



Is This Just a Simple Venous Ulcer, or Something More Complex?

These other conditions should be in your differential diagnoses.

BY ADAM R. JOHNSON, DPM

When a patient presents with an ulceration of the lower leg, venous insufficiency ulceration is often the most common thought upon diagnosis. However, here are some other potential differentials to consider.

Calcinosis Cutis

Calcinosis cutis describes the deposition of insoluble calcium salts in the skin and subcutaneous tissues. Clinically, patients present with non-healing ulcerations that may contain visible deposits of calcium salt aggregates.

Dystrophic calcinosis cutis results from local tissue damage, due to burns, trauma, surgery, or infection. This is a local process and systemic calcium and phosphate metabolism remain normal. The tissue damage leads to local hypoxia causing an increase in intracellular calcium.

Metastatic calcinosis cutis occurs due to abnormal calcium or phosphate metabolism. Calcium moves into the skin and subcutaneous tissue where it aggregates. Calcification may also be found in blood vessels, kidneys, lungs, and gastric mucosa. Metastatic calcinosis

cutis may be caused by any systemic disease that alters serum calcium or phosphate levels; the most common cause is chronic renal failure.

Calciophylaxis, or uremic gangrene syndrome, is a type of calcinosis cutis leading to calcification of the small and medium-sized blood vessels in the skin and subcutaneous

tissues. Initially, retiform purpura (Figure 1A) occurs, which eventually leads to necrosis and ulcer formation (Figure 1B).

Laboratory workup may be useful. If the calcinosis is a local process (i.e., from trauma) labs would return within normal limits. In cases of a metabolic calcinosis, abnormal lab values would occur. Such labs include serum calcium, serum phosphorus, urinary calcium (24-hour), serum parathyroid hormone level and serum vitamin D level.

Plain radiographs may be useful as calcium salt aggregates are easily visualized. These studies can be useful for determining the extent of tissue involvement, especially before attempts at excision of the aggregates.

Excision of the calcium salt aggregates is recommended if this can be accomplished without extensive dissection and damage to the surrounding tissues. It may be too difficult for the body to form granulation tissue over these deposits. However, some aggregates may be too large to resect and alternative measures to assist in granulation should be considered, such as use of cellular and tissue prod-

Continued on page 80



Figure 1A: Retiform purpura. Right lower leg with violaceous reticulated patches characteristic of calciophylaxis.



Figure 1B: Eventual necrosis of tissues due to calciophylaxis.



Venous Ulcer (from page 79)

ucts, negative pressure wound therapy, and medical management.

Diltiazem is a calcium channel blocker which may be useful in reducing the growth of calcium salt aggregates.¹ Colchicine and minocycline may also prove beneficial given their systemic anti-inflammatory effects,^{2,3} especially when painful ulcerations are present. When a patient presents with complex systemic disease, it is recommended to consult with the patient's internist, or in the case of dialysis patient, their nephrologist, before adjusting medication.

Panniculitis

Panniculitis refers to inflammation primarily affecting subcutaneous fat lobules. Ulcerations form after necrosis of fat, creating ulcerations with "oily" drainage, undermining and tunneling



Figure 2A: Ulcerations demonstrating changes related to panniculitis. The two ulcerations connect through the subcutaneous tissues under the skin bridge.



Figure 2B: Continued skin breakdown from panniculitis. The periwound skin has been coated with zinc oxide paste to assist in protection from the high levels of drainage occurring with this ulceration.

Lipodermatosclerosis, also known as sclerosing panniculitis, is a form of panniculitis that usually occurs in the setting of venous insufficiency.

(Figures 2A and 2B). Panniculitis may occur after local infection or trauma, or be systemically due to pancreatic disease or malignancy.

Local infection from cellulitis or abscess may start the inflammatory cascade. Systemic inflammatory conditions may also lead to the process. For instance, erythema nodosum is often associated with streptococcal pharyngitis. It presents with painful nodules on the shins due to underlying panniculitis. However, ulceration of these nodules is rare. Nodules may also occur on the thighs and forearms and often be accompanied with joint pain, fever, and malaise. Trauma may be obvious after local injury, or subtle, such as due to deposition of urate crystals in the subcutaneous fat from hyperuricemia.

Lipodermatosclerosis, also known as sclerosing panniculitis, is a form of



Figure 3: Fibrotic ulceration seen in the presence of Lipodermatosclerosis.

panniculitis that usually occurs in the setting of venous insufficiency. The legs are often described as an "inverted wine bottle." The indurated, fibrotic tissues that form as a result of inflammation⁴ adheres the skin to the subcutaneous tissues leading to increases in shear trauma and re-occurring ulcerations of the affected skin (Figure 3). Worsening the condition, the area of scar tissue often becomes absent of capillaries, making healing slow. Clinically, this condition is termed "atrophie blanche" and appears as an area lacking pigmentation (Figure 4).

If infectious causes are of concern, finding the source and eliminating them should be considered a first priority. Surgical resection and/or serial debridement of devitalized and necrotic adipose to reduce inflammation may also be considered. Pentoxifylline has been shown to be useful blocking TGF-Beta 1 function which adds to dermal fibrosis.⁵ Colchicine and minocycline may also be considered for their anti-inflammatory affects.

