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REVIEW

Extracutaneous involvement of pyoderma gangrenosum

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Abstract
Pyoderma Gangrenosum (PG) is an inflammatory neutrophilic dermatosis (ND) associated with underlying chronic inflammation and/or malignancy. Diagnosis remains to be challenging as a gold standard diagnostic test is lacking. Initial manifestations may include papules, vesicles, or pustules that subsequently develop into ulceration with features of undermining and violaceous borders. Timely recognition of pyoderma gangrenosum is impeded by clinical findings shared with other etiologies, such as granulomatosis with polyangiitis, polyarteritis nodosa, and antiphospholipid syndrome. As with any other ND, extracutaneous involvement may also occur preceding, during, or following the appearance of skin lesions. Sterile neutrophilic infiltrates have been found to affect internal organs supporting the concept of PG being a systemic disease, with lung being the most common extracutaneous manifestation followed by ocular and visceral compromise. Therefore, in this review, we describe the current knowledge of extracutaneous involvement of PG and its respective clinical manifestations to aid dermatologists in diagnosis, management, and determining prognosis.

Keywords Pyoderma gangrenosum · Extracutaneous · Neutrophilic dermatosis · Pulmonary · Ocular · Renal · Bone

Introduction

Pyoderma Gangrenosum (PG) is considered an inflammatory neutrophilic dermatosis (ND) often associated with underlying chronic inflammation and neoplastic disease [13]. The pathophysiology of this rare skin condition is not completely understood; however, neutrophilic dysfunction, immune dysregulation, and genetic variations have been proposed as main contributors to PG pathogenesis [5]. The annual world-wide incidence is estimated to be 3–10 cases per million population, affecting all genders and age groups with peak incidence between age 20 and 50 years [5, 46].

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Different variants of PG exist, such as ulcerative, bullous, pustular, vegetative, peristomal, and post-surgical [2]. Although a panel of experts recently proposed diagnostic criteria of ulcerative PG [42], a gold standard diagnostic test is still lacking. Initial clinical findings might include papules, vesicles, or pustules that develop into an ulcer featured by undermining, violaceous/necrotic borders, and excruciating pain. These lesions may be associated with preceding trauma (i.e., pathergy), malignancies, or inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease [5]. In addition, pyoderma-like ulcers have been described in other entities associated with systemic manifestations, such as granulomatosis with polyangitis (GPA) [24, 40], polyarteritis nodosa (PAN) [8, 23], and antiphospholipid syndrome (APL) [23, 56] (Table 1).

PG is the prototype of NDs, and with any other ND, non-cutaneous involvement may occur before, during, or after the skin lesions [61]. In general, these non-cutaneous findings are categorized into three subtypes: (1) systemic inflammation common to other diseases associated with ND, such as gastrointestinal, hematologic, and rheumatologic conditions [39]; (2) non-specific inflammatory findings such as myalgia, fever, and joint pain; (3) sterile neutrophilic infiltrates found in organs other than skin [39]. The latter has been of special interest in patients with PG, as visceral involvement

Table 1 Differential diagnosis of cutaneous and extracutaneous pyoderma gangrenosum

