nuclear antibody, coagulopathy panel including antiphospholipid antibody test, cryoglobulins, rheumatoid factor, and circulating antineutrophil cytoplasmic antibodies. Further work-up for associated conditions may include chest x-ray (for infections or systemic vasculitis), fecal occult blood test and sigmoidoscopy or colonoscopy for IBD, and evaluation for hematologic disease (serum protein electrophoresis, urine spot protein or urine protein electrophoresis, immunofixation electrophoresis, peripheral smear, and bone marrow biopsy), especially in cases of bullous PG.[47,93,102] Infectious causes should be excluded including HIV, hepatitis serologies, and rapid plasma reagin, if risk factors exist.

A thorough neurologic exam should be performed. Radiologic studies may help exclude underlying osteomyelitis, and Doppler ultrasound can be useful in cases where vascular occlusion or insufficiency is suspected. Serum levels of iodide and bromide may help rule out halogenodermas.[47] Though nonspecific, elevated erythrocyte sedimentation rate and a serum neutrophilia are often seen with PG.[33]

6. Treatment

There is no gold standard for the treatment of PG. PG has both a systemic inflammatory component and a wound component, thus an effective treatment strategy must address both processes.[47] A combination of local wound care, topical, and/or systemic therapy is ideal, as proposed in our treatment algorithm (figure 3). In order to synthesize this treatment algorithm, a comprehensive search of the English literature for PG was performed on 20 January 2012 using PubMed with the keywords 'pyoderma gangrenosum' alone and in combination with 'treatment,' 'refractory,' 'corticosteroids,' 'cyclosporine,' 'topical,' 'biologics,' 'therapy,' and 'wound care.'

Goals of therapy are to control inflammation, reduce pain, optimize wound healing, and to minimize exacerbating factors. Treatment decisions should be made based on the size, number, location, and type of PG lesions, the progression of lesion