May-Thurner Syndrome

May-Thurner syndrome is characterized as venous outflow obstruction, typically due to compression of the iliac vein. It most commonly occurs in the left lower extremity due to local anatomy. The left



Figure 4: "Atrophie Blanch" areas showing hypopigmentation.

Continued on page 81

WOUND MANAGEMENT

Venous Ucler (from page 80)

iliac vein runs between the right common iliac artery and the fifth lumbar vertebrae, creating risk for compression of the venous outflow. However, it may also occur in the right lower extremity due to compression of the inferior vena cava (IVC) by the right common iliac artery.

May-Thurner syndrome is characterized as venous outflow obstruction, typically due to compression of the iliac vein.

While many patients with May-Thurner syndrome are asymptomatic, others present with swelling of the affected lower extremity from increased venous pressure or the development of venous thrombosis. In some, this leads to ulcerations. When these ulcerations occur on



Figure 5: Circumferential ulceration of the left lower extremity.

the lower extremities, they may progress to become expansive, and often circumferential ulcerations (Figure 5), failing standard wound care in the process. This even includes wound care plans geared toward venous leg ulcerations utilizing compression therapy.

Duplex ultrasound may be useful in identifying iliac vein stenosis. However, while venous duplex has high sensitivity and specificity to deep vein thrombosis and reflux, the deep location of the proximal iliac vein may prevent this test from visualizing

a stenosis and delay the correct diagnosis.

If ulceration of the lower extremity is resistant to traditional treatment with compression and venous duplex, and initial reflux studies fail to present collaborating information, additional imaging should be considered. Advanced imaging, including CT scans, CT venography and MR venography are more sensitive in the diagnosis of May-Thurner syndrome. If suspicion is warranted, referral to vascular intervention service for catheter-based venography should be considered.

Continued on page 82

WOUND MANAGEMENT

Venous Ulcer (from page 81)

Pyoderma Gangrenosum

Pyoderma gangrenosum is a neutrophilic dermatosis that leads to inflammation and ulceration of the

6). Pain is usually present and typically out-of-proportion for the clinical appearance of the ulceration. Many patients with pyoderma gangrenosum have an associated underlying systemic disease such as inflammato-

Pyoderma gangrenosum is a neutrophilic dermatosis that leads to inflammation and ulceration of the skin.

skin. The condition commonly presents as an inflammatory papule or pustule that progresses to a painful ulcer. In the legs, ulcerations often present with deep hue around the border and a purulent base (Figure

ry bowel disease, hematologic disorders, or inflammatory arthritis.

A diagnosis of pyoderma gangrenosum is a diagnosis of exclusion. There are no diagnosis-specific

Continued on page 83

TABLE I

Diagnostic Criteria of Classic, Ulcerative Pyoderma Gangrenosum

Major Criteria (must have both):

1) Rapid progression of a painful, necrolytic cutaneous ulcer with an irregular, violaceous, and undermined border (1 to 2 cm per day or 50% increase in size within one month)

2) Other causes of cutaneous ulceration have been excluded (usually necessitates skin biopsy and laboratory investigations)

Minor Criteria (must have two):

1) History suggestive of pathergy or clinical finding of atrophic, cribriform scarring

2) Systemic disease associated with pyoderma gangrenosum (inflammatory bowel disease, arthritis, IgA gammopathy, or malignancy)

3) Histopathologic findings (sterile dermal neutrophilia, \pm mixed inflammation, \pm lymphocytic vasculitis)

4) Treatment response (rapid response to systemic glucocorticoid treatment)

Adapted from Su WP, et al. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. Int J Dermatol. 2004;43(11):790.

WOUND MANAGEMENT

Venous Ulcer (from page 82)

pathognomonic, clinical, or histologic findings. Neutrophil dysfunction, increased cytokine production, and increases in TNF-alpha are all present in pyoderma, but none are specific to the condition. While diagnosis cannot be made via biopsy, it may be useful for exclusion of other disease processes. Biopsy should be obtained if no prior history of pyoderma is present or in patient with an established history of pyoderma when presentation and/or response to treatment is atypical. Suggested diagnostic criteria (Table 1) requires the exclusion of all other diagnoses before the diagnosis of pyoderma gangrenosum may be made.⁶



Figure 6: Pyoderma gangrenosum of the lower extremity with necrosis into the subcutaneous fat level and violaceous hue at periphery of ulceration.

Prednisone is the most common first line treatment for pyoderma gangrenosum. Other therapies have been used to augment healing and/or to allow for a reduced

**Prednisone is
the most common first line treatment
for pyoderma gangrenosum.**

or avoided use of prednisone. Alternative oral options include colchicine, minocycline, and Dapsone (diaminodiphenyl sulfone) due to their systemic anti-inflammatory effects. Local topical options include corticosteroids such as clobetasol and calcineurin inhibitors such as tacrolimus and pimecrolimus.⁷ When a patient presents with complex systemic disease, it is recommended to consult with the patient's internist, or in the case of patients with known autoimmune disorder, their rheumatologist, before adjusting medications.