Manifestations	Pyoderma gangrenosum[a]	Granulomatosis with polyangiitis	Polyarteritis nodosa	Antiphospholipid syndrome
Cutaneous	Classic type: papule, vesicle, or pustule progressing to ulcers with central necrosis and erythematous, violet-blue borders and undermining Variants: bullous, pustular, vegetative, and peristoma/post-surgical May be associated with pathergy Most commonly affecting legs	Painful, palpable purpura with macules and papules, cystic nodules, indurated erythema Can progress to deep, vasculitic ulcers Bullae/vesicles reported that might become purulent and/or hemorrhagic Most commonly on legs	Painful nodules/purpura with indurated erythema Associated with livedo (typically a "burst" pattern around lesion) and ulcers Petechia and auto-amputation reported May have hemorrhagic lesions Most commonly on legs Relapsing/remitting shows benign course	Livedo reticularis most common, can be persistent and widespread Superficial thrombophlebitis, skin ulcers ± necrosis, atrophie blanchie Catastrophic antiphospholipid syndrome associated with painful purpura fulminant, retiform lesions, and widespread hemorrhagic skin infarctions Raynaud's, digital gangrene, subungual/splinter hemorrhages, cyanotic lesions hands or feet, local necrosis or ecchymoses, painful skin nodules also reported
Extracutaneous	Fever, malaise, myalgia, arthralgia Spleen, liver, sclera, pulmonary, and kidney may have sterile granulomas, nodules, or abscesses Pulmonary interstitial fibrosis, cavitations, nodules, and pleural effusions Ulcerations of eyelid leaving permanent defects Scleritis and corenal ulcers also reported Sterile, neutrophilic myositis and polyarthrosis	Fever, malaise Pulmonary nodules, cavitations, and alveolar hemorrhage are commonly seen Sinusitis/hemorrhagic rhinorrhea, may result in obstruction Associated with mononeuritis Pauci-immune crescentic glomerulonephritis/renal failure Oral ulcers	Fever, malaise, arthritis, myalgias, arthralgias, weight loss Poly-neuropathies may also be present Elevated diastolic blood pressures It may also involve liver/kidney Associated with viral infections HBV, HCV, HIV	Arterial/venous thromboembolisms Pregnancy morbidity (miscarriages, preterm delivery, eclampsia) Cardiac valve vegetations (Libman-sacks) Pulmonary embolism, acute respiratory distress syndrome, diffuse alveolar hemorrhage Strokes, epilepsy, headache, and cognitive dysfunction Renal artery/vein thrombosis, nephrotic syndrome, malignant hypertension, renal failure Ocular vascular occlusions causing amaurosis fugax, scotomas, blurred vision, visual field defects Avascular bone necrosis adrenal insufficiency due to hemorrhage from adrenal vein thrombosis Mesenteric insufficiency/infarcts, Budd Chiari syndrome
Laboratory	Elevated ESR, CRP Leukocytosis Negative blood and tissue cultures Workup for IBD, hematologic malignancy, and other autoimmune disorders	ANCA positive, usually pr3 +/c-ANCA Elevated ESR and CRP Normocytic normochromic anemia indicating chronic disease Hematuria/proteinuria if renal involvement	Elevated ESR and CRP, y-globulin Normocytic normochromic anemia indicating chronic disease Elevated IgM anti-phosphatidylserine–prothrombin complex Anti-streptolysin O antibody (+) Negative for ANCA, RF, cryoglobulins ANA (+), lupus anticoagulant (+) HBV, HCV, HIV associations	Anti-cardiolipin antibody, lupus anticoagulant, anti-Beta2-glycoprotein I antibody (IgG or IgM) Hemolytic anemia, thrombocytopenia, and prolonged PT/PTT Newer tests: phosphatidylethanolamine antibodies, annexin A5 resistance assay

Table 1 (continued)

Manifestations	Pyoderma gangrenosum[a]	Granulomatosis with polyangiitis	Polyarteritis nodosa	Antiphospholipid syndrome
Biopsy	Mixed infiltrate without evidence of vasculitis. Chronic inflammatory cells in dermis Edge of ulcer with perivascular, lymphocytic infiltrate and fibrinoid necrosis of vessel walls suggestive of secondary vasculitis. Negative DIF	Leukocytoclastic vasculitis common with fibrinoid necrosis and perivascular, neutrophilic infiltrate. IgG deposits in subepidermal blood vessel walls or dermo-epidermal junction. C3 deposits in blood vessel walls Negative IF for immune complexes	Leukocytoclastic vasculitis of small to medium arteries in deep dermis and hypodermis Necrotizing vasculitis involving small muscular, subcutaneous arteries. Fibrinoid degeneration of arterial walls with mixed infiltrate. IF may show C3, IgM, IgG (less often IgA) Destruction of internal elastic lamina. No deposits in dermo-epidermal junction. No small vessel involvement. Absent giant cells Simultaneous presence of varying stages of inflammation in vessels from active infiltrate to necrosis and fibrosis	Microvascular thrombosis with absence of inflammation involving vessel wall Livedoid vasculopathy with fibrin deposits within wall and lumen of superficial dermal vessels
Differential diagnosis	Severe acne, cutaneous vasculitis, Sweet's syndrome, bacterial or fungal infections, malignancy	Henoch–schonlein purpura, polyarteritis nodosa, microscopic polyangitis	Erythema nodosum, microscopic polyangitis, Wegener's granulomatosis, Henoch–Schonlein purpura, erythema induratum, livedoid vasculopathy, urticarial vasculitis	Microangiopathic syndromes, heparin-induced thrombocytopenia, systemic lupus erythematosus, Behcet's syndrome, cutaneous vasculitis

