Skin Disorders in Kidney Disease: Core Curriculum 2026

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Skin disorders occur commonly in patients with chronic kidney disease (CKD) and may greatly impact their quality of life. These skin disorders have varying underlying pathophysiologies, but there are a few common mechanisms including the accumulation of uremic solutes, metabolic disturbances, and inflammation. Pruritus in the setting of CKD (CKD-associated pruritus or CKD-aP), acquired perforating disorder (APD), calcinosis cutis, calciphylaxis, cutaneous lupus, and vasculitis are skin disorders often occurring in association with kidney disease and with which clinicians should be familiar. CKD-aP is reported to have a prevalence of 40% among patients receiving dialysis and 20% with earlier stages of CKD. Acquired perforating disorder (APD) is a skin disorder seen commonly in patients with diabetes mellitus and kidney failure that presents typically with crater-shaped nodular eruptions with a central hyperkeratosis. Calcinosis cutis is a skin disorder that occurs when calcium salts deposit into skin and subcutaneous tissues. Calciphylaxis is a rare cutaneous vasculopathy characterized by microvascular calcium deposition and thrombosis leading to tissue ischemia and subsequent skin necrosis. Lupus erythematosus and the vasculitides are systemic disorders with distinct skin manifestations that may offer clues as to the underlying disorder.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Skin disorders are common in chronic kidney disease (CKD) and present with diverse manifestations depending on both kidney disease stage and the underlying etiology. They are a cause of major symptom burden and in some cases increased mortality. Although there is no unifying underlying mechanism for all skin disorders that occur in CKD, there are several pathophysiologic themes, including the ones we will discuss, that are implicated.

Accumulation of Uremic Solutes

In the setting of CKD, solutes that are normally excreted by the kidneys begin to accumulate. In advanced CKD, urea may deposit in the skin, causing the whitish-gray appearance of uremic frost that is now quite rare in the era of kidney replacement therapies. There are also several unmeasured large solutes that, despite adequate urea clearance, could play a role in the development of skin disorders such as pruritus.

Metabolic Disturbances

High serum phosphorous levels may lead to calcification of both small and medium-sized vessels within the dermis and subcutaneous tissues. Vascular calcification has been implicated in the pathogenesis of peripheral vascular disease and calciphylaxis, and elevated serum calcium levels and skin trauma can result in calcinosis cutis and exacerbate calciphylaxis.

Inflammation and Autoimmunity

The development of autoantibodies and systemic inflammation underlie skin and kidney manifestations in a number of disorders such as systemic lupus erythematosus (SLE).

Chronic Kidney Disease–associated Pruritus

Case 1: *A 52-year-old man with kidney failure due to type 1 diabetes mellitus has been on in-center hemodialysis (HD) for 5 years after the failure of his allograft. For the preceding 6 months he reported intense pruritus that does not worsen or improve during his HD treatments. His dialyzer has been changed, and he is no longer given heparin during his dialysis treatments, but there has been no improvement in his symptoms. Intravenous diphenhydramine given during his dialysis treatments has not provided any relief. Examination of the exposed areas of his skin at dialysis has revealed generalized xerosis of the bilateral shins and ankles with areas of ichthyosiform change and scattered lightly hyperpigmented macules and patches (Fig 1). He is dialyzed with a high-flux polysulfone dialyzer. Laboratory studies from his outpatient dialysis unit include a single-pool Kt/V of 1.4, calcium of 8.7 mg/dL, phosphorous of 3.9 mg/dL, hemoglobin A_{1C} (HbA_{1c}) of 6.6%, albumin of 3.1 g/dL, and intact parathyroid hormone (PTH) of 670 pg/mL.*

Question 1: Which of the following is the most appropriate *initial* pharmacologic therapy to manage this patient's pruritus?

(a) Emollients
(b) Cinacalcet
(c) Calcitriol
(d) Difelikefalin

For the answer to this question, see the following text.

Pruritus is a common complaint among patients with CKD. It may be a minor annoyance for some patients, but others can find it debilitating,

leading to missed dialysis treatments, diminished quality of life, sleep impairment, depression, and infection. For many years, this disorder was referred to as "uremic pruritus," but the preferred nomenclature is now CKD-associated pruritus (CKD-aP). Its prevalence is estimated to be 40% among patients on dialysis and 20% among those with CKD. However, these values are likely underestimated because patients often do not report their symptoms. The diagnosis is therefore more likely to be made when the interdisciplinary care team actively inquires about itching.

Risk Factors

The traditional risk factors thought to be associated with the development of CKD-aP were metabolic derangements that occur in the setting of CKD, such as derangements in levels of calcium, phosphorous, calcium × phosphorous product, PTH, or serum urea nitrogen (SUN). In the setting of long-term dialysis, an inadequate Kt/V was also thought to be associated with the development of CKD-aP. More recent studies have cast doubt on their relevance as risk factors and have shown that markers of malnutrition and inflammation—such as low serum albumin, high C-reactive protein, and high ferritin—are associated with the development of CKD-aP. Hepatitis B and C virus infections also appear to be independently associated with the development of CKD-aP.

Presentation and Diagnosis

The diagnosis of CKD-aP may be made only after excluding other potential etiologies, including liver and biliary tract disease, allergic reactions, and primary skin disorders. A full skin examination should be done whenever practical. Given the limitations of physical examination within a dialysis unit setting, multidisciplinary care involving the primary care provider and dermatologist is often helpful in establishing a diagnosis and assessing for other systemic risk factors.

In addition to considering allergic reactions to oral medications, attention should be focused on the dialysis prescription (including the dialyzer) for potential allergic reactions and on intravenous heparin as an anticoagulant, particularly for those individuals who experience pruritus only during the dialysis treatment or in those for whom the pruritus becomes more intense during the dialysis treatment.

For patients treated with peritoneal dialysis, special consideration should be given to allergic reactions to icodextrin, which has been implicated in an exfoliative skin rash that occurs usually first on the palms and soles but may also be found on the trunk and extremities.

Finally, the underlying disease that caused CKD may cause pruritus. For example, SLE may cause CKD and pruritic skin lesions, as will be discussed in a later section.

