Bilateral Ankle Ulcerations and Gangrene of the Toes

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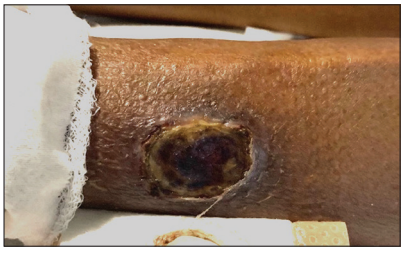

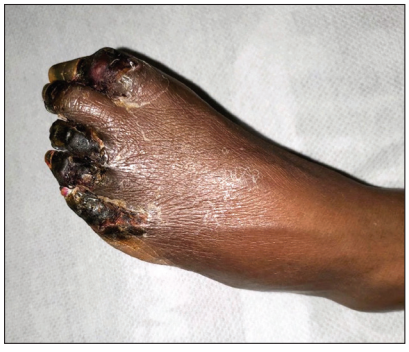

A 74-year-old woman presented to the hospital with large tender ulcerations on both ankles as well as gangrene of the toes of 6 to 8 weeks' duration. The patient had a history of hypertension as well as seropositive nonerosive rheumatoid arthritis that had been diagnosed 8 years prior and was well controlled with leflunomide and prednisone as needed for flares. She denied any history of similar ulcers as well as any recent illnesses, medication changes, or joint pain or swelling. She was evaluated by vascular surgery 1 week prior to the current presentation, at which time her ankle-brachial index score was normal. Skin examination revealed noninflammatory retiform purpura surrounding ulcerations on both ankles (top) and necrosis of all toes (bottom) with peripheral retiform purpura. Joint examination revealed swan neck deformities of multiple fingers with normal range of motion, and there was no effusion or tenderness of the joints of the fingers on palpation. No rheumatoid nodules were present. Laboratory testing revealed elevated rheumatoid factor, anti–cyclic citrullinated peptide, C-reactive protein, and anti–Sjögren syndrome–related antigen A levels and low C4 levels. Cryoglobulins, antineutrophil cytoplasmic antibodies, and serum protein electrophoresis were negative. Biopsy of an ulcer on the right ankle showed medium-sized vessel vasculitis with fibrinoid necrosis, including endothelium necrosis and a perivascular lymphocytic infiltrate. Direct immunofluorescence demonstrated dense, granular, intraperivascular deposition of IgM and IgG with slightly weaker deposition of IgA, C3, and C5b-9 in the dermis and subcutis with a greater effect on medium-sized vessels.

THE BEST **DIAGNOSIS IS:**

a. cutaneous polyarteritis nodosa
b. nonuremic calciphylaxis
c. peripheral vascular disease
d. rheumatoid vasculitis
e. type I cryoglobulinemia

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THE **DIAGNOSIS:** Rheumatoid Vasculitis

A diagnosis of rheumatoid vasculitis (RV) was made based on the clinical features, histopathology, and laboratory results in the setting of rheumatoid arthritis (RA). The distal gangrene was surgically managed with bilateral transmetatarsal amputation followed by ankle collagen graft placement. The patient was started on a prednisone taper for 1 month (40 mg/d for 3 days, then 30 mg/d for 3 days, then 20 mg/d for 24 days) before transitioning to rituximab (375 mg/m^2 once weekly for 4 weeks), which improved the size and depth of the ulcers.

Rheumatoid vasculitis is an inflammatory disease that affects small- to medium-sized blood vessels in patients with RA. The pathogenesis involves immune complex deposition and complement system activation, leading to vessel wall destruction.[1] Rheumatoid vasculitis is an extra-articular complication of RA that primarily is observed in seropositive patients with long-standing severe disease.[1,2] The mean duration between RA diagnosis and RV onset is 10 to 14 years.[2] Rheumatoid vasculitis manifests heterogeneously and can affect many organs; however, it most frequently affects the skin. Cutaneous manifestations vary in severity. Palpable purpura, pyoderma gangrenosum, and distal ulcers can be seen in addition to extensive digital ischemia with necrosis, as was present in our patient.[1]