The diagnosis of pyoderma gangrenosum is very challenging. Most physicians consider this still a diagnosis of exclusion. Being familiar with the cutaneous and extracutaneous manifestations of ailments which present similar to PG is necessary and helpful when facing these patients in clinical practice

ANA antinuclear antibodies, *ANCA* antineutrophil cytoplasmic antibodies, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *RF* rheumatoid factor

[a]In patients diagnosed with PG only without the presence of any comorbidities

supports the idea of PG being a systemic disease [41, 61, 62]. Among the systemic manifestations of PG, pulmonary involvement is the most common, followed by ocular and other visceral involvements [27, 51]. Thus, the focus of this review is to describe extracutaneous manifestations of PG as these could aid in the diagnosis, management and prognosis of PG patients.

Methods

A search for all reported instances of extracutaneous PG was conducted using 12 key terms (pulmonary, lung, renal, kidney, ocular, eye, brain, gastrointestinal, heart, muscle, spleen, and extracutaneous) in combination with the search phrase "pyoderma gangrenosum" within the databases PubMed and Web of Science. All relevant English articles published between 1973 and 2018 were reviewed by two independent researchers. When the data were unclear, the senior author was asked to clarify the data extraction. Ninety-six cases were identified with extracutaneous manifestations of PG. Forty-one cases were reported as pulmonary involvement (41/96, 42.7%), 34 as ocular involvement (34/96, 35.4%), 7 as bone involvement (7/96, 7.2%), 6 as spleen compromise (6/96, 6.2%), and 3 as renal involvement (3/96, 3.1%). Less commonly involved organs, including brain, gastrointestinal, muscle, and heart compromise, were reported in 5 cases (5/96, 5.2%).

Extracutaneous manifestations of PG

PG and pulmonary involvement

The most common manifestation of extracutaneous PG is pulmonary involvement [22, 28, 38, 55]. If present, PG with pulmonary involvement may result in life-threatening consequences and requires prompt recognition and treatment [55]. Pulmonary disease in patients with PG has a wide clinical presentation, ranging from asymptomatic to severe respiratory distress [22] (Fig. 1). Most cases involve cavitating or non-cavitating lesions that can be associated with necrosis and superimposed infections [38]. Interstitial infiltrates, consolidation or mediastinal lymphadenopathy can also occur [38, 55]. PG with pulmonary involvement must be thoroughly evaluated for other etiologies and is a diagnosis of exclusion. Evaluation for mycobacterial and fungal infection, systemic vasculitides, and malignancies may be relevant to exclude other causes for pulmonary lesions besides PG lung involvement [38, 55].

Accurate diagnosis is often delayed as common etiologies such as cancer, infection, and necrotizing vasculitis can have similar presentations [22]. Though superimposed infections may further complicate diagnosis, negative tuberculosis and fungal testing can further support PG diagnosis in the presence of cavitating or necrotic lesions [55]. Due to the rarity of pulmonary PG and its variability in clinical course, there are still no clinical guidelines for when and how to test PG patients for pulmonary involvement. Hence, a diagnostic algorithm has been developed in a recent systematic review [28]. Lung disease in PG can also be mistaken for GPA, as lung infiltrates, nodules, and cavitation are also common findings for GPA [14, 48, 59, 60]. Similar to PG, GPA may present with a wide range of clinical symptoms, ranging from asymptomatic to severe respiratory distress [14]. Unlike PG, approximately 85% of patients with GPA will develop lung disease, and pulmonary involvement is considered a diagnostic criteria for the disease [59]. Many cases of pulmonary GPA are also associated with underlying systemic involvement [48]. However, those who have localized disease of GPA in the lungs have a relatively benign disease course [48]. Additionally, most cases of PG with pulmonary involvement initially present with skin ulcerations [28], though rare and questionable cases of lung involvement preceding skin disease have been reported [22]. PG patients with lung involvement are often idiopathic and mainly associated with hematologic malignancies [28]. Both pulmonary manifestations of PG and GPA can cause unilateral or bilateral lung disease; however, pulmonary involvement in patients with PG can affect all lung zones while GPA appears to spare the apices [14, 22]. Pulmonary disease in PG can represent a challenge to distinguish from GPA strictly by clinical presentation, thus negative anti-neutrophil cytoplasmic antibody with cytoplasmic pattern (c-ANCA) testing (and other autoimmune work up), and biopsy can improve diagnostic confidence. Histopathology from lung tissue in patients with PG and pulmonary involvement usually reveals chronic inflammation with a predominance of neutrophils and an absence of vasculitis or malignant cells [22, 28, 55].