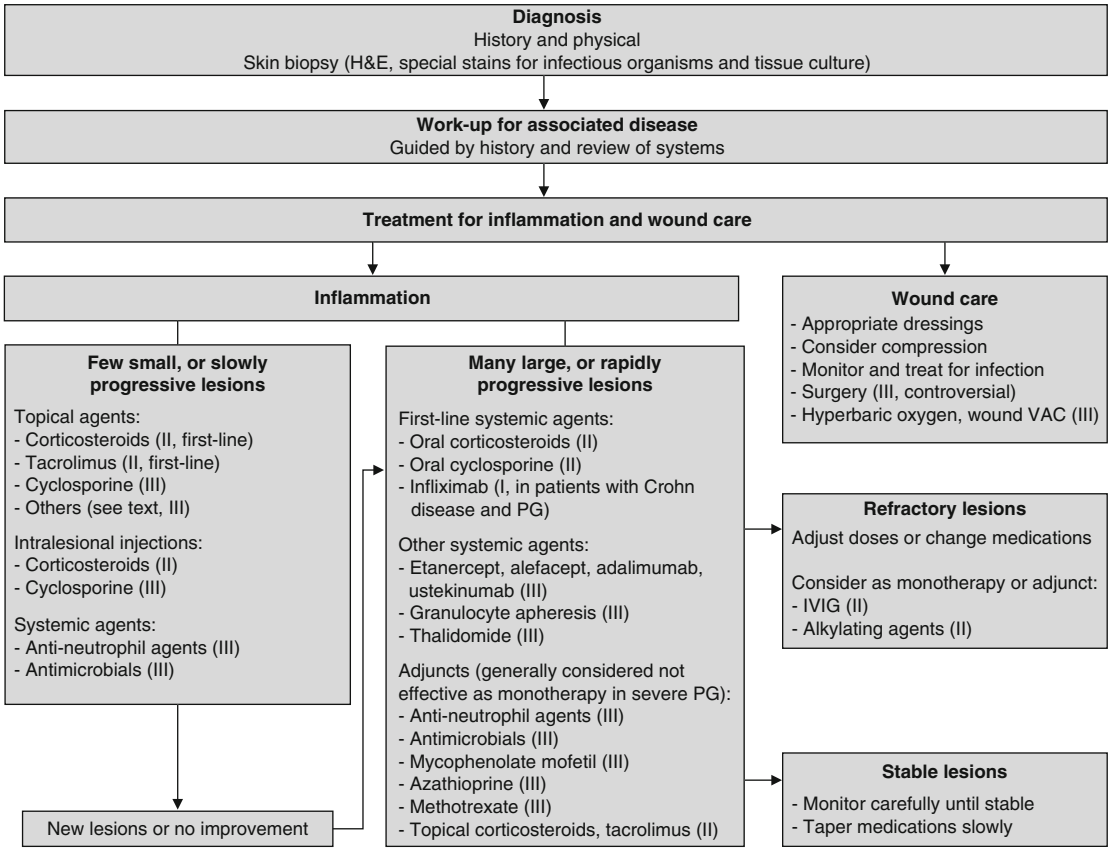

Fig. 3. Diagnostic and therapeutic algorithm for pyoderma gangrenosum (PG). **H**&**E** = hematoxylin and eosin; **IVIG** = intravenous immunoglobulin; **VAC** = vacuum-assisted closure. Level I = prospective controlled trials; Level II = retrospective studies, small uncontrolled trials, large case series, many case reports; Level III = small case series or single case reports.

formation, and the presence of an underlying disease. It is important to measure and record the size and depth of the lesion at each clinical evaluation. The initial approach should begin with optimizing wound care, achieving pain control, topical therapy, and the use of antimicrobial or anti-neutrophilic agents, especially for cases in which a diagnostic work-up is ongoing to exclude occult infection or malignancy. Systemic immunosuppression should be considered, especially in the setting of rapidly evolving PG.

PG lesions are almost universally painful. Pain management should include both regular pain level monitoring and judicious use of NSAIDs, opioids, and pain specialist and psychiatric consultants as needed for patients affected by chronic pain or depression.[103] When monitoring therapy, early relief of pain may be the first sign of healing before evidence of ulcer re-epithelialization.

Lesions of PG are often refractory to treatment and require multiple trials of medications or concomitant use of multiple medications before an effective therapy is found. One retrospective analysis noted an average of 12 months to healing in 86 patients with PG.[47] Physicians must set realistic expectations, maintain close follow-up, and create individualized therapeutic strategies. Smoking cessation, glycemic control in diabetes mellitus, optimizing nutrition, and minimizing edema (if present, as in venous insufficiency) may be important adjunctive interventions. The effects of smoking cessation on PG are controversial yet noteworthy. Multiple, large, retrospective and prospective studies demonstrate increased rates of wound infection and reduced rates of healing of post-operative wounds in smokers.[104] In contrast, there is evidence that topical nicotine may be beneficial in refractory PG, as reported in one case of an IBD patient with PG ulcers completely resolving with nicotine patches[105] and two cases of PG successfully treated with topical nicotine cream.[106]

6.1 Wound Care

Optimizing wound care is essential for the successful treatment of PG. Moisture-retentive occlusive dressings such as films and hydrogels are recommended for chronic wounds as

they increase the rate of re-epithelialization, promote angiogenesis and collagen synthesis, and provide a barrier to infection.[107] However, these dressings may not be appropriate for highly exudative lesions as they can trap excessive moisture, leading to maceration of surrounding skin. In these lesions, more absorptive dressings such as hydrocolloids, foams, and alginate fibrous dressings or the use of iodine cadexomer starch gel pastes under dressings are more appropriate.[107] Wet to dry dressings should be avoided, as the debridement associated with dressing removal may trigger pathergy. The area around the wound can also be susceptible to irritation or allergy due to adhesive tape and topical antibiotic ointments. Barrier ointments including zinc oxide and petrolatum can help to protect these areas. Layering petrolatum-impregnated gauze over the topical agents and the peripheral edges of the ulcer may prevent trauma caused by overlying bandages. Compression can be useful if edema is present and there is no evidence of arterial insufficiency.[108]

It is imperative to monitor for signs of infection including fever, skin warmth, edema, erythema and lymphangitic streaking, foul odor, increased drainage, and pain. Topical antimicrobials such as mupirocin ointment are effective for Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, while topical metronidazole is effective for anerobic organisms. Silver sulfadiazine is effective for many common skin pathogens including Gram-negative bacilli; however, it may have toxic effects on keratinocytes.[107] Topical antimicrobials such as bacitracin and neomycin commonly induce contact dermatitis and should be avoided.[109] Topical antimicrobials can lead to bacterial resistance and delayed wound healing with inappropriate use, and should be utilized only when clinically significant infection is confirmed and not as empiric therapy.[110] Acetic acid soaks may be helpful to limit *Pseudomonas aeruginosa* biofilm development. If there is evidence of a deeper tissue infection, such as cellulitis or lymphangitis, appropriate oral antibiotics should be prescribed, guided by bacterial culture and antibiotic susceptibility data.