Pathophysiology

The underlying pathogenesis of CKD-aP is not well understood. Toxins that accumulate in CKD have been thought to cause pruritus. It is now well documented, however, that CKD-aP may occur in dialysis patients who are well dialyzed in terms of small solute clearance (Kt/V) and in patients with milder degrees of kidney dysfunction. Bolstering the argument that uremic toxins may play a role in the pathogenesis of CKD-aP are the findings that as residual kidney function declines the risk of CKD-aP rises. In the Netherlands Cooperative Study on the Adequacy of Dialysis, higher residual kidney function and lower serum phosphate levels were both found to be associated with a lower risk of chronic pruritus.

The immune system has also been postulated to play a role in the pathogenesis of CKD-aP. C-reactive protein, ferritin, and interleukin 6 tend to be elevated in patients with chronic pruritus in the setting of kidney failure. Systemic inflammation coupled with inflammation occurring specifically within the skin milieu could lead to chronic pruritus.

Peripheral neuropathy is a common occurrence in patients with kidney failure and pruritus, and some investigators have suggested that pruritus may be a manifestation of peripheral sensorimotor neuropathy and dysautonomia. Finally, there is a relationship between the peripheral nervous system's pain circuits and itching. Opioids that are used to treat pain are also known to cause pruritus. An imbalance between the stimulation of central μ-opioid receptors and antagonism of peripheral κ-opioid receptors could also underlie the pathogenesis of itching associated with CKD.

Treatment

Treatment strategies for CKD-aP have centered on the underlying pathophysiologic mechanisms. As a first step for all dialysis patients, attention should be paid to small solute clearance and metabolic parameters. Kt/V should meet recommended targets. Phosphorous should be controlled by dietary restriction, phosphate-lowering medications, and optimization of dialysis prescription. PTH levels should be controlled with vitamin D analogues and calcimimetics and in medication-refractory cases with parathyroidectomy. Residual kidney function should be preserved to the extent possible by avoiding nephrotoxins, optimizing the dialysis prescription to avoid hypotensive events, and using renin-angiotensin system blockers for their residual kidney function–sparing effects.

Pharmacologic therapies

Topical agents

- Emollients:
  - Given their low cost and safe treatment profile, emollient creams are recommended as first line of pharmacologic therapy for CKD-aP.
  - Creams should be applied to wet or damp skin after bathing to increase their penetration and efficacy.
- Analgesics:
  - Topical analgesics such as pramoxine have been used to treat CKD-aP because of their ability to block the conduction of nerve impulses from the skin.

Figure 1. A 52-year-old man with kidney failure due to type 1 diabetes mellitus who is receiving hemodialysis presents with generalized xerosis of the bilateral shins and ankles with areas of ichthyosiform change and scattered lightly hyperpigmented macules and patches.

Systemic agents

- Antihistamines such as diphenhydramine, hydroxyzine, and cetirizine are often used to treat CKD-aP although trials have not shown a clear benefit.

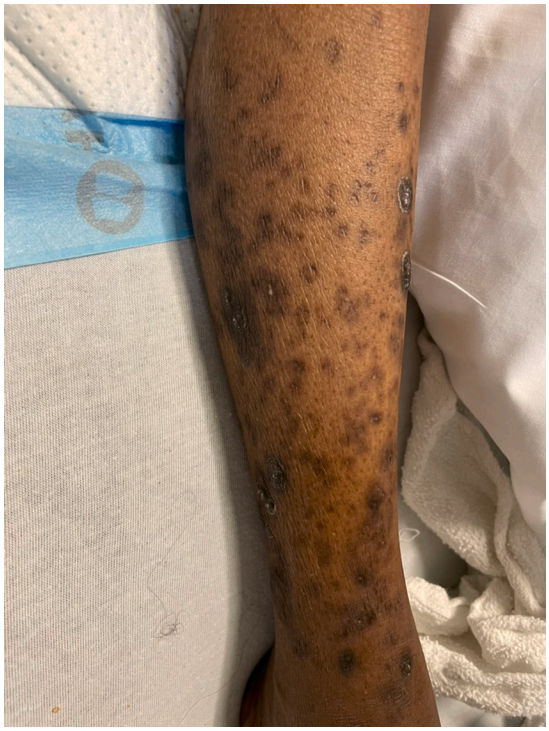

Figure 2. A 59-year-old woman with kidney failure due to type 2 diabetes mellitus who is receiving in-center hemodialysis presents with multiple hyperkeratotic plaques on both arms and legs.

- Intravenous and oral diphenhydramine have commonly been administered in dialysis units in the United States for itching and for anxiety. However, caution should be exercised with this medication given its potential for adverse cardiac events.

Mast-cell stabilizers

- Cromolyn sodium has been shown to improve pruritus in a small, placebo-controlled, randomized trial.

Gabapentinoids

- Gabapentin and pregabalin, which are used to treat peripheral neuropathy, may be beneficial in treating CKD-aP by blocking neuronal calcium influx, preventing the propagation of the sensation of itching.
- Careful attention must be paid to dosing of the gabapentinoids given the potential for neurotoxicity.

Opioid agonists and antagonists

- Nalfurafine: This oral peripheral κ-opioid receptor agonist is approved to treat resistant pruritus in Japan.
- Difelikefalin, a peripheral κ-opioid receptor agonist, significantly improved the worst itching intensity compared with placebo in a randomized trial. Use of difelikefalin is currently limited by the fact that it must be administered intravenously and its cost.

Nonpharmacologic therapies

Phototherapy has been used to treat pruritus related to a number of systemic and dermatologic conditions. Studies with a relatively small number of patients have shown improvement in symptoms with narrow-band UV-B phototherapy. This treatment is generally reserved for patients whose symptoms are refractory to other therapies.

After the available options are considered, the best answer to Question 1 is (a), emollients.

