REVIEW

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Skin Deep: A Narrative Case Series and Review of Cutaneous Vasculitis and Possible Doppelgängers

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ABSTRACT

Cutaneous vasculitis presents with a wide variety of lesions. These may occur in systemic vasculitis, represent isolated cutaneous vasculitis, or signal mimickers arising from non-rheumatologic etiologies, highlighting the importance of a broad differential diagnosis. The consumption of recreational drugs and various adulterants has been increasingly recognized for their cutaneous manifestations that may mimic a vasculitic lesion. This combination review and case series highlights the vascular anatomy of the skin and a suggested clinical approach when evaluating vasculitic-appearing lesions through 4 vignettes.

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KEYWORDS: Cutaneous vasculitis; Immunoglobulin A vasculitis; Leukocytoclastic vasculitis; Levamisole; Xylazine

INTRODUCTION

Vasculitis comprises a diverse group of disorders. The size, type, and distribution of affected blood vessels determine clinical presentations. The wide variety of cutaneous lesions that may occur secondary to vasculitis often presents a diagnostic challenge. Cutaneous findings may herald systemic vasculitis, represent isolated cutaneous disease, or signal mimickers. These mimics may encompass broad categories such as thromboembolism, non-inflammatory vasculopathy, infection, and hematologic disorders, which clinicians must consistently consider in their differential.

Another etiologic consideration is evolving from recreational drug use and unwitting coingestion of adulterants. Although there is a better understanding of the clinical patterns among prescription drugs implicated in drug-induced vasculitis, there is a paucity of knowledge on cutaneous manifestations of adulterants utilized in recreational drugs. The aforementioned ambiguity likely stems from a combination of factors not limited to the evolving landscape of drug adulteration, lack of clinically available testing to identify adulterants, and clinician naivety.

Understanding the vascular anatomy of the skin is foundational to interpreting cutaneous vasculitis and guides the diagnostic approach based on the presenting skin lesion. The skin's vascular system is composed of a deep plexus at the dermohypodermic junction and a superficial subpapillary plexus, with nourishing arteries rising from the hypodermis to feed dermal capillaries. Small-vessel involvement (superficial plexus) tends to manifest as persistent urticarial plaques, papules, pustules, or palpable purpura, whereas deeper vessel involvement produces nodules, erosions, ulcers, or livedo. Necrosis or eschar can occur with either type of vessel involvement but is more common when thrombosing vasculopathy is present.[1,2]

When clinicians are engaged in these cases, a thorough history is paramount. Ascertaining prescription drug history, determining recreational drug exposure, assessing for underlying rheumatological disease, and evaluating for systemic manifestations of vasculitis are essential to guide testing, prognostication, and management. Objective testing requires mandatory investigations and personalized testing based upon presentation. Skin biopsy, including direct immunofluorescence, is essential and often provides the most yield. Direct immunofluorescence is particularly important for identifying immune complex deposition. Practice guidelines support biopsy of well-developed and

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early cutaneous lesions within 1-2 days of appearance. Cutaneous lesions suggesting deeper vessel vasculitis require a deep punch or incisional biopsy for assessment of the deep plexus.[3] Initial labs should include chemistries, complete blood count (CBC), and urinalysis with microscopy. Although inflammatory markers are often elevated in cutaneous vasculitis, they offer limited diagnostic specificity. A chest x-ray may shed light on systemic involvement or give clues to alternative diagnoses.

A comprehensive assessment for systemic manifestations (constitutional symptoms, arthralgias, pulmonary, renal, gastrointestinal, and neurologic symptoms) and a review of past medical history can guide additional testing. If infectious etiologies are suspected or treatment with immunosuppressives is being considered, assessment for hepatitis B, hepatitis C, tuberculosis, and human immunodeficiency virus should be pursued. Blood cultures, anti-streptolysin O titers, RF, and echocardiogram may also be appropriate. Antinuclear antibodies and subsequent testing for extractable nuclear antigens, if positive, rheumatoid factor (RF), complement levels (C3, C4), cryoglobulins, and antineutrophil cytoplasmic antibodies (ANCA) are appropriate for lesions suggestive of small vessel vasculitis. Serum protein electrophoresis, peripheral blood smear, and age-appropriate cancer screening should be considered in those with risk factors for neoplastic causes. Doppler ultrasonography should be utilized in patients with lesions or ulcerations characteristic of venous insufficiency and peripheral arterial disease or when there is diagnostic uncertainty.