6.2 Topical Medications

Topical medications are important in the treatment of PG both as monotherapy for mild and superficial lesions and also as adjuncts to systemic treatment. Topical therapies offer the benefit of fewer adverse effects and contraindications compared with systemic regimens; however, they require frequent application, sometimes several times a day. Although there is a paucity of literature regarding topical therapy for PG, most authors agree that topical corticosteroids, topical tacrolimus, and topical cyclosporine are important components of the therapeutic algorithm.[102,111-116] Investigators recommend the use of topical agents specifically at the inflamed border of the ulcer and not within the ulcer base.

In one of the few comparative trials in the literature on the treatment of PG, 24 patients with peristomal PG were treated with either topical tacrolimus 0.3% or topical clobetasol propionate 0.05%.[117] Seven of 11 patients in the tacrolimus group had complete healing of their lesions compared with 5 of 13 in the clobetasol group (no p-value given). In this study, complete healing with tacrolimus occurred in an average of 5.1 weeks versus 6.5 weeks with clobetasol (not statistically significant) and tacrolimus was more effective in PG lesions greater than 2 cm ($p < 0.05$).[117] Caution should be advised when using topical tacrolimus as it can be highly absorbed through ulcerated tissue; serum tacrolimus levels have been shown to be equivalent to those achieved in systemic tacrolimus administration even when applied to limited (<5%) body surface area.[118] Topical cyclosporine (ophthalmic preparation) may not have similar concerns for systemic absorption, as several reports indicate serum cyclosporine levels in the subtherapeutic range and minimal adverse effects with topical use.[112,116]

Additional reports describe success with other topical agents. 5-Aminosalicyclic acid is the active component of sulfasalazine, which is commonly used to treat IBD. One report describes full healing of a PG lesion in a patient with Crohn disease after topical application of 10% 5-aminosalicylic acid for 5 weeks.[119] Additionally, Braun-Falco et al.[120] reported a case of PG with accelerated healing after application of the topical platelet-derived growth factor, becaplermin. One percent sodium cromoglycate has also been reported to be effective in a case series of five patients with PG with complete healing of all lesions within 5–8 weeks.[121] Cromoglycate may be effective in wound healing through inhibition of mast cell degranulation and platelet activation, and down-regulation of neutrophil chemotaxis.[121,122] Chlormethine (mechlorethamine or nitrogen mustard) is an alkylating agent often used in cancer therapy and has immunosuppressive and anti-inflammatory properties; Tsele et al.[123] reported a single case of complete resolution of a PG lesion with 20% topical nitrogen mustard.

6.3 Intralesional Therapy

Moschella[124] first reported the use of intralesional corticosteroids (6 mg/mL) in PG with complete healing in 21 days. Intralesional corticosteroids have since been described as a useful adjunct to systemic treatment for PG. Various concentrations (up to 40 mg/mL) of corticosteroids and at varying

dosing schedules have been used successfully in PG according to the literature.[125] Two unusual cases of deep retrosternal and maxillary sinus PG were treated successfully with dexamethasone flushes via catheter.[76] Intralesional corticosteroids should be used with caution as too frequent injections or an excessively high concentration of corticosteroid can lead to pathergy and disrupt wound healing.[110] Intralesional injections every 4–6 weeks likely balances pathergy risk with the anti-inflammatory benefits of this treatment. Intralesional cyclosporine has also been reported to be effective in healing lesions of PG in a single patient.[126]

6.4 Surgery

The role of surgical treatment in PG is controversial as 25–50% of PG lesions demonstrate pathergy and theoretically could worsen with surgical intervention.[108,127] Nonetheless, there are reports of excellent outcomes after surgery including the use of gentle debridement, a free flap to cover a large lesion, and the use of cultured keratinocyte autografts.[128-130] Split-thickness skin grafting has been shown to alleviate pain in PG.[108] In general, surgical intervention should be considered on a case-by-case basis and should only be used as an adjunct to anti-inflammatory treatment.