Additional Readings

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Acquired Perforating Dermatosis

Case 2: *A 59-year-old woman with kidney failure due to type 2 diabetes mellitus has been receiving in-center HD for 13 years. She presents to a hospital emergency*

department with intense pruritus that has caused her to sign off from her HD treatment 1 hour early. Review of her dialysis treatments shows that she has completed 3 hours or less of her prescribed 4-hour dialysis for the last month. Her vital signs are stable on presentation. Skin examination reveals multiple hyperkeratotic plaques on both her arms and legs. Her medications include amlodipine, 10 mg daily; sevelamer carbonate, 1,600 mg with meals; hydroxyzine, 10 mg at bedtime; gabapentin, 300 mg 3 times weekly after dialysis; and calcitriol, 0.5 μg 3 times weekly. Laboratory studies from her outpatient dialysis unit reveal a single-pool Kt/V of 1.0, calcium of 9.0 mg/dL, phosphorous of 6.1 mg/dL, HbA_{1C} of 6.0%, albumin of 3.1 g/dL, and PTH of 423 pg/mL. Her skin lesions are shown in Figure 2.

Question 2: Which of the following therapies may be useful in treating this patient's skin lesions?

(a) Oral prednisone
(b) Azathioprine
(c) Topical salicylic acid (2%-10%)
(d) Mycophenolate mofetil

For the answer to this question, see the following text.

The skin lesions described in this patient are characteristic of a perforating skin disorder, in this case acquired perforating dermatosis (APD). The perforating skin disorders include a number of primary skin disorders: Kyrle disease, perforating folliculitis, elastosis perforans serpiginosa, and reactive perforating collagenosis. APD is a distinct secondary perforating skin disorder that occurs in patients with CKD or diabetes mellitus but may also occur in the setting of other systemic diseases and as a response to some medications. It is common in the setting of kidney failure secondary to diabetic nephropathy.

The lesions of APD are typically crater-shaped nodular eruptions of 2-10 mm in diameter with a central hyperkeratosis. These lesions occur most often along the trunk and extensor surfaces and may follow a linear distribution. They are called perforating lesions because of the "perforation" of dermal connective tissue through the epidermis.

Risk Factors

The major risk factors for APD are diabetes mellitus and CKD. Other disease entities associated with APD include liver disease, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome hypothyroidism, hyperparathyroidism, atopic dermatitis, autoimmune diseases, and certain neoplasms such as pancreatic cancer, Hodgkin disease, and myelodysplastic syndrome. A number of medications, including medications used as immunosuppressants for kidney transplantation (azathioprine and sirolimus), have been associated with development of APD.

Presentation and Diagnosis

APD typically presents with pruritic to painful nodules occurring in a patient with known risk factors. Given that the lesions frequently arise on portions of the skin that are not readily visible during a dialysis treatment, they may go unrecognized by health care professionals despite the fact that an in-center HD patient is usually seen 2 to 3 times weekly for treatment.

The diagnosis may be made based upon the clinical findings of characteristic skin lesions along with histopathologic findings. The diagnostic criteria proposed by Faver and colleagues include:

- Clinical presentation of umbilicated papules or nodules with a central adherent keratotic plug
- Elimination of necrotic basophilic collagen tissue into a cup-shaped epidermal depression on skin biopsy
- Onset of skin lesions after age 18

Pathophysiology

The pathophysiology of APD is poorly understood. However, because intense pruritus and the Koebner phenomenon (ie, the development of new skin lesions on previously unaffected skin as a result of trauma) are usually present, one hypothesis is that APD arises as a response to superficial skin trauma from scratching. In the setting of CKD and diabetes with their associated vasculopathy, dermal necrosis ensues, and the necrotic tissue ultimately breaks through the epidermal surface.

Treatment

There is no proven specific treatment for APD. The control of pruritus is the most important first step because scratching may exacerbate the condition, leading to the creation of new nodules. To that end, adequate dialysis, phosphate control, and glycemic control are standard recommendations.

Topical agents

- Emollients
  - o Strong topical or intralesional corticosteroids
  - o Keratolytics:
    - salicylic acid (2%-10%)
    - urea (10%-40%)
- Topical retinoids

Systemic medications

- Antihistamines
- Systemic retinoids
- Allopurinol

Nonpharmacological treatments

- Narrow-band UV phototherapy
- Kidney transplantation: Some case reports have noted resolution of skin lesions after kidney transplantation.

The best answer to Question 2 would be application of an emollient: (c) topical salicylic acid (2%-10%).

Additional Readings

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Calcinosis Cutis

Case 3: *A 48-year-old man presents to urgent care with complaints of fatigue, weakness, anorexia, and firm, nontender nodules measuring about 1 cm in diameter on both elbows, shoulders, and lower extremities, similar to those depicted in Figure 3. Some lesions have eroded and are expressing a chalky white material. He had been in his usual state of health until about 4 months prior when he began to feel fatigued. His systemic symptoms have progressed over the last 3 months, and the skin lesions began to develop about 3 weeks prior to presentation. He does not take any medications. He has not been taking supplemental calcium or vitamin D. His physical examination is otherwise unremarkable. The laboratory studies are notable for a SUN of 68 mg/dL, creatinine of 5.4 mg/dL (baseline creatinine 1.1 mg/dL, 6 months prior), hemoglobin of 8.3 g/dL, calcium of 12.1 mg/dL, phosphorous of 5.7 mg/dL, and PTH of 9 pg/mL. His 1,25-dihydroxyvitamin D level was 75 pg/mL (normal: 18-64 pg/mL).*

Question 3: Which of the following disorders might explain this patient's presentation?

(a) Tertiary hyperparathyroidism
(b) Calciphylaxis
(c) Milk-alkali syndrome
(d) Sarcoidosis

For the answer to this question, see the following text.

Calcium homeostasis is crucial for regulating the physiologic processes within several tissues, including the skin. These processes include epidermal proliferation, differentiation, and cell-cell adhesion. Derangements in intracellular and extracellular calcium homeostasis may result in cutaneous calcification or ossification.

Calcinosis cutis (CC) occurs when insoluble calcium salts are deposited into the skin and subcutaneous tissue. It is comprises 5 main subtypes, depending on etiology: dystrophic, metastatic, mixed, idiopathic, and iatrogenic.

Metastatic CC, the subtype of concern in CKD, occurs secondary to abnormal serum calcium and phosphorous levels despite initially healthy tissues. This is in contrast to dystrophic CC where damaged tissue acts as a nidus for calcium deposition in the setting of normal serum calcium and phosphorous levels. Mixed CC is a combination of dystrophic and metastatic CC; it is initiated by calcium dysregulation but propagated by tissue trauma. Iatrogenic CC occurs secondary to medical administration of calcium- or phosphate-containing products. Idiopathic cases occur infrequently.