Through 4 vignettes, this case series will explore the approach to vasculitic-appearing lesions and differentiation from mimickers related to recreational drug use (Table).

CLINICAL SIGNIFICANCE

- Cutaneous findings may indicate systemic vasculitis, represent isolated cutaneous disease, or signal mimickers including thromboembolism, noninflammatory vasculopathy, infection, or hematologic disorders. Clinicians must consistently consider these in their differential.
- Cutaneous manifestations of recreational drug adulterants (xylazine and levamisole) may be confused for cutaneous vasculitis.
- Understanding the vascular anatomy of the skin is foundational to interpreting cutaneous vasculitis and guides diagnostic approach based on the presenting skin lesion.

CASE 1

A male in his 40s was brought to the emergency department (ED) for suspected opiate overdose. He received naloxone for altered mental status and respiratory depression. There was reported partial improvement in his mentation and respiratory rate with naloxone, but ED providers noted persistent somnolence. His medical history was notable for polysubstance abuse. Respiratory status improved with time and supportive care, and the patient was subsequently admitted for detoxification and bilateral lower extremity leg wounds.

The patient reported a 3-month history of bilateral leg wounds on his anterior shins. Before his presentation, he noted coalescence of ruptured blistering lesions, leading to ulceration. Examination revealed a large, linear, ovoid ulcer with exposed subcutaneous fat on the right medial tibia, bordered by raised, hyperpigmented skin (Figure 1). X-rays showed soft tissue edema without osseous abnormalities. He was started on broad-spectrum antibiotics and received wound care. Additional history from consultants revealed no antecedent trauma, skin pathergy, or desquamative rashes. He denied new or chronic prescription medication use, subjective fevers, unintentional weight loss, malaise, dysuria, penile discharge, history of rheumatologic diseases, or symptoms compatible with mononeuritis multiplex. He reported postprandial "gnawing" abdominal pain but no gastrointestinal bleeding. He stated he was intermittently homeless. The patient noted regular fentanyl use. Previously, he would administer fentanyl intravenously, but due to increasing difficulty accessing his peripheral veins, he started injecting fentanyl into his shins. In a discussion regarding potential adulterants, the patient queried the possibility of his fentanyl being mixed with xylazine, colloquially known as "Tranq."

Laboratory studies for this patient demonstrated normal CBC and chemistry. Ultrasound of the bilateral lower extremities ruled out arterial stenosis or venous thromboembolism. Blood cultures were negative, and echocardiography showed no endocarditis. Hepatitis B studies were suggestive of recovery from prior infection, and hepatitis C studies demonstrated active viremia. Rheumatoid factor was positive, and serum protein electrophoresis revealed diffuse hypergammaglobulinemia without monoclonal spikes. Serum cryoglobulins were negative. Computed tomography (CT) angiography of the abdomen and pelvis was performed to evaluate for polyarteritis nodosa; however, it showed no aneurysms, dissections, or stenosis characteristic of this disease. The diagnosis of xylazine-induced ulcerations was made.

Xylazine is a peripheral and central nervous system alpha-2 receptor agonist with Food and Drug Administration (FDA)-approved use in veterinary medicine for sedation and analgesia in domestic animals. It is structurally similar to clonidine and dexmedetomidine, which are also utilized for their sympatholytic effects. The recognition of xylazine as an adulterant with fentanyl has been increasingly identified.[4] The prevalence of its use displays wide geographic variability: San Diego County identified xylazine in only 1.7% of law enforcement seized fentanyl samples, and in Philadelphia, 78% of patients who tested positive for fentanyl via urine-based assays also tested