The treatment of PG with pulmonary involvement is challenging and the disease can be fatal. Systemic corticosteroids and other immunosuppressants are most commonly used [28, 38], though corticosteroid resistance has been reported [55]. Patients being treated for pulmonary disease are immunosuppressed and carry a significant risk for life-threatening infections [22, 28, 55]. Currently, there is a lack of long-term outcome studies in patients who suffer from PG with pulmonary involvement, but prognosis is generally favorable after treatment with no report of relapse [22].

PG and ocular involvement

Ocular manifestations in PG are rare, with only several case reports currently in the literature [19, 27, 45, 50] (Fig. 1). Early diagnosis of ocular PG is especially challenging,

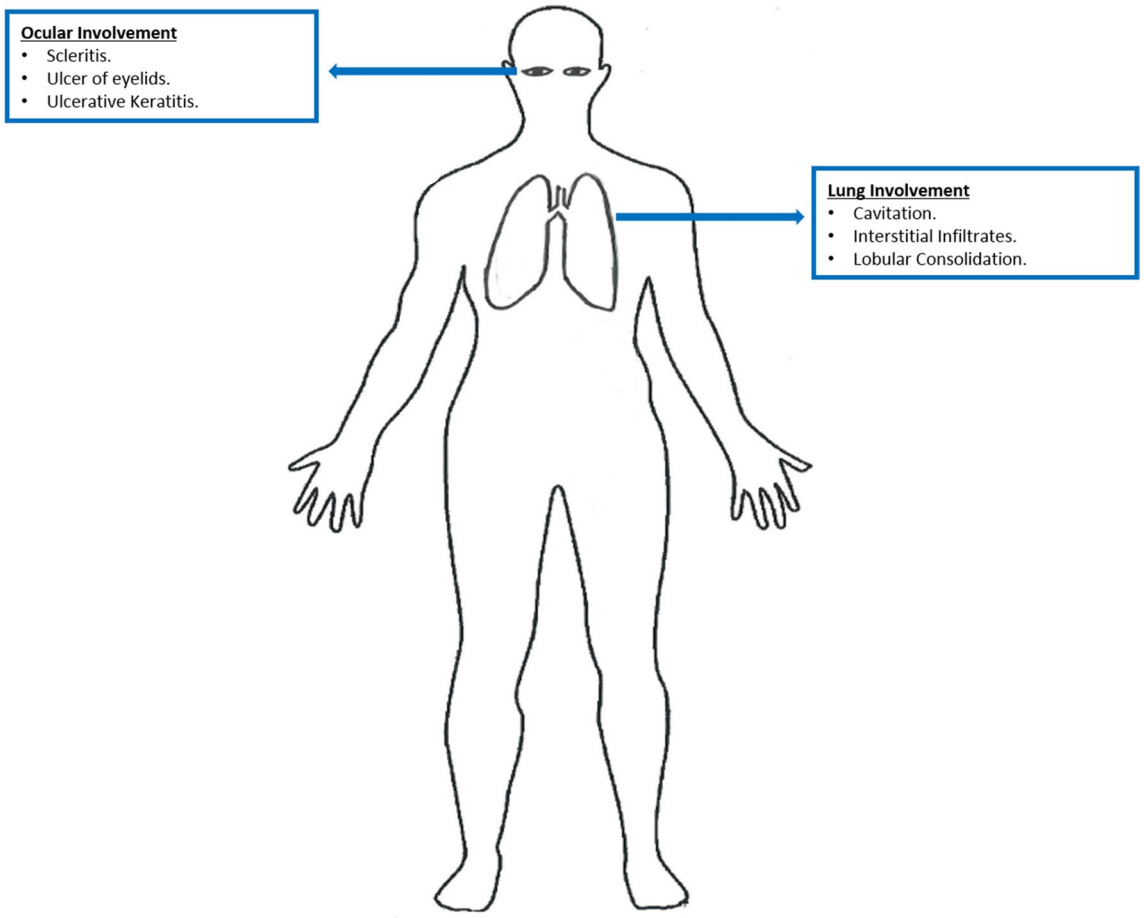

Fig. 1 Most common extracutaneous involvement in pyoderma gangrenosum

delaying initiation of appropriate treatment resulting in poor patient outcomes. Poor recognition of PG with ocular involvement is due to both the rarity and variability in its presentation.