Risk Factors

In addition to kidney failure, alternative causes of aberrant calcium-phosphate metabolism are risk factors for the development of metastatic CC. The most commonly implicated conditions include hypervitaminosis D, milk-alkali syndrome, tumoral calcinosis (familial), hyperparathyroidism, and calcium-altering neoplasms, such as multiple myeloma or adult T-cell leukemia/lymphoma. In the patient in Case 3, his clinical presentation and laboratory studies are suggestive of sarcoidosis, answer (d).

Presentation and Diagnosis

Although occurrence of metastatic CC within CKD is rare, with a prevalence of 0.5% to 3%, kidney failure is the most common cause of metastatic CC. Patients present with benign nodular calcification, which is characterized by hard, white-to-yellow papules, plaques, or nodules from which a chalky white substance may extrude. The lesions are usually distributed on periarticular sites, with involvement of the shoulders, elbows, and hips being most common, but there have also been reports of the digits, genitals, and neck being affected.

Cutaneous calcification may also be a clinical clue for visceral involvement, as calcification can occur in the heart, lungs, kidneys, stomach, or esophagus. The number and size of lesions tend to correlate with severity of abnormal phosphate levels. Patients are often asymptomatic but may report bothersome joint pain and stiffness secondary to lesional pressure on surrounding structures. In severe cases, patients may present with infection secondary to skin ulceration, fever, nerve compression, or fistula formation.

In the setting of CKD, the diagnostic workup for CC should commence with evaluation of calcium and phosphate metabolism. Serum levels of calcium, phosphorous, PTH, and vitamin D_3 should be measured. Radiological examinations, including plain film or computed tomography (CT) scan, may be helpful in determining the extent of tissue involvement and response to therapy.

Pathophysiology

The underlying pathophysiology of CC is due to derangements in calcium and phosphorous homeostasis in the setting of CKD. For a detailed discussion, see the Core Curriculum by Murray and Wolf.

Treatment

Normalization of serum calcium and phosphorous levels by adherence to a low phosphorous diet and avoiding dietary calcium supplements should be the initial treatment because the lesions may regress following restoration of physiologic levels. Vitamin D analogues to treat

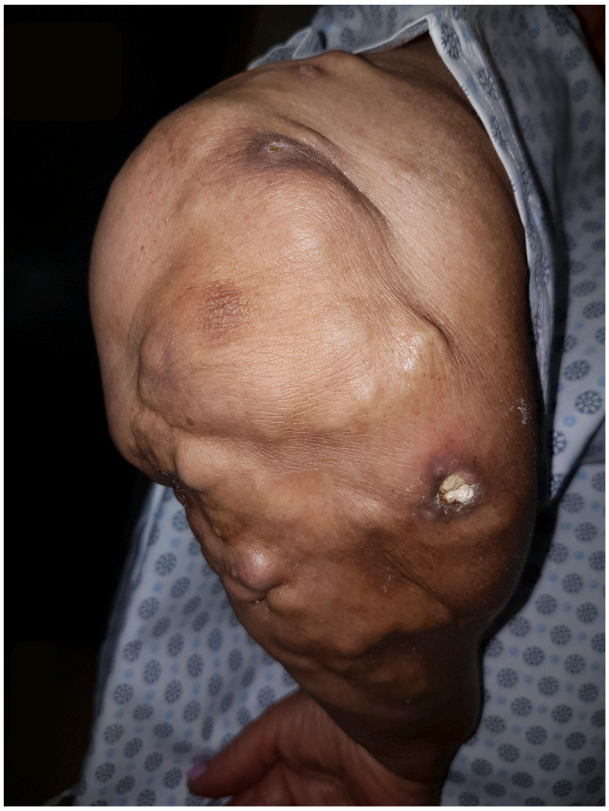

Figure 3. Progressive, painful subcutaneous nodules in right arm and forearm. Some lesions have eroded and are expressing an off-white chalky material. Image ©2022 Society of General Internal Medicine; reproduced with the permission of the copyright holder from Del Barrio-Díaz P, Mellado-Francisco G, Vera-Kellet C. Generalized Dystrophic Calcinosis Cutis in a Patient with Dermatomyositis. *J Gen Intern Med*. Published online January 31, 2022. doi:10.1007/s11606-021-06672-1

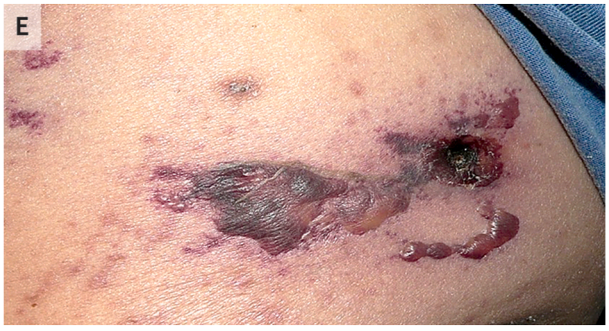

Figure 4. A 55-year-old woman with kidney failure on hemodialysis presents with a painful left thigh rash characterized by multiple plaques with livedo reticularis. Image ©2018 Massachusetts Medical Society; reproduced with the permission of the copyright holder from Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. Ingelfinger JR, ed. *N Engl J Med*. 2018;378(18):1704-1714. doi:10.1056/nejmra1505292

secondary hyperparathyroidism are not recommended due to the inherent risk for vascular calcification in this patient population. Additionally, high calcium concentration dialysate may increase the risk of metastatic calcification.

Helpful medications include non-calcium-containing phosphate binders and calcimimetics. Bisphosphonates are generally not recommended in patients who have an estimated glomerular filtration rate (eGFR) below 30-35 mL/min/1.73 m^2 because these are excreted by the kidneys; however, they can be effective in preventing the release of proinflammatory cytokines and in reducing osteoclast function, thereby preventing mobilization of calcium and phosphorous from bone.