Table 1 Review Table

	Xylazine-Induced Ulcers	Levamisole-Induced Vasculitis	Leukocytoclastic Vasculitis	IgA Vasculitis
Etiology	Adulterant in recreational drugs (eg, fentanyl); alpha-2 agonist causing vasoconstriction	Adulterant in recreational drugs (eg, cocaine); triggers neutrophil NETosis against endothelial cells	Histopathologic diagnosis. Idiopathic, secondary to drugs, infection, sepsis, neoplasm, or part of another type of vasculitis	IgA immune complex deposition often triggered by infection, vaccination
Cutaneous lesions	Large deep ulcers with devitalized tissue	Purpura >>> blisters ~ livedoid ~ erythematous plaques and papules	Purpura, petechiae, urticaria, bullae, ulcers	Purpura >>> petechiae ~ ulcers
Location	Local sites of recreational drug administration (common), distant sites (rare)	Extremities, ears, and nose	Variable	Lower extremities >>> upper extremities > buttocks ~ abdomen
Histopathology and immunofluorescence	Epidermal and dermal necrosis; minimal inflammatory cells. (−) Immune complexes	Small vessel vasculitis, thrombotic vasculopathy. (+) Immune complexes	Neutrophil infiltration of vessel walls with leukocytoclasia, fibrinoid necrosis, and extravasated RBCs. (+) Immune complexes	Small vessel vasculitis; IgA predominant immune complexes
Systemic involvement	(−)	Heme (leukopenia and neutropenia), arthralgia, ENT (nasal obstruction, epistaxis, septal perforation)	Variable depending upon underlying etiology	Hematuria, proteinuria, oligoarthritis, gastrointestinal involvement

ENT = ear, nose, and throat; IgA = immunoglobulin A; RBCs = red blood cells.

positive for xylazine.[5,6] Clinicians should be cognizant of potential xylazine co-ingestion in suspected opiate overdoses, especially when respiratory and central nervous system depression are refractory to naloxone.

In the periphery, xylazine is postulated to preferentially agonize the alpha-2b subtype predominantly found in vascular smooth muscle cells, which mediate vasoconstriction. The subsequent effect of vasoconstriction results in decreased perfusion, yielding ulceration, necrosis of the epidermis and dermis, and increased susceptibility to superimposed infection.[4] Although ulcer formation is most likely to occur at injection sites, case reports have noted the development of leg ulcerations in the absence of patients injecting these sites.[7] Case series have sought to identify

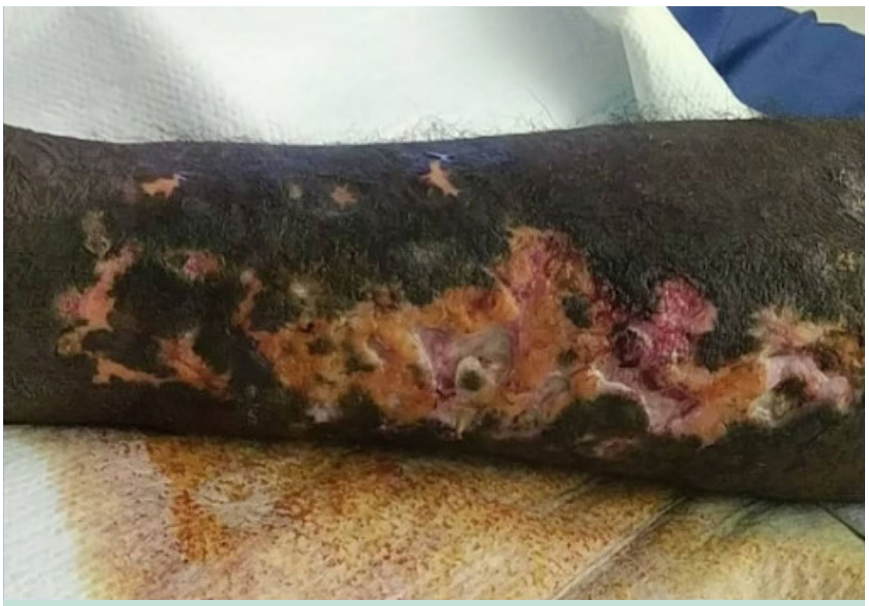

Figure 1 Xylazine-induced ulceration.