When RA patients present with skin changes that are concerning for vasculitis, RV should be suspected. Currently, there are no validated diagnostic criteria for RV. Diagnosis is made based on clinical presentation and tissue biopsy. Histopathology shows small- and medium-sized vessel wall destruction with neutrophilic, granulomatous, or lymphocytic infiltration, which may be observed only in the lower dermis sparing superficial vessels.[3] Direct immunofluorescence shows IgM, IgA, and C3 deposition within and around vessels.[3,4] Laboratory findings including elevated inflammatory markers, positive rheumatoid factor, positive anti–cyclic citrullinated peptide, and hypocomplementemia support a diagnosis of RV.[1,2]

Mortality rates for RV remain high, necessitating aggressive treatment. High-dose corticosteroids typically are combined with immunosuppressant or biologic agents, frequently cyclophosphamide or rituximab.[1] Consistent with other reported cases, our patient's ulcers improved with rituximab and oral steroids.

The differential diagnosis for our patient included type I cryoglobulinemia, cutaneous polyarteritis nodosa (CPAN), peripheral vascular disease (PVD), and non-uremic calciphylaxis. Type I cryoglobulinemia manifests due to direct occlusion of vessels by precipitation of monoclonal immunoglobulin.[5] It commonly is associated with lymphoproliferative diseases such as Waldenström macroglobulinemia and multiple myeloma. While our patient's history of RA was a risk factor for mixed cryoglobulinemia as opposed to type I cryoglobulinemia, the clinical presentation aligned more closely with type I cryoglobulinemia. The clinical manifestations of type I cryoglobulinemia are related to intravascular obstruction, including Raynaud phenomenon, retiform purpura, ischemic ulcers, distal gangrene, and cold-induced urticaria.[6-8] Type I cryoglobulinemia also frequently has neurologic and renal manifestations. Histopathology, along with the detection of serum cryoglobulins, is the gold standard for diagnosing cryoglobulinemia.[6] On histopathology, type I cryoglobulinemia typically shows a thrombotic vasculopathy with amorphous eosinophilic periodic acid–Schiff–positive thrombi.[7] False-negative results are particularly common with serum cryoglobulins, so repeat testing often is needed. While many clinical features overlap, RV is the most likely diagnosis in a patient with long-standing RA who is negative for cryoglobulins and has no history of lymphoproliferative disorders.

Cutaneous polyarteritis nodosa is a necrotizing vasculitis that similarly affects small- and medium-sized vessels. The exact etiology is unknown, but the high prevalence of anti–phosphatidylserine/prothrombin complex antibodies among patients with CPAN suggests that prothrombin bound to apoptotic endothelial cells may initiate the immune response.[9] Underlying infection and inflammatory and autoimmune diseases (including group A ß-hemolytic streptococcus, hepatitis B, inflammatory bowel disease, myasthenia gravis, and RA) also may trigger CPAN.[9,10,11] The most common clinical manifestations of CPAN are tender subcutaneous nodules, livedo reticularis, leg ulcers, and cutaneous necrosis. Extracutaneous symptoms such as myalgias and arthralgias also can be associated with CPAN. There is no specific serologic test to diagnose CPAN; the diagnosis is made based on clinicopathologic correlation, with characteristic histopathology showing leukocytoclastic vasculitis in the small- and medium-sized arteries of the deep dermis or hypodermis.[9]

Peripheral vascular disease is a manifestation of atherosclerosis that affects the legs. Risk factors for atherosclerosis, especially smoking and diabetes mellitus, similarly increase the risk for PVD.[12] The most common clinical manifestation of PVD is intermittent claudication, but rarely PVD can progress to critical limb ischemia, which is characterized by pain at rest, nonhealing ulcers, or gangrene of the legs.[12] Common findings on physical examination include diminished or absent pedal pulses, abnormal skin color, and skin that is cool to the touch.[12] The standard diagnostic test for PVD affecting the legs is evaluation via the ankle-brachial index, with a score of 0.90 or lower being diagnostic of PVD, a score of 0.91 to 1.00 being borderline, and a score of 1.01 to 1.40 being normal.[13]