Sevelamer and lanthanum, non-calcium-containing phosphate binders, are both effective in reducing phosphate absorption. Calcimimetics such as cinacalcet effectively prevent the excessive release of PTH by increasing the sensitivity of calcium-sensing receptors to activation by extracellular calcium. In cases of tertiary hyperparathyroidism unresponsive to medical management, parathyroidectomy may be indicated.

If the lesions do not regress after the normalization of serum calcium and phosphorous levels, alternative modalities such as surgical removal or carbon dioxide laser may be employed. Although there is no standard of care in treating CC—the current options are largely based on observational evidence and expert opinion—calcium channel blockers, colchicine, and minocycline have been used with variable efficacy. In the case of metastatic CC, the treatment strategy should be aimed at correcting the underlying cause.

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Calciphylaxis

Case 4: *A 55-year-old woman with kidney failure who has been receiving HD presents to the emergency department with a painful rash on her left thigh. The rash has been present for about 2 weeks, with the associated pain progressively intensifying. She has not had a fever or chills. Her past medical history is notable for kidney failure secondary to diabetic nephropathy, heart failure with reduced ejection fraction, atrial fibrillation, gout, anemia of CKD, and secondary hyperparathyroidism. Her medications are oral*

calcium acetate, 1,334 mg before every meal; metoprolol succinate, 50 mg daily; warfarin, 5 mg daily; calcitriol, 0.5 μg, 3 times weekly; iron sucrose, 100 mg with each dialysis treatment; and epoetin beta, 75 μg every 2 weeks. She cannot tolerate cinacalcet due to severe nausea. Her laboratory studies from the outpatient dialysis clinic showed a single-pool Kt/V of 1.4; calcium of 9.8 mg/dL; phosphorous of 6.2 mg/dL; and PTH of 821 pg/mL. The lesion on her left thigh is shown in Figure 4.

Question 4: Which of the following medications may be implicated in the pathogenesis of or the worsening of her skin lesion?

(a) Calcitriol
(b) Calcium acetate
(c) Warfarin
(d) Iron sucrose
(e) All of the above

For the answer to this question, see the following text.

Calciphylaxis, formerly known as calcific uremic arteriolopathy, is a rare cutaneous vasculopathy characterized by microvascular calcium deposition and thrombosis leading to tissue ischemia and subsequent skin necrosis. Although individuals with kidney failure are at highest risk for calciphylaxis, it may occur in the absence of kidney disease, making nephrogenic and non-nephrogenic more accurate modifiers when defining the condition.

Early recognition and management are critical to improving outcomes, but due to the diversity of presentations and largely clinical diagnostic modalities, recognition is often delayed.

Risk Factors

Nephrogenic calciphylaxis in CKD stage 3 or higher represents the majority of cases, with dialysis-dependent kidney failure the most significant risk factor. Other comorbidities thought to increase risk include diabetes mellitus, liver disease, malignancy, hyperparathyroidism, hyperphosphatemia, and connective tissue disease. Prior use of corticosteroids or vitamin K antagonists, calcium-based phosphate binders, vitamin D, and intravenous iron have also been associated with higher risk for calciphylaxis. Female gender, age older than 60 years, and body mass index $> 30\ kg/m^2$ have been identified as demographic risk factors. The patient in Case 4 was taking a calcium-based phosphate binder, an activated vitamin D supplement, a vitamin K antagonist, and intravenous iron, so the best answer to the question is (e), all of these medications.

Presentation and Diagnosis

Calciphylaxis should be suspected in high-risk patients who present with characteristic skin findings, particularly in areas of high adiposity, such as the abdomen, buttocks, thighs, and breasts. However, the clinical presentation varies with differences in extent of disease, skin pigmentation, and anatomic distribution, allowing multiple conditions to mimic calciphylaxis (Box 1). Additionally, mechanical debridement can disrupt the primary morphology, further contributing to diagnostic difficulty.

In earliest stages of disease, patients often present with pain out of proportion to the physical examination and before any visible skin changes. This patient-reported finding can alert clinicians to suspect the development of calciphylaxis, particularly in an individual with kidney failure. Early disease can present with localized skin erythema that appears similar to cellulitis. However, calciphylaxis usually lacks warmth and is associated with underlying induration and pain out of proportion to the clinical examination. Other early findings include nonblanching retiform purpura or branching, purpuric patches and plaques. *Peau d'orange* textural changes may also accompany the induration. Early or subtle erythema and purpura may be missed in patients with higher baseline melanin content in the absence of a careful examination with adequate lighting. Purpura in darker skin tones may also appear more hyperpigmented than violaceous, underscoring the importance of a careful and thorough examination.

As calciphylaxis progresses, vesicles or bullae may form, and the skin may begin to ulcerate, eventually forming an overlying leathery black eschar.

There is no gold standard diagnostic test for calciphylaxis. The diagnosis remains primarily clinical. However, skin biopsy and imaging may be helpful in some clinical settings. The role of skin biopsy remains controversial. False-negative results may be seen due to sampling technique, lack of typical histologic features, or lack of pathology expertise. Prototypical features may include calcification of small vessels within the deep dermis and subcutaneous tissue, with fibrin thrombi and overlying dermal and epidermal necrosis.

Box 1. Common Mimickers and Differential Diagnosis of Calciphylaxis

- Atherosclerotic vascular disease
- Cellulitis
- Cholesterol embolization
- Diffuse dermal angiomatosis
- Dystrophic calcinosis cutis
- Hematoma
- Livedoid vasculopathy
- Martorell's ulcer
- Necrotizing vasculitis
- Nephrogenic systemic fibrosis
- Oxalosis
- Panniculitides
- Peripheral vascular disease
- Pressure-induced skin injury
- Purpura fulminans
- Pyoderma gangrenosum
- Venous stasis ulcer
- Warfarin-induced skin necrosis

However, false-positive results are increasingly common, and it is proposed that the presence of both stippled calcium and thrombosis are needed to increase the specificity of findings. Additionally, the Koebner phenomenon has been reported in calciphylaxis. Therefore, the pros and cons of pursuing biopsy must be weighed in each case.

Imaging may be useful in supporting a diagnosis of calciphylaxis, particularly when the biopsy results are inconclusive or sampling is contraindicated. Effective modalities include noncontrast CT scan and ultrasound. Vascular calcifications appear as bright, linear structures on noncontrast CT. Point-of-care ultrasound can also be useful, particularly when the lesions affect areas where a biopsy should be avoided, such as the penis.