Strategies to prevent pathergy or disease exacerbation include ensuring the patient's PG is clinically quiescent prior to surgery.[131-133] Systemic therapy should be tapered slowly postoperatively, as abrupt cessation has been shown to result in recurrence.[131,133] Pathergy may be avoided by the use of subcuticular sutures or surgical tapes or glues as alternatives to suturing.[132]

Reported adjuncts to surgery in PG include the use of wound vacuum-assisted closure (VAC) devices, with two case reports demonstrating healing in patients with stable PG.[130] VAC devices utilize subatmospheric pressure applied to the wound surface leading to reduction of local edema, increased perfusion, and enhanced cellular proliferation. Hyperbaric oxygen has also been postulated as an effective adjunct to surgery in PG by increasing oxygen delivery to the ulcer.[110]

6.5 Systemic Treatments

Effective treatment of PG may require systemic therapy. Choice of agent includes consideration of potential adverse effects, the medical history and general health of the patient, and in relevant cases, the patient's underlying disease. Whereas corticosteroids and cyclosporine were previously considered first-line treatments, the emergence of TNFα inhibitors is transforming the therapeutic ladder, with infliximab being the only systemic agent with level I evidence supporting its use for the treatment of PG.

6.5.1 Anti-Neutrophilic Therapies

Colchicine has anti-mitotic and immunomodulatory properties by interfering with neutrophil chemotaxis and phagocytosis and has demonstrated efficacy as an adjunct to corticosteroid therapy.[134] It was also used successfully as a monotherapy at a dosage of 0.6 mg three times a day in a case of penile PG.[29]

The mechanism of action of sulfonamides and sulfones is not completely understood but likely stems from inhibition of neutrophil chemotaxis. Dapsone is effective in other neutrophilic disorders such as Sweet syndrome, erythema elevatum diutinum, and subcorneal pustular dermatosis. Alone or in combination with corticosteroids, dapsone has been used successfully in PG at a dosage of 50–200 mg/day.[30,135,136] Dapsone was used successfully as a monotherapy in a patient with PG and Behcet disease.[137] Adverse effects include methemoglobinemia, anemia, and neuropathy. Topical dapsone has also recently been reported to be effective in improving peristomal PG.[138] Topical application appears to cause significantly lower (100-fold less) systemic levels of dapsone and its metabolites, likely protecting against dose-dependent hematologic reactions.[139]

6.5.2 Antimicrobials

Minocycline and other tetracyclines exhibit anti-inflammatory properties by decreasing neutrophil chemotaxis. One report of four cases showed successful treatment with minocycline 200–300 mg/day with response noted in weeks.[140] Clofazimine is another antimicrobial agent with anti-inflammatory properties, with conflicting reports of its efficacy in PG.[110]

6.5.3 Corticosteroids

The literature demonstrates that systemic corticosteroids (prednisone 0.5–1 mg/kg/day, methylprednisolone up to 0.8 mg/kg/day) are effective in a large number of cases and are a common first-line systemic therapy.[110,141,142] Response is usually rapid (2–3 days), halting lesion progression and preventing development of new lesions.[103] Long-term corticosteroid use is limited by many common and serious adverse effects including osteopenia, weight gain, glaucoma, cataracts, hyperglycemia and diabetes, Cushing syndrome, immunosuppression, adrenal insufficiency, and corticosteroid psychosis. One common treatment strategy utilizes systemic corticosteroids as initial therapy, with rapid transition to a corticosteroid-sparing agent once disease control is achieved.[110,141] Pulsed-dose cortico-

steroids can also be used, but should be reserved for rapidly progressive disease given the potential for sudden electrolyte shifts and cardiac arrhythmias.[4,62] In one study, six of eight patients healed with methylprednisolone 1 g/kg pulse therapy daily for 3–5 days followed by prednisone 40–60 mg daily with tapering as the lesions healed (average of 5.5 months).[62] As corticosteroid therapy may be extended, prophylaxis for osteoporosis including calcium, vitamin D, and bisphosphonates (if not contraindicated), as well as for *Pneumocystis carinii* pneumonia, should be considered.

6.5.4 Cyclosporine

Cyclosporine is also considered first-line treatment for PG and may be particularly useful in rapidly progressive disease (especially when given intravenously). Two case series demonstrated complete healing in 13 patients treated with oral cyclosporine at a dosage of 3–10 mg/kg/day.[143] The only reported adverse effect in both studies was tuberculosis reactivation in one patient. Another series of 11 patients with corticosteroid-refractory PG and IBD were treated with intravenous cyclosporine 4 mg/kg/day for 7–22 days (followed by oral cyclosporine 4–7 mg/kg/day), demonstrating epithelialization of lesions in a mean time of 1.4 months with no reported adverse effects. Additionally, all seven patients with active IBD symptoms at the time of cyclosporine initiation went into remission, suggesting cyclosporine is an effective choice for PG in the setting of IBD.[144] Adverse effects include hypertension, hepatotoxicity, tremor, electrolyte abnormalities, myelosuppression, increased risk of infection, and renal toxicity; it is generally not recommended for use longer than 1 year at a time.[145] Thus, some argue that cyclosporine, like prednisone, should be used for acute control of PG or in idiopathic disease, but is not appropriate as a long-term maintenance therapy for patients with chronic underlying conditions such as IBD.[103]