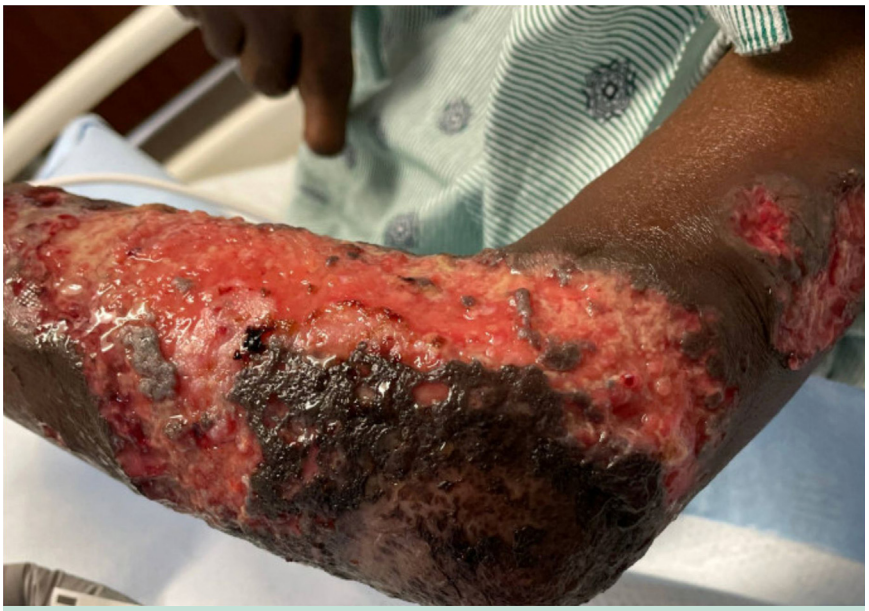

Figure 2 Levamisole-induced vasculitis.

common clinical features of wounds associated with xylazine exposure and outcomes. One series found that 90% of wounds associated with exposure to xylazine were located on the extremities, and 60% of wound beds had eschar.[8] Another series of 82 patients found 54% xylazine-associated wounds had associated osteomyelitis, and surgery was recommended in 78% of cases.[9] Retrouvey et al[10] have proposed management strategies ranging from wound care to amputation, dependent upon depth and type of soft tissue involvement when xylazine is implicated.

CASE 2

A female in her 60s with rheumatoid arthritis was admitted for the progression of several enlarging ulcers located on her extremities. She had been admitted to the hospital in the preceding month for ulcerations located on her left elbow and right hand. Wound cultures demonstrated polymicrobial growth with clinical concern for skin and soft tissue infection without osteomyelitis. She was discharged on a course of levofloxacin and wound care.

Upon interval presentation, she endorsed progressive enlargement and depth of preexisting ulcerations and development of several new ulcerations despite adherence to Levaquin (Janssen Pharmaceuticals, Inc, Beerse, Belgium). Examination revealed a large, deep, and wide ulceration with exposed subcutaneous tissue and interspersed overlying necrotic tissue over the left elbow (Figure 2). Several similar-appearing ulcerative, circular, quarter-sized lesions with exposed subcutaneous tissue and oozing blood were noted. No peripheral synovitis was appreciated. Dried blood was noted in the left nares without polyps or nasal ulceration. The review of systems was notable for prior episodes of epistaxis, and the patient revealed daily use of intranasal crack cocaine. The patient denied intravenous drug use or hemoptysis, and had no findings suggestive of mononeuritis multiplex on examination.

Initial skin biopsy of the ulcer bed demonstrated extensive necrosis and inflammation of dermal collagen bundles. No viable epidermal tissue or blood vessels were identified. Testing revealed a low positive RF, erythrocyte sedimentation rate, and C-reactive protein; normal C3 and C4 levels; and a positive perinuclear ANCA via immunofluorescence at a titer of 1:640. Myeloperoxidase antibodies via enzyme-linked immunosorbent assay were also positive. A repeat skin biopsy performed at the edge of a lesion demonstrated marked inflammation and superficial to mid dermal perivascular inflammation with fibrinous material suggestive of vasculitis. Immunofluorescence showed a positive signal for fibrinogen. The diagnosis of levamisole-induced vasculitis was made.

Levamisole is an anthelmintic agent approved by the FDA in 1971 for treating parasitic infections. Its immunomodulatory properties led to its use in treating autoimmune conditions such as rheumatoid arthritis. Severe side effects —agranulocytosis, vasculitis, and leukoencephalopathy— prompted withdrawal of FDA-approved use, though it remains in veterinary use in the Western Hemisphere.[11] Since 2003, levamisole has emerged as a cocaine adulterant, detected in 83%−88% of cocaine users' samples, enhancing cocaine's psychotropic effects while reducing production costs.[12]

The most common morphologic skin lesion associated with levamisole-induced vasculitis is purpura. Blisters, ulcerations, livedo, and erythematous plaques and papules have also been reported in a systematic review. These lesions frequently affect the extremities, nose, and ears. Histopathology frequently identifies small vessel vasculitis, thrombotic vasculopathy, or both.[13] Extracutaneous manifestations include arthralgias and nasal involvement (nasal