Coumadin-Induced Necrosis

Warfarin-induced skin necrosis is a complication of skin ulceration occurring after starting warfarin (Cou-

Continued on page 84



Venous Ulcer (from page 83)

madin) therapy. Skin necrosis and eventual ulcerations occur in the first few days to first week after starting warfarin therapy (Figure 7). A delayed onset of ulcerations may occur if heparin is used to bridge a patient to their INR goal, with necrosis occurring after discontinuation of the heparin. Symptoms are dose dependent and ulceration is more common when a large loading dose is used.⁸

At onset of use, warfarin acts as a pro-clotting agent. This is due to warfarin's mechanism of action in-

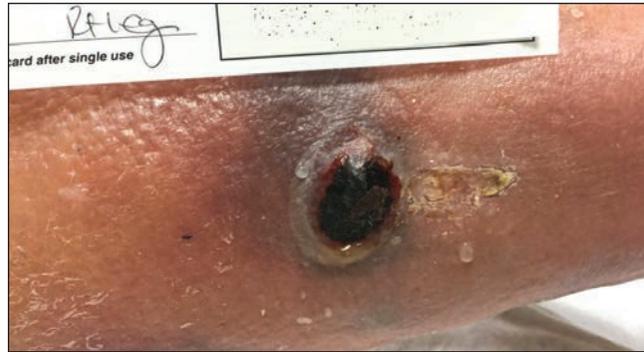


Figure 7: Skin ulceration as a result of warfarin-induced skin necrosis.

ed, its effect on individual factors in the clotting cascade varies as each factor has a different half-life.⁹ Protein C has a shorter half-life and is depleted more rapidly, leading

administration of protein C concentrate or fresh frozen plasma should also be considered.¹⁰ **PM**

References

- ¹ Balin SJ, et al. Calcinos cutis occurring in association with autoimmune connective tissue disease: the Mayo Clinic experience with 78 patients, 1996-2009. *Arch Dermatol.* 2012 Apr;148(4):455-62. Epub 2011 Dec 19.
- ² Robertson LP, et al. Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline. *Ann Rheum Dis.* 2003;62(3):267.
- ³ Taborn J, et al. Colchicine suppression of local and systemic inflammation due to calcinosis universalis in chronic dermatomyositis. *Ann Intern Med.* 1978 Nov;89(5 Pt 1):648-9.
- ⁴ Pappas PJ, et al. Morphometric assessment of the dermal microcirculation in patients with chronic venous insufficiency. *J Vasc Surg.* 1997;26(5):784.
- ⁵ Hung KY, et al. Pentoxifylline modulates intracellular signalling of TGF-beta in cultured human peritoneal mesothelial cells: implications for prevention of encapsulating peritoneal sclerosis. *Nephrol Dial Transplant.* 2003 Apr;18(4):670-6.
- ⁶ Su WP, et al. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol.* 2004;43(11):790.
- ⁷ Lyon CC, et al. Topical tacrolimus in the management of peristomal pyoderma gangrenosum. *J Dermatolog Treat.* 2001 Mar;12(1):13-7.

⁸ McGehee WG, et al. Coumarin necrosis associated with hereditary protein C deficiency. *Ann Intern Med* 1984; 101:59.

⁹ Sallah S, et al. Recurrent warfarin-induced skin necrosis in kindreds with protein S deficiency. *Haemostasis* 1998; 28:25.

¹⁰ Schramm W, et al. Treatment of coumarin-induced skin necrosis with a monoclonal antibody purified protein C concentrate. *Arch Dermatol* 1993; 129:753.

Warfarin-induced skin necrosis

is a complication of skin ulceration occurring after starting warfarin (Coumadin) therapy.

hibiting vitamin K epoxide reductase, which impairs the entire clotting cascade. Inhibiting this enzyme also has an effect on the anti-clotting agents protein C and protein S.

When warfarin therapy is start-

ed, its effect on individual factors in the clotting cascade varies as each factor has a different half-life.⁹ Protein C has a shorter half-life and is depleted more rapidly, leading to an imbalance in clotting versus anti-clotting factors. Often, skin necrosis is seen in individuals with protein C deficiency and to a lesser degree, other inherited thrombophilia disorders such as factor V Leiden and protein S deficiency. It may also be seen during transient periods of reduced protein C levels such as in the setting of cancer.

When warfarin therapy is initiated, the short-term period of hypercoagulability leads to small vessel vascular occlusion and local tissue infarct. These erythematous lesions then darken in hue. This is followed by extravasation of blood into the tissues, leading to the classic blood-stained necrosis of the tissue (Figure 8).

If tissue ulceration is detected, intervention should include immediate discontinuation of warfarin and reversal via administration of intravenous vitamin K. Heparin should administered to anti-coagulate the patient. Finally,



Figure 8: Blood-stained appearing necrosis as a result of initiation of warfarin therapy.



Dr. Johnson is currently a staff physician at the Sanford Bemidji Wound Care and Hyperbaric Center. The center is part of Sanford Health located in Bemidji, Minnesota.