Calciphylaxis most frequently is seen in patients with end-stage kidney disease; however, it also has been less commonly reported in patients with normal kidney function, known as nonuremic calciphylaxis. It is characterized by calcification of arteries, arterioles, and soft tissues, which can lead to thrombosis and eventually ischemia and necrosis of the skin.[14] Calciphylaxis initially causes tender, indurated, erythematous to purpuric plaques that quickly progress to retiform and stellate ulcers with overlying necrotic eschars.[15] Disease typically occurs on the legs and areas that are rich in adipose tissue, such as the abdomen and thighs.[16] Skin biopsy is needed for diagnosis of calciphylaxis. Characteristic histopathologic findings include calcification, microvascular thrombosis, and fibrointimal hyperplasia of small dermal and subcutaneous arteries and arterioles.[16]

We present a rare case of RV in a patient with well-controlled RA. While the incidence of RV is decreasing in the United States and United Kingdom due to the initiation of earlier and more aggressive RA therapies, mortality remains high.[1] Thus, it is important to include RV in the differential diagnosis when there are skin changes concerning vasculitis in patients with seropositive, long-standing RA, even if the RA is well controlled.

REFERENCES

1. Kishore S, Maher L, Majithia V. Rheumatoid vasculitis: a diminishing yet devastating menace. *Curr Rheumatol Rep*. 2017;19:39. doi:10.1007/s11926-017-0667-3
2. Makol A, Matteson EL, Warrington KJ. Rheumatoid vasculitis: an update. *Curr Opin Rheumatol*. 2015;27:63-70. doi:10.1097/BOR.0000000000000126
3. Patterson J. The vasculopathic reaction pattern. In: Patterson J, ed. *Weedon's Skin Pathology*. 5th ed. Elsevier; 2021:241-301.
4. Lora V, Cerroni L, Cota C. Skin manifestations of rheumatoid arthritis. *G Ital Dermatol Venereol*. 2018;153:243-255. doi:10.23736/S0392-0488.18.05872-8
5. Kolopp-Sarda MN, Miossec P. Cryoglobulinemic vasculitis: pathophysiological mechanisms and diagnosis. *Curr Opin Rheumatol*. 2021;33:1-7. doi:10.1097/BOR.0000000000000757
6. Silva F, Pinto C, Barbosa A, et al. New insights in cryoglobulinemic vasculitis. *J Autoimmun*. 2019;105:102313. doi:10.1016/j.jaut.2019.102313
7. Harel S, Mohr M, Jahn I, et al. Clinico-biological characteristics and treatment of type I monoclonal cryoglobulinaemia: a study of 64 cases. *Br J Haematol*. 2015;168:671-678. doi:10.1111/bjh.13196
8. Desbois AC, Cacoub P, Saadoun D. Cryoglobulinemia: an update in 2019. *Joint Bone Spine*. 2019;86:707-713. doi:10.1016/j.jbspin.2019.01.016
9. Morgan AJ, Schwartz RA. Cutaneous polyarteritis nodosa: a comprehensive review. *Int J Dermatol*. 2010;49:750-756. doi:10.1111/j.1365-4632.2010.04522.
10. Criado PR, Marques GF, Morita TC, et al. Epidemiological, clinical and laboratory profiles of cutaneous polyarteritis nodosa patients: report of 22 cases and literature review. *Autoimmun Rev*. 2016;15:558-563. doi:10.1016/j.autrev.2016.02.010
11. Daoud MS, Hutton KP, Gibson LE. Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. *Br J Dermatol*. 1997;136:706-713.
12. Campia U, Gerhard-Herman M, Piazza G, et al. Peripheral artery disease: past, present, and future. *Am J Med*. 2019;132:1133-1141. doi:10.1016/j.amjmed.2019.04.043
13. Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association [published correction appears in Circulation. 2013 Jan 1;127:e264]. *Circulation*. 2012;126:2890-2909. doi:10.1161/CIR.0b013e318276fbcb
14. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis*. 2015;66:133-146. doi:10.1053/j.ajkd.2015.01.034
15. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med*. 2018;378:1704-1714. doi:10.1056/NEJMra1505292
16. Gomes F, La Feria P, Costa C, et al. Non-uremic calciphylaxis: a rare diagnosis with limited therapeutic strategies. *Eur J Case Rep Intern Med*. 2018;5:000986. doi:10.12890/2018_000986