There are several features of PG with ocular involvement that may aid the prompt diagnosis of this disease. PG with ocular involvement can affect the periorbital tissues and skin, usually presenting with eyelid swelling and nodules early on in the disease course [50]. Affected periorbital tissues may further progress to purulent discharge and necrosis of the affected tissues [27, 50]. A common manifestation is necrotic ulceration and fistula in the eyelids leading to defects in the eyelid itself, especially affecting the medial third upper lid and the lateral two-thirds of the lower lids [50]. Healing often takes months and recurrence is extremely common, with orbital involvement associated with a higher rate of relapse [27]. Orbital involvement can present with scleritis, proptosis, and conjunctival injection [19, 45, 50]. The difficulty establishing PG with ocular involvement is further convoluted by the fact that inflammatory bowel disease can experience ocular manifestations such as episcleritis and uveitis, mainly in association with concomitant musculoskeletal manifestations [27]. However, PG with eye involvement has been associated with IBD in only 15% of these cases and mainly affects the cutaneous tissues around the eye and the orbit [27].

Diagnosis of ocular PG is challenging, thus skin biopsy can be helpful, even though up to 40% of PG is associated with pathergy. Some cases of ocular involvement after minor trauma or surgical ophthalmic procedure have been reported [19]. However, the risk of delaying the treatment of PG, especially with eye involvement, greatly exceeds the concern for pathergy. Histology of ocular PG involves a sterile, inflammatory process with an acute or chronic infiltrate that may be associated with necrosis or dermal abscess [27, 45]. Though necrosis and fistulas of the periorbital tissues may be relatively non-specific and confuse the clinical picture to appear like GPA, the presence of painful eyelid nodules early on in the disease course is highly suggestive of PG rather than ocular GPA [50]. To further distinguish PG with eye involvement from GPA, absence of nasolacrimal obstruction and sinus disease makes GPA less likely [31, 59]. Frank, full-thickness necrosis in the eyelids, as seen in

more advanced periorbital disease of PG, is also less characteristic of ocular GPA [27, 30, 31, 50, 59].

PG with eye involvement may lead to permanent damage to the orbit, resulting in vision loss. PG patients can suffer from corneal perforations leading to blindness, due to ulceration of the eyelids leading to full-thickness necrosis of the eyelids [27, 50]. Orbital-cutaneous fistulas may also arise as a complication of untreated ocular PG [45], and other residual effects may involve loss of visual acuity, lagophthalmos, and defective eye motility [27].

PG and renal involvement

Renal involvement in PG has been rarely reported. It may present as pyuria, hematuria, aseptic leukocyturia, oliguria, and proteinuria as a result of different types of renal compromise [9, 10, 39, 57]. Though few in number, several renal conditions have reportedly been associated with PG, such as chronic sclerosing glomerulonephritis, chronic kidney disease, end-stage renal disease (ESRD), renal carcinoma, and renal transplant, among others [3, 4, 6, 11, 26, 29, 33, 49, 53, 57] (Fig. 2).

Few cases have reported the association of PG with chronic kidney disease and end-stage renal disease (CKD/ESRD); however, the underlying pathophysiology is yet to be elucidated [11, 26, 29, 53]. Several theories have been proposed about the underlying mechanism of PG in patients with CKD/ESRD. Goto et al. proposed an underlying mechanism of hypersensitivity in a patient with CKD and uveitis associated with recurring PG lesions at injection sites (i.e., pathergy) [26]. Akatsuka et al. suggested the presence of monoclonal gammopathy (MG) as the possible cause of PG-associated CKD, in which MG leads to a rapidly progressive renal failure [3]. Others propose a mechanism that might include an underlying vascular insufficiency, especially in patients with ulcerative PG in the lower extremities [11]. The most common locations for PG found in these patients include the lower extremities, skin overlying an arteriovenous fistula, and previous surgery sites [3, 11, 26, 53]. Furthermore, ulcerative, vegetative, and atypical PG have been reported in this patient population [3, 11, 21, 26, 53]. Even though CKD is a risk factor for wound healing