6.5.5 Biologic Therapy

Biologic agents are emerging as useful treatment options for PG and are frequently used to treat specific associated conditions including Crohn disease. Infliximab, an anti-TNFα monoclonal antibody binding both soluble and membrane-bound TNFα, is the only biologic that has shown efficacy in classic PG in a randomized, double-blind, controlled trial (level I evidence).[146] Thirty patients were given either infliximab 5 mg/kg or placebo. At 2 weeks, 6 of 13 patients in the infliximab group showed improvement in the severity and/or size of ulcers, versus only 1 of 17 in the placebo group. After 2 weeks, the 16 non-responders in the placebo group were switched to infliximab and by week 6, 20 of 29 patients treated with infliximab demonstrated improvement in their PG lesions, with 6 of 29 showing complete resolution.[146] Further studies are needed to determine the efficacy of infliximab in idiopathic PG.

Etanercept is a recombinant fusion protein of the TNFα receptor bound to the Fc portion of immunoglobulin, binding soluble TNFα. In one study, etanercept resulted in the resolution of 8 of 11 lesions of PG (in seven patients), demonstrating complete healing in a mean of 12.5 weeks.[85] The remaining three ulcers showed a marked reduction in size with no serious adverse effects reported.

Adalimumab is a fully humanized monoclonal antibody that binds both soluble and membrane-bound TNF. One case series of three patients with PG who failed to respond to oral and intravenous corticosteroids, thalidomide, cyclosporine, and mycophenolate mofetil were treated with adalimumab 40 mg once a week with improvement in two of the three patients.[147]

Alefacept, a selective T-cell activation inhibitor blocking CD2:lymphocyte function-associated antigen 3 (LFA3) interactions, has been used in PG with limited success. In one series, four patients were given intramuscular alefacept 15 mg weekly for 20 weeks and then followed up 12 weeks later. One patient cleared completely, two patients showed marked improvement, and one patient had slight improvement.[148]

Efalizumab is a fully humanized recombinant monoclonal antibody that binds to and inhibits the CD11a subunit of LFA1, which mediates leukocyte adhesion and migration. This agent showed initial promise, completely resolving lesions of recalcitrant PG in two cases; however, it was withdrawn from the US and European markets in 2009 due to a concern for increased risk of progressive multifocal leukencephalopathy.[149,150]

Finally, a recent case reported the successful use of ustekinumab, an anti-IL-12/IL-23p40 monoclonal antibody, in a PG lesion leading to complete healing in 14 weeks.[151] Interestingly, the report also found an elevated expression of IL-23A by polymerase chain reaction in the PG lesion compared with normal skin, suggesting a possible mechanism for the efficacy of ustekinumab.

Adverse effects with all biologics include increased risk of infections (and reactivation of tuberculosis), transaminitis, demyelinating disease, a lupus-like syndrome, and a possible increased risk of malignancy. Biologics should be avoided in patients with a history of congestive heart failure, a history of malignancy or risk factors for malignancy (especially lymphoma, melanoma, and chronic obstructive pulmonary disease with a smoking history), and a history of major infection such as tuberculosis.

6.5.6 Other Modes of Immunosuppression

Other immunosuppressive therapies including mycophenolate mofetil, methotrexate, and azathioprine have been used with some success in PG, although are generally considered most effective as adjunctive treatments.[54,103,148,152] Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase, decreasing recruitment and inducing apoptosis of activated T cells.[153] In one series, six of seven patients showed improvement with the addition of mycophenolate mofetil to their regimen. Anemia was reported in one patient in this series.[54] Other common adverse effects include nausea, myelosuppresion, and increased risk of lymphoproliferative disorders. Methotrexate has been shown to decrease neutrophil chemotaxis and found to be effective as an adjunct to cyclophosphamide pulse therapy in one study.[103,152] Azathioprine, a purine analog, acts as an anti-inflammatory agent by impairing DNA synthesis in lymphocytes. Azathioprine has also proven effective in combination with cyclophosphamide in PG.[152] Azathioprine has a slow onset of action (4–6 weeks) and is not appropriate for rapid control of disease. Adverse effects include myelosuppression and gastrointestinal intolerance.