Pathophysiology

The mechanisms underlying the development of calciphylaxis require further investigation; however, the 3 primary pathological steps include endothelial dysfunction, microvascular calcification, and thrombosis. An imbalance in the actions of calcification promoters and inhibitors in such a way that promotes a procalcific milieu is implicated in the origin of microvascular calcification of calciphylaxis. This procalcific milieu may be attributable to decreased levels of calcification inhibitors such as fetuin A, pyrophosphate, and carboxylated matrix Gla protein (MGP). Warfarin, commonly used in patients with CKD, blocks vitamin K-dependent carboxylation of MGP and therefore promotes vascular calcification. The calcification occurs in a circumferential pattern within the vascular media of small and medium vessels, with intimal fibroplasia. This is in contrast to atherosclerosis, which is characterized by intimal thickening, and chronic vascular disease, which is characterized by vessel fibrosis.

Treatment

Establish multidisciplinary care team

There is currently no therapy approved by the US Food and Drug Administration (FDA) for calciphylaxis, and management of these complex patients depends on a multidisciplinary combination of risk factor reduction through medical optimization, administration of systemic therapies, wound care and infection prevention, and pain management. Nephrology, dermatology, pain and palliative medicine, wound care, surgery, and nutrition are crucial services to involve.

Optimize medical management to reduce risk factors

Medical management should focus on mitigating risk factors for progression of the disease. This includes optimizing mineral levels, particularly calcium and phosphorous, and avoiding high PTH levels. Calcimimetic agents such as cinacalcet are preferred to parathyroidectomy in patients with elevated PTH to avoid the phenomenon of hungry bone syndrome, which requires the administration of supplemental calcium to treat the severe hypocalcemia that occurs in this setting. However, if the PTH is not falling rapidly in response to calcimimetics, parathyroidectomy is indicated, given the potentially downhill and fatal course of the disease. Medications should also be reviewed to ensure calcification-promoting therapies have been discontinued.

For patients requiring anticoagulation, nonwarfarin modalities, such as apixaban or unfractionated heparin, should be considered. Where possible, subcutaneously injected medications should be avoided because skin trauma can induce additional lesion formation. Patients with kidney failure may benefit from intensification of their dialysis regimen—for example, longer treatment times or more frequent treatments—to optimize clearance of phosphorous and other solutes.

Wound care

Dermatology, wound care, and surgery collaboration are crucial for optimizing healing and preventing further devitalization of tissue. Conservative eschar and necrotic tissue removal can be pursued when local enzymatic debridement is inadequate or if wounds are infected. When feasible, chemical debridement is preferred to routine surgical debridement in noninfected wounds to avoid propagating disease activity, or surgical intervention can be delayed until active purpura have abated with medical management.

To minimize the risk of sepsis, antibiotics are recommended with significant purulent drainage, new or expanding erythema in previously stable disease, or abnormal vital signs. Identifying the causative organism with wound culture is unreliable because ulcers are typically heavily colonized, so broad spectrum antibiotics should be considered when selecting therapy, with vigilance for fungal infections, particularly in immunocompromised patients.

Additionally, hyperbaric oxygen therapy (HBOT) has shown promise for improved wound healing and reduced mortality. Anxiety and claustrophobia may need to be addressed when implementing HBOT due to the nature of the enclosed chamber within which treatment is performed. HBOT also poses a scheduling challenge for thrice-weekly HD patients.

Pharmacotherapeutic agents

Sodium thiosulfate. Although not FDA approved for this indication, sodium thiosulfate is commonly used to treat calciphylaxis based upon its vasodilatory, anticalcific, and anti-inflammatory properties. The evidence for its efficacy is based solely on observational studies and case reports. It may be administered intravenously during HD, usually at a starting dose of 12.5 g per treatment with titration up to a goal of 25 g as tolerated and can be administered via peripheral line in nondialysis patients as well. The optimal treatment duration is not established, but it is most commonly administered for about 3 months

in clinical practice. The adverse effects include nausea, vomiting, anion-gap metabolic acidosis, prolongation of the QT interval, and bone demineralization (with long-term use). Sodium thiosulfate may also be directly injected into active skin lesions.

Pentoxiphylline. Pentoxiphylline acts as an antioxidant to inhibit vascular calcification. It is used in many ischemic skin conditions due to its ability to increase red blood cell flexibility and perfusion.

Vitamin K. In a phase 2 double-blind clinical trial, phytonadione (vitamin K_1) was associated with improvement in pain intensity and total lesion surface area.

Palliative care and pain management

Although survival estimates have improved, with a recent study showing an all-cause mortality rate of 44.1%, patients with calciphylaxis continue to experience severe, frequently opioid-resistant ischemic and neuropathic pain. Pain management, palliative care, and psychiatric concerns have been inconsistently addressed within this patient population, and they warrant early consultation with a pain specialist. Multimodal therapy may be necessary, including agents such as ketamine, benzodiazepines, spinal anesthetics, and cryoneurolysis.

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Lupus Erythematosus

Case 5: *A 45-year-old woman who has been in generally good health presents to her primary care provider with a patchy, scaly rash involving her shoulders and back (Fig 5). She has no other complaints. Her past history is notable for hypertension and gastroesophageal reflux disease (GERD). She takes hydrochlorothiazide, 25 mg daily, and omeprazole, 20 mg daily. Her blood pressure is 121/68 mm Hg. She has no peripheral edema. Urinalysis reveals no hematuria or proteinuria. The laboratory studies reveal a creatinine of 0.7 mg/dL, hemoglobin of 11.8 g/dL, antinuclear antibody (ANA) titer of 1:640, anti-Ro titer of 1:128, and anti-double-stranded DNA negative.*

Question 5: This patient's presentation is most consistent with which of the following:

(a) Cutaneous lupus erythematosus
(b) Psoriasis
(c) Atopic dermatitis
(d) Calcinosis cutis

For the answer to this question, see the following text.