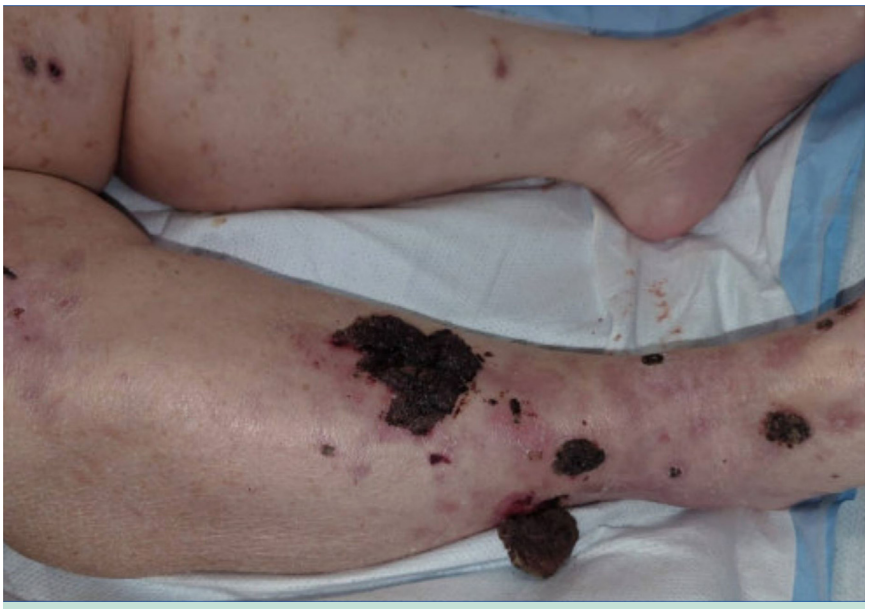

Figure 3 Leukocytoclastic vasculitis.

obstruction, epistaxis, necrotizing ulcerative lesions, extensive crusting, and septal perforation). Hematologic abnormalities such as leukopenia and neutropenia are frequent, contrasting with ANCA-associated vasculitis' typical inflammatory profile.[13]

Antibody profiles in levamisole-induced vasculitis differ markedly from ANCA-associated vasculitis. Antineutrophil cytoplasmic antibodies are detected in 93.8% of cases, with perinuclear ANCA (59.3%) prevailing and 43.2% showing dual anti-myeloperoxidase and anti-proteinase 3 positivity. In ANCA-associated vasculitis, ANCA positivity is usually singular (myeloperoxidase in microscopic polyangiitis, proteinase 3 in granulomatosis with polyangiitis). Additionally, 67.9% of patients exhibit anti-phospholipid antibodies, a feature virtually absent in ANCA-associated vasculitis. Dual antineutrophil cytoplasmic antibodies and anti-phospholipid antibodies positivity, alongside leukopenia, serves as a diagnostic "red flag" for levamisole exposure. Cessation of levamisole typically resolves symptoms, unlike ANCA-associated vasculitis's unpredictable relapses requiring immunosuppressive therapy.[13]

CASE 3

A female in her 70s presented to the hospital for progression of a rash. She had a recent admission for sepsis with methicillin-sensitive *Staphylococcus aureus* bacteremia. The source of the bacteremia was attributed to cellulitis of the right lower extremity wherein the patient was noted to have multiple small superficial erosions with some demonstrating overlying eschar and others with surrounding erythema. She was discharged on a 4-week course of cefazolin. Two months after completion, the patient was readmitted with the progression of previously noted lesions on the right lower extremity and the development of new lesions. The patient endorsed a uniform evolution of the lesions occurring over several weeks, initially manifesting as erythematous patches, followed by tense bullae and subsequent rupture, and lastly development of eschar. The patient denied having any oral or genital lesions. Other than cefazolin, she denied exposure to new prescription or over-the-counter medications.

Physical examination of the right lower extremity demonstrated a large, irregular-shaped eschar over the right shin surrounded by faint purpura. Several smaller circular eschars were noted (Figure 3). Circular and ovoid erosions without eschar were identified in the skin folds of the left lower abdomen and the left shoulder and axilla. A few lesions still maintained their bullous morphology.