Thalidomide is proposed to be effective in PG based on its inhibition of macrophage phagocytosis and neutrophil chemotaxis. Thalidomide 400 mg/day showed dramatic improvement in one patient with PG and Behcet disease.[154] A second patient, who was unresponsive to methylprednisolone, showed complete healing in 10 weeks on oral thalidomide.[155] Adverse effects include significant teratogenicity, drowsiness, and neuropathy.

Alkylating agents have also been effective in PG; however, the adverse effects associated with these medications including myelosuppression and hemorrhagic cystitis (with cyclophosphamide) generally limits their use to severe, refractory cases.[156,157] In one study, six patients with corticosteroid-unresponsive PG were given oral chlorambucil 2–4 mg/day (two patients were given chlorambucil alone and four patients were given chlorambucil in combination with corticosteroids).[157] Benefits were noted in all six patients within 6 weeks and corticosteroids were eventually discontinued in all patients. Leukopenia was noted in one patient.[157] Pulse cyclophosphamide was demonstrated to induce complete remission in seven of nine patients and partial remission in another patient in one series.[158] Adverse effects included transient hematologic and gastrointestinal toxicity.

According to the literature, 25 patients with PG have been successfully treated with intravenous immunoglobulin (IVIG), with one treatment failure.[159] In all cases the disease was long standing, refractory, severe, and other treatment options were limited. Dosages ranged from 0.5 mg to 1 g/kg/day for 2 days, or 0.4 g/kg/day for 5 days with the number of monthly treatments ranging from 2 to 6.[159,160] Adverse effects of IVIG include headache, nausea, fever, anaphylaxis, and renal failure.

6.6 Emerging Therapeutics

Granulocyte apheresis is a new therapeutic modality for IBD that exerts immunomodulatory effects by selectively removing activated granulocytes and monocytes from peripheral blood. Several case reports have demonstrated efficacy in PG lesions refractory to multiple systemic treatments including cyclosporine.[161,162] Apremilast is an orally active phosphodiesterase-4 inhibitor shown to reduce TNFα production both *in vitro* and in mouse models for psoriasis and rheumatoid arthritis.[163,164] This promising agent has also recently demonstrated improvement in psoriasis efficacy scores in a single-arm, open-label pilot study, without significant adverse effects,[165] though it has yet to be studied in PG.

7. Outcomes

Long-term results of PG treatment are variable, and outcome data are lacking. Some studies have noted higher rates of recurrence and worse clinical outcomes in systemic disease-associated PG compared with the idiopathic form.[4,166] However, in a series of 42 patients with a median follow-up of 26.5 months, no significant difference in prognosis was seen between patients with idiopathic and disease-associated PG; an overall recurrence rate of 56% was noted.[48] Bennett et al.,[47] in a retrospective case series of 86 patients, observed a mean time to remission with treatment of 11.5 ± 11.1 months in classic PG, versus only 9.0 ± 13.7 months in bullous PG ($p = 0.03$), with five patients in this cohort whose PG remained refractory to multiple treatments. In a retrospective case series of 21 patients followed for at least 3 years, Mlika et al.[64] reported a 30% rate of complete resolution and a 46% recurrence rate, regardless of whether patients received systemic corticosteroids or clofazimine. More follow-up studies will be needed to establish a consistent understanding of disease outcomes as a function of both disease variants and treatments.

8. Concluding Remarks

Nearly a century after it was first described, PG continues to challenge those seeking to understand, diagnose, and treat this complex disorder. Current research supports an understanding of PG as a systemic inflammatory reaction pattern due to innate

immune dysregulation and altered neutrophil chemotaxis. Diagnosis remains difficult in the absence of a disease-specific laboratory or histologic finding; however, recently proposed clinical criteria are useful. Approximately half of all cases are associated with a systemic disease, justifying a thorough search for the most common associated conditions in any patient with a new presentation of PG. There is no gold standard for treatment. The central goals of management are to control inflammation and optimize wound healing. In most cases this will require a combination of wound care, topical agents, and in severe or refractory disease, systemic antimicrobials or immunosuppressants. While historically the first-line systemic agents have been corticosteroids and cyclosporine in severe cases, TNFα inhibitors have recently demonstrated success and will likely play an increasing role in treating this disease in the future. Further clinical trial evidence is needed to better define the short- and long-term efficacy of available and emerging treatments.

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