Lupus erythematosus (LE) comprises a diverse spectrum of diseases that can be subclassified into 4 main groups: systemic (SLE), cutaneous (CLE), drug-induced, and neonatal. SLE, a chronic autoimmune disease that primarily affects women between puberty and menopause, is the most common subtype and is complicated by its ability to affect any organ with varied manifestations. Skin involvement is reported in up to 85% of SLE cases. CLE can occur without systemic signs or symptoms or as a manifestation of SLE. CLE is subclassified based on clinical and histological features into acute (ACLE), subacute (SCLE), intermittent (ICLE), and chronic (CCLE). ACLE exhibits the highest level of association with SLE (~90%).

Presentation and Diagnosis

Patients who present with ACLE are most often women within the third decade of life. ACLE can manifest with localized or diffuse skin findings lasting days to weeks. Localized disease classically presents with the "butterfly rash" of sun-exacerbated malar erythema that can consist of pink to violet coalescing macules and papules and involve the cheeks and nasal bridge but spare the nasolabial folds. The more widespread form of ACLE presents with erythematous macules and papules in sun-exposed areas. ACLE can precede systemic symptoms by weeks to months, warranting interdisciplinary collaboration between dermatology and rheumatology and careful monitoring for the development of SLE.

SCLE occurs most frequently in young to middle-aged women and is characterized by nonscarring and non-indurated skin lesions that can last for months to years due to high photosensitivity. If SCLE is present in older patients, drug-induced disease should be considered because 25% to 40% of SCLE cases are drug-induced, with proton pump inhibitors, thiazide diuretics, terbinafine, and calcium channel blockers as the most implicated.

Omeprazole and hydrochlorothiazide were likely culprits in the pathogenesis of the SCLE of the patient presented in Case 5; therefore, the correct answer to Question 5 is (a), cutaneous lupus erythematosus. Examination findings are most often distributed on sun-exposed areas of the neck, shoulders, upper extremities, and trunk and morphologically fall into 1 of 2 subtypes: an annular, polycyclic subtype or a papulosquamous subtype. The latter presents with erythematous scaly papules and plaques that may resemble psoriasis. In addition to more subtle erythema and a tendency toward violaceous tones, skin of color displays a greater propensity for post-inflammatory hyperpigmentation after lesion resolution. The subsequent postinflammatory hypo- or depigmentation is more prominent in darker skin.

ICLE, also known as lupus erythematosus tumidus, is often categorized as a rare subtype of CCLE. ICLE is characterized by

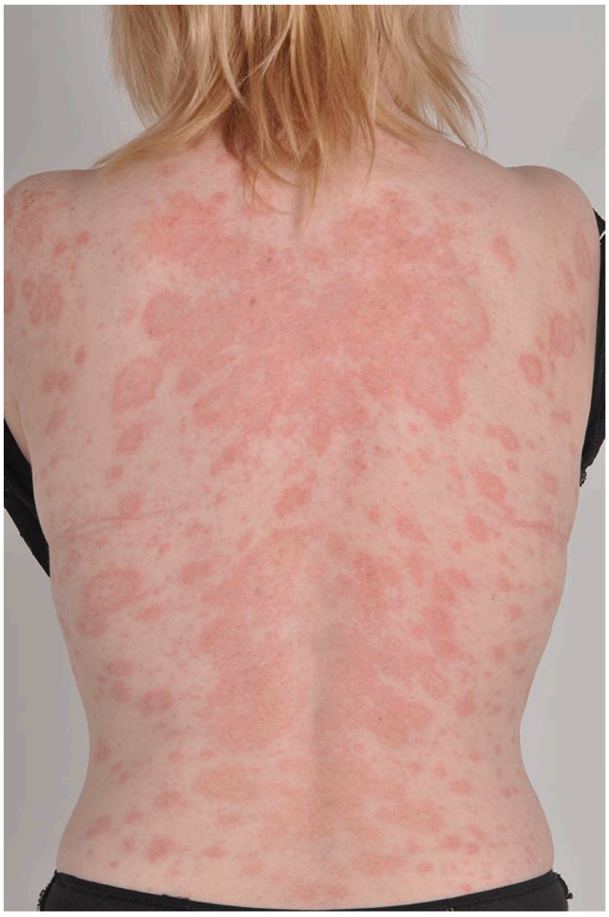

Figure 5. A 45-year-old woman presents with an annular erythematous rash involving her shoulders and back. Image ©2014 BMJ Publishing Group Ltd.; reproduced with the permission of the copyright holder from Balasubramaniam S, Franks A. SCLE: a paraneoplastic presentation. *BMJ*. 2014;348(apr09 1):g2521-g2521. doi:10.1136/bmj.g2521

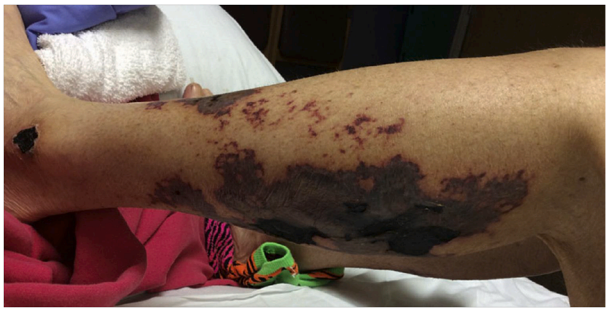

Figure 6. Painful, worsening, reticulated, and angulated purpuric plaques with necrotic ulcers. Image ©2021 American Academy of Dermatology, Inc; released under a CC BY-NC-ND license from Runge JS, Pearson TL, Keren DF, et al. Multiple myeloma presenting as cryoglobulinemic vasculitis. *JAAD Case Reports*. 2021;11:81-83. doi:10.1016/j.jdcr.2021.03.026

nonscaly erythematous, round papules and plaques that occur in sun-exposed areas of the skin, including the face, neck, and chest and that heal without scarring.