Laboratory investigation revealed moderate leukocytosis, stable chronic normocytic anemia, and mild thrombocytosis. Chemistry demonstrated evidence of acute kidney injury. Urinalysis with microscopy demonstrated microscopic hematuria and pyuria. The patient received intravenous fluids and broad-spectrum antibiotics out of concern for sepsis. Blood and urine cultures were negative, and non-contrast CT of the chest, abdomen, and pelvis did not demonstrate any acute findings or infectious foci. No valvular vegetations were appreciated on echocardiography.

Antinuclear antibodies, anti-double-stranded deoxyribonucleic acid, serum cryoglobulins, Sjögren's syndrome-related antigen A and B, and RF were negative. Autoantibodies targeting desmoglein, BP180, and BP230 obtained in the evaluation for blistering dermatoses were also negative. Complement levels were within normal limits. Antineutrophil cytoplasmic antibodies via indirect immunofluorescence was positive in an atypical ANCA pattern at a titer of 1:160. Enzyme-linked immunosorbent assay for proteinase 3 was negative, but a low positive was noted for myeloperoxidase. Histopathology on skin biopsy

demonstrated small vessel inflammation and fibrinoid necrosis. Direct immunofluorescence noted immunoglobulin G, immunoglobulin A (IgA), immunoglobulin M, and C3 immune complex deposition. The renal biopsy obtained was most suggestive of acute tubular necrosis and lacked stigmata of renal vasculitis. In the setting of leukocytoclastic vasculitis on histopathology, drug-induced immune complex vasculitis secondary to cefazolin was suspected.

Leukocytoclastic vasculitis is a histopathologic pattern of findings characterized by the presence of neutrophilic infiltration with signs of leukocytoclasia, fibrinoid necrosis, and damaged endothelial cells, evidenced by extravasated erythrocytes affecting small vessels.[14] As a histopathologic entity, the aforementioned findings do not equate a clinical diagnosis as leukocytoclastic vasculitis can be identified in ANCA-associated vasculitis, immune complex mediated vasculitis, vasculitis associated with a systemic autoimmune or rheumatic disease, or vasculitis associated with a probable etiology (drugs, infection, sepsis, neoplasms).[15] Published studies have reported variable findings regarding the association of leukocytoclastic vasculitis on skin biopsy and a clinically diagnosed form of systemic vasculitis. Percentages range from 8%-55%.[16–18] Leukocytoclastic vasculitis deemed "idiopathic" or not associated with a systemic vasculitis, rheumatic disease, drug exposure, or infection ranges from 18.8%-46%.[16,17] Direct immunofluorescence with detection of immune complex deposition may help discern between subtypes of immune complex vasculitis, which includes IgA vasculitis (IgAV), cryoglobulinemic vasculitis, hypocomplementemic urticarial vasculitis, and immunoglobulin M and immunoglobulin G immune complex vasculitis.

Clinically, leukocytoclastic vasculitis may present palpable purpura, petechiae, persistent urticarial lesions, and, less commonly, vesicles or bullae, which may progress to ulceration or necrosis in severe cases.[19] Additional investigations into the etiology of leukocytoclastic vasculitis should always be tailored based on patient presentation. Treatment varies depending upon the aforementioned etiologic considerations.

CASE 4

A male in his 40s was admitted to the hospital for evaluation of acute onset rash. In the preceding days, he noted the development of numerous painful, pruritic, circular, red, and purple papules of varying sizes across his lower abdomen, bilateral lower extremities, and buttocks. He reported concurrent acute-onset knee and ankle pain in the absence of inciting factors and left-sided abdominal pain. This was the first reported manifestation of this constellation of symptoms. He denied headache, photosensitivity, phonosensitivity, neck pain or stiffness, dysuria, or penile discharge. There were no reported symptoms compatible with an upper respiratory tract infection, pneumonia, gastroenteritis, or urinary tract infection preceding his presentation. He denied using prescription or recreational drugs or over-the-counter supplements and had not received any recent vaccinations.

Examination demonstrated numerous palpable purpura in the aforementioned distribution, with some lesions demonstrating a small necrotic eschar (Figure 4). Trace effusions were appreciated in the knees and left tibiotalar joint with intact active and passive range of motion. No abnormalities were detected on neurological examination. The patient reported tolerating oral intake without provocation of symptoms and denied abnormal appearance of his stools.