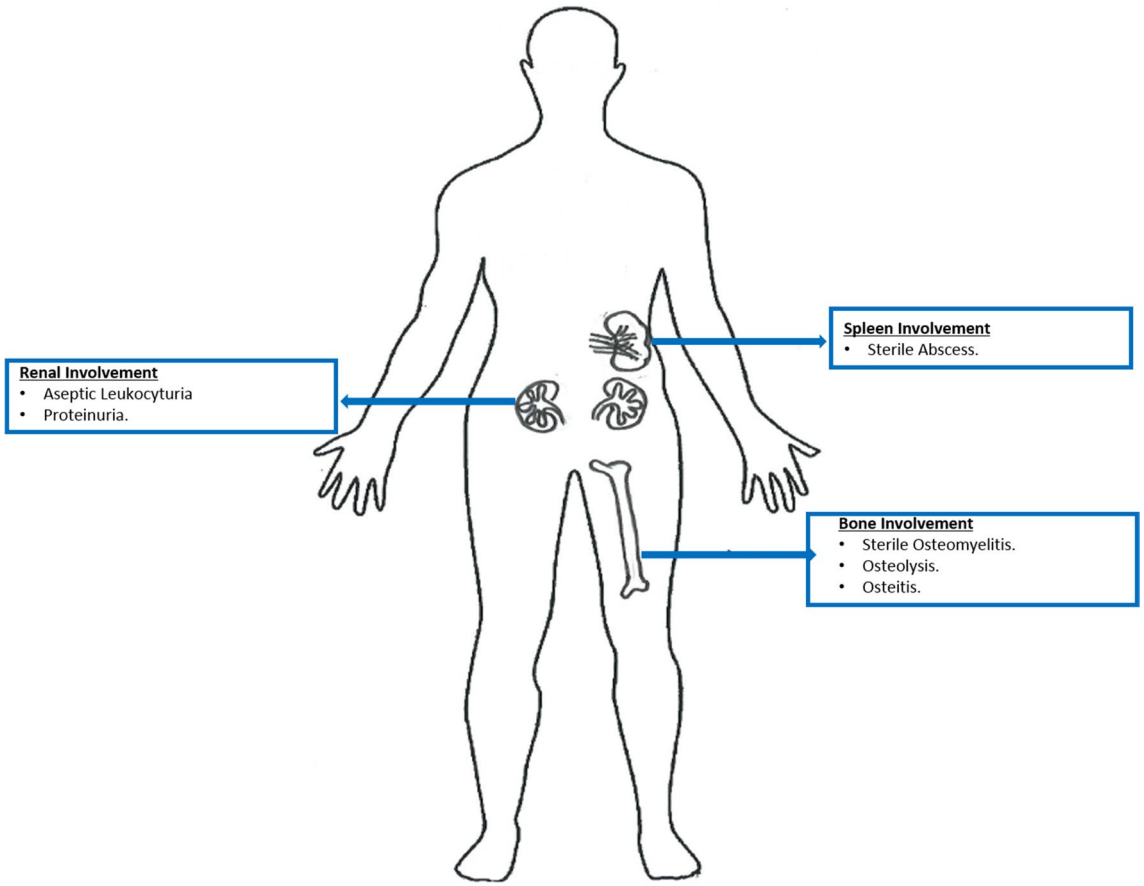

Fig. 2 Less common extracutaneous involvement in pyoderma gangrenosum

impairment, these lesions respond well to either topical or systemic corticosteroid therapy as well as topical or intralesional steroids in conjunction with gradual improvement of the renal function.

PG and bone involvement

Bone involvement of PG is also rare, with only few case reports in literature. Sterile osteomyelitis represents the main type of involvement in patients with extracutaneous PG compromising the bone [17, 18, 35, 52, 54, 58, 61] (Fig. 2). In seven case reports found in the literature, sterile osteomyelitis has been described in four patients [17, 18, 54, 58, 61] whereas osteitis and osteolysis were described in two patients [35, 52]. High temperature, arthralgia, and myalgia are usually the general symptoms present in these patients. The onset of bone involvement may be preceded [35, 54, 58, 61] or followed [17, 18, 52] by the diagnosis of PG. Five out of these seven patients with bone involvement were pediatric, ranging from 9 months to 10 years of age, and the remaining two patients were older adults in their 70 s. Bone biopsy in these cases showed acute or chronic inflammatory infiltrates (i.e., multinucleated giant cells, pigmented plasma cells, histiocytes, and lymphoid aggregates), resorption of bone trabeculae, and fibrosis. Though bone involvement may manifest as osteolysis of underlying bone, cultures from bone and blood were negative [52]. All patients were treated with corticosteroids that improved both cutaneous and skeletal findings.

PG and spleen involvement

Splenic involvement in PG is extremely rare but can affect any age, including a few pediatric cases under the age of 10 [7, 34] (Fig. 2). Lesions are often detected on imaging as abscesses, with tissue analysis revealing sterile, non-specific neutrophilic infiltrate. All cases of splenic PG were associated with cutaneous ulcers characteristic of PG, though the timing of these lesions may vary. Most often, splenic lesions are found preceded by characteristic skin lesions, especially in patients with known history of PG [20, 32, 44,

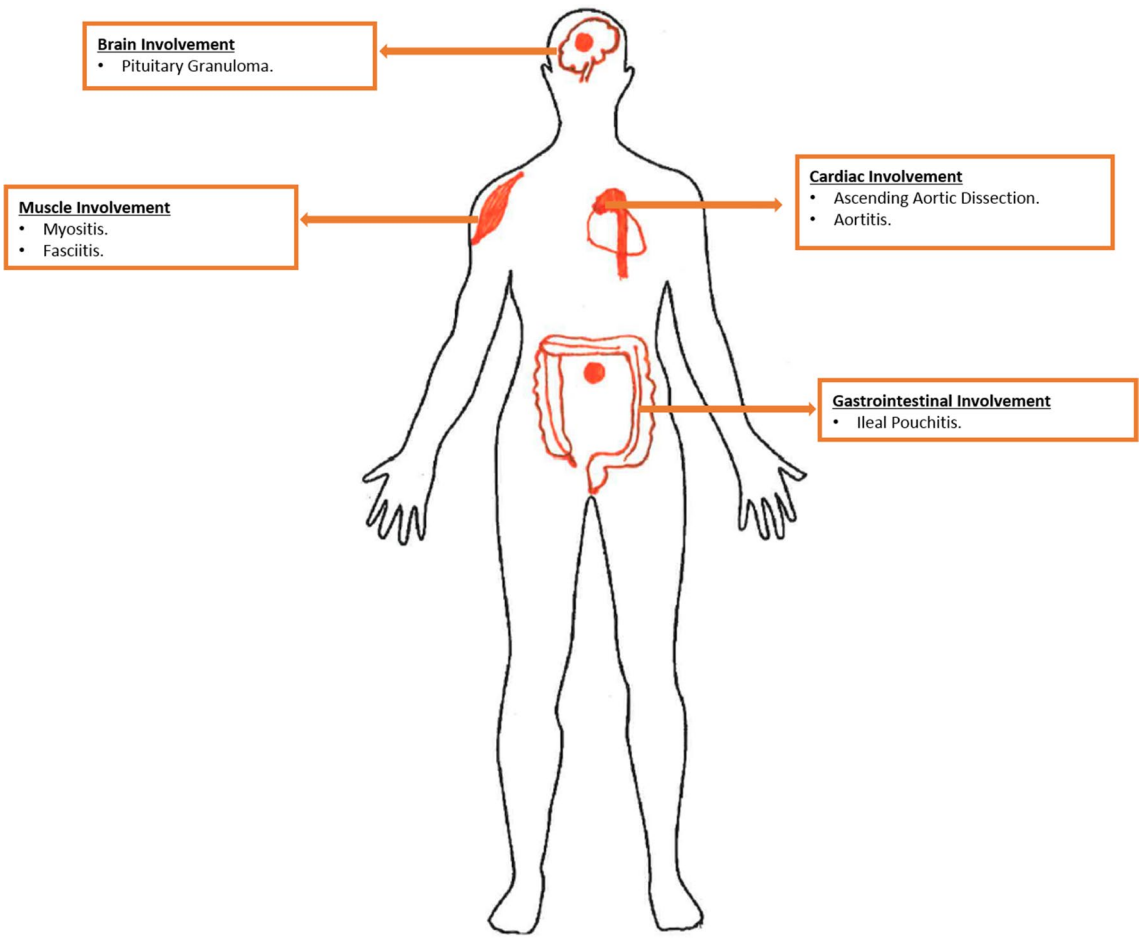

Fig. 3 Rare extracutaneous involvement in pyoderma gangrenosum. Brain, muscle, heart, and gastrointestinal involvement are the least commonly reported in the literature

45], although one case reported spleen involvement as the initial presenting symptom [61].