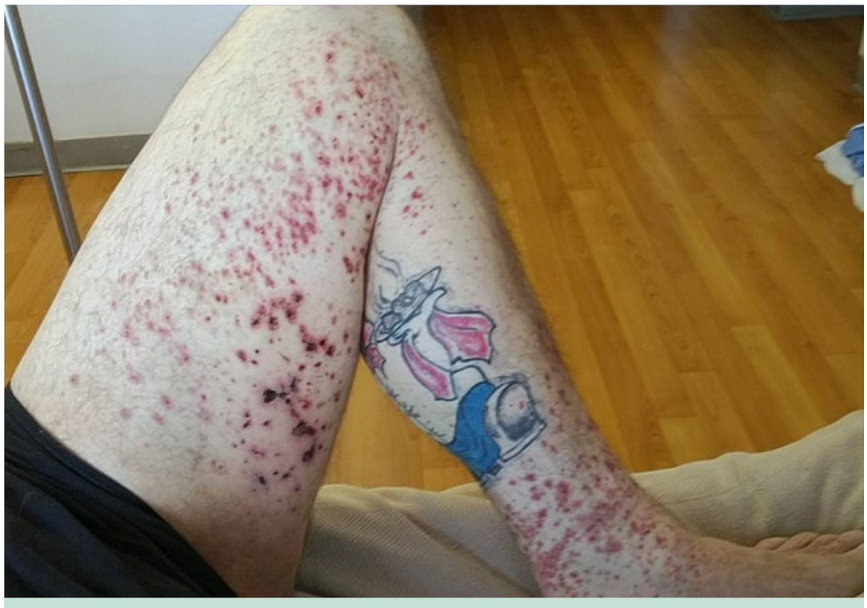

Figure 4 Immunoglobulin A vasculitis.

Lab studies demonstrated a grossly normal CBC and chemistry. Lactic acid and lipase were within normal limits. Antinuclear antibodies, RF, and ANCA via IF and enzyme-linked immunosorbent assay were negative. Complement levels and quantitative values for immunoglobulins A, G, and M were within normal limits. A non-contrast CT scan of the abdomen and pelvis was obtained in the ED. Interpretation noted focal dilation of the proximal loops of the jejunum with mild thickening of the bowel wall and mesenteric panniculitis with extensive subcentimeter mesenteric adenopathy. Findings were felt to possibly represent vasculitis affecting the intestinal vasculature. An excisional biopsy of the skin demonstrated subepidermal splitting and small vessel vasculitis with direct immunofluorescence studies staining positive for IgA and C3 deposition. The diagnosis of IgAV was made.

Immunoglobulin A vasculitis is a small-vessel immune-complex mediated vasculitis characterized by the classic tetrad of palpable purpura, renal involvement, abdominal pain, and arthritis or arthralgia. Although the vast majority of index cases arise in children, adult-onset cases do occur, with one cohort identifying a mean age of diagnosis of 50.1 years among 260 patients with adult-onset IgAV.[20,21] Compared with other types of cutaneous vasculitis, the cutaneous manifestations of IgAV are much more homogeneous, with purpura being considered a ubiquitous part of the disease presentation and included in classification criteria.[22] Ulcerative skin lesions may also be present with frequencies ranging between 13% and 35% among different cohorts.[21,23,24] Distribution of purpura is similarly homogenous with lower limb purpura nearly always present, followed by upper limb purpura, and abdominal purpura in terms of frequency.[21] Joint manifestations most commonly arise in the knees and ankles and, when present, are associated with more frequent gastrointestinal involvement.[25] In contrast to pediatric IgAV, there is a higher incidence of renal involvement, the presence of IgAV nephritis (IgAVN), and progression to end-stage renal disease in adults. Older age at diagnosis, pre-existing chronic kidney disease, and hypertension at diagnosis have been associated with worse renal outcomes in IgAV.[26-28] Kidney Disease Improving Global Outcomes has previously commented on the limited evidence base for adult-onset IgAVN and how many of the recommendations are extrapolated from IgA nephropathy. In the 2021 Clinical Practice Guideline for the Management of Glomerular Diseases,[29] they recommend shared decision-making when considering initiation of glucocorticoids among patients with IgAVN who are at high risk for progressive chronic kidney disease and, if utilized, following dosing protocols utilized in IgA nephropathy.

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