PG with splenic involvement can be associated with additional involvement of other organs including the liver [45], kidney [10], lung [7], and bone [61]. Though underlying hematologic disease has been associated with PG, its relationship with splenic involvement is unclear. One case was associated with known IgA gammopathy [44] and another reported elevation of total IgA [7]. Chronic monomyelocytic leukemia was reported in one patient [61].

Differential diagnoses for splenic lesions in PG include vasculitis, tumor, and infection. However, invasive procedures to rule out these entities are generally avoided due to concerns of pathergy. The treatment of PG with splenic involvement generally involves systemic immunosuppression, and refractory cases have reported some success using biologics such as infliximab or adalimumab [7, 32]. Most patients usually improve with systemic immunotherapy, though challenging cases can experience recurrences requiring increasing dose of systemic steroids or addition of systemic cyclosporine. One death was reported after recurrence of PG with splenic involvement, though the ultimate cause of death was attributed to generalized peritonitis due to bowel infarction of unknown etiology [15].

Other extracutaneous involvement

Other systemic extracutaneous involvements of PG have been reported sporadically and are even more rare (Fig. 3) which include joints [16, 43, 47], pituitary granuloma [12], aortitis [36], myositis [25, 37], and ileal pouchitis [1] (Table 2).

Table 2 Features of types of extracutaneous pyoderma gangrenosum

Systemic involvement	Clinical manifestation	Laboratory findings	Histology	References
Pulmonary	High temperature Variable pulmonary symptoms It may present either before or after skin ulceration	Chest x ray: interstitial infiltrates mediastinal or hilar lymphadenopathy, and consolidation. Cavitating or non-cavitating lesions	Neutrophil infiltration Granulomatous inflammation	[22, 28, 38, 55]
Renal	Pyuria, hematuria, and oliguria Most common locations of skin ulceration include lower extremities, skin overlying an arteriovenous fistula, and previous surgery sites	Aseptic leukocyturia and proteinuria High levels of creatinine and BUN (depending on the level of compromise)	Dense granular and mononuclear infiltrate, xanthomatous macrophages Necrosis can also be found	[10]
Ocular	Periocular ulceration. Fistula to the eyelids may also be present Extracutaneous (involving the eye itself) Most commonly unilateral Ulcerative PG is the most common type	Non-specific	Neutrophil infiltration and/or acute inflammatory infiltrate Necrosis, dermal abscesses Chronic inflammatory infiltrate	[27, 45, 50]
Spleen	Abdominal pain Splenic PG may occur before or after skin lesions	MRI: intra-splenic and subdiaphragmatic collection CT and US: splenic abscess-negative culture	Neutrophilic infiltration	[7, 10, 34, 44]
Bone	High temperature Arthralgia Regional tenderness and swelling Myalgia Bone involvement may occur before, concurrently, or after the skin lesions Regional lymphadenopathy	Bone scan: uptake findings consistent with osteolysis X ray: moth-eaten erosive changes. Radiolucent lesion with periosteal reaction CT: Osteolysis	Sterile osteomyelitis: chronic inflammatory cells (i.e., lymphocytes and histiocytes) Fibrosis Osteitis and osteolysis	[17, 18, 35, 52, 54, 58, 61]

Pulmonary and ocular extracutaneous manifestations of PG are the most common among these patients. Visceral involvement which includes renal, spleen, and bone involvement and among others have also been reported

Conclusion

The association of PG with underlying inflammatory conditions is well known. However, extracutaneous systemic manifestations of PG are considered uncommon but still important in the management of these patients. Being aware of extracutaneous involvement of PG may provide clinical clues to improve diagnostic work up of challenging cases (e.g., PG vs GPA) as overlapping systemic manifestations of classically associated comorbidities can coexist. The use of systemic immunosuppressive therapy should be warranted in patients with PG and extracutaneous manifestations regardless of the severity of the cutaneous lesion. In PG patients, though the presence of extracutaneous manifestations apparently does not impact mortality, the impact on long-term morbidity remains unknown. That being said, it is necessary to establish multicenter collaboration and registries to address the limited knowledge we have of the natural course of this disease and its associated extracutaneous manifestations.

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