CCLE is often used interchangeably with its most common variant, discoid LE (DLE), which accounts for ~80% of cases. In patients with DLE, 5% to 15% progress to develop systemic symptoms, which most often occur within the first few years after a DLE diagnosis. Another potential sign of increased risk for SLE is lesions found both above and below the neck. It is unusual for patients to display lesions below the neck in the absence of disease above the neck, and generalized DLE is considered when both distributions are present. Patients classically present with raised or scarred atrophic, erythematous or violaceous plaques, often with overlying scale, frequently found on the scalp or sun-exposed areas of the face and arms, with the conchal bowl being a characteristic site of involvement. The scalp is the most involved site and is often associated with scarring alopecia. Following healing, atrophy, telangiectasia, central depigmentation, peripheral hyperpigmentation, and follicular plugging may remain. In darker skin tones, atrophy with pigmentation changes are more prominent, and active plaques may appear dark brown or violaceous rather than the more pink and red tones easily appreciated in lighter skin colors.

CLE can present in isolation or represent the initial or simultaneous presentation of SLE, necessitating dermatologic and rheumatologic expertise. The diagnosis of CLE is largely clinical, but it can be supported by medical history, such as known underlying SLE, or by histopathologic examination when there is diagnostic uncertainty.

Treatment

The treatment strategy for CLE relies on avoiding the typical triggers, such as UV light and cigarette smoke exposure, and on dampening the effects of key immunological reactions.

Topical

Avoidance of UV light where possible and use of broad-spectrum sun protection are recommended for all patients. Sunscreen or sun-protective clothing should have both UV-A and UV-B protection with an SPF ≥ 50, and patients should be made aware that UV-A is not filtered by window glass.

For localized skin lesions, high-potency topical corticosteroids, such as clobetasol, halobetasol, or fluocinonide, are a first-line treatment. Intralesional triamcinolone may also be effective in active lesions, especially on the scalp, with injections repeated every month while present. Patients should be monitored and counseled regarding potential side effects, such as cutaneous atrophy and hypopigmentation, particularly for darker skin tones.

Topical calcineurin inhibitors, such as pimecrolimus and tacrolimus, may be helpful in maintaining remission, and they can be used chronically but are often not effective in active disease flares.

Systemic

In widespread CLE or CLE that is unresponsive to topical treatments, a variety of systemic treatments are used. Antimalarials such as hydroxychloroquine are a first-line therapy and are thought to modulate the immune response through inhibition of type I interferon (IFN) production. Systemic glucocorticoids are also options but exert a broad immunosuppressive effect.

Alternative options include methotrexate, mycophenolate mofetil, and dapsone. Systemic retinoids, such as acitretin or isotretinoin, are also second-line options, particularly for the treatment of hypertrophic CLE lesions. Thalidomide and lenalidomide may be used in severe or refractory cases, but strict contraception and monitoring for neurological side effects are necessary due to teratogenic and neurotoxic side effects. The above-mentioned drugs have immunosuppressive or immunomodulatory actions but do not act in a targeted manner.

Anifrolumab, a monoclonal antibody to the type I IFN receptor, has been approved for the treatment of SLE and has been shown to be highly effective in the treatment of refractory CLE.

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Vasculitides

Case 6: *A 62-year-old woman presents to the emergency department with a raised, nonpruritic rash on his lower extremities, as seen in Figure 6. The rash began around her ankles but has now spread up to her knees bilaterally. She has not been getting medical care regularly and is taking no medications. On examination, her blood pressure is 221/107 mm Hg. She has nonblanching violaceous papules of both lower extremities with 2+ pitting edema. The laboratory studies reveal a creatinine of 3.1 mg/dL, hemoglobin of 9.2 g/dL, human immunodeficiency virus antibody negative, hepatitis C virus antibody positive, ANA negative, and rheumatoid factor positive. Urinalysis shows 3+ protein and 2+ blood.*

Question 6: Which of the following is the most likely unifying diagnosis to explain this patient's skin and systemic findings?

(a) Shingles
(b) Vasculitis
(c) Psoriasis
(d) Contact dermatitis

For the answer to this question, see the following text.

The vasculitides are a heterogenous group of rare autoimmune diseases characterized by blood vessel inflammation. The various subtypes of vasculitis are categorized based upon the size of involved vessels: large, medium, or small. This section will focus on the small vessel vasculitides because cutaneous manifestations hinting at kidney-impacting systemic processes are most pronounced in this subset.

The small vessel vasculitides may be further subdivided into antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which can often involve both small and medium vessels, and immune complex vasculitis. AAV features loss of tolerance to neutrophil primary granule proteins, most often leukocyte proteinase 3 (PR3 or myeloblastin) or myeloperoxidase (MPO), resulting in necrotizing vasculitis syndromes. Immune complex vasculitis is characterized by vessel wall deposits composed of immunoglobulin and/or complement. The 3 AAVs include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The immune complex vasculitides to be discussed in this section include cryoglobulinemic vasculitis (CV) and immunoglobulin A (IgA) vasculitis/Henoch-Schönlein purpura (HSP).

Presentation and Diagnosis

Cutaneous manifestations may be the presenting feature in up to 35% of patients with confirmed AAV. Skin disease is most commonly reported in the presentation of EGPA (47%), followed by GPA (34%) and MPA (28%). Furthermore, patients who have skin findings frequently have more than 1 type of cutaneous manifestation.

The presence or absence of particular skin findings is not specific to certain subtypes of AAV, but some helpful patterns are commonly observed. For example, pruritus, urticaria, and rash composed of macules and papules are most commonly reported in patients with EGPA or ANCA-negative disease, whereas urticaria occurs in fewer than 1% of patients presenting with GPA and MPA. Livedo reticularis and livedo racemosa are more commonly identified as signs of MPA or MPO-ANCA-positive AAV. Overall, petechiae and purpura are the most observed cutaneous manifestation across all subtypes of AAV. Additional cutaneous manifestations that should alert the physician to underlying AAV are shown in Box 2.

Cutaneous manifestations develop in nearly all cryoglobulin syndromes, making skin examination an important diagnostic component in evaluating patients with potential CV. Recurrent palpable purpura are the most common and frequent manifestation seen in CV, with lesions most typically occurring on the lower extremities. Lesions may occur spontaneously, in response to cold exposure, or with prolonged standing. The combination of purpura with arthralgia and weakness comprises Meltzer's triad, which is characteristically observed at disease onset.

Box 2. Additional Cutaneous Manifestations of ANCA-associated Vasculitis

GPA
- Nodules
- Pyoderma gangrenosum–resembling necrotic ulcerations (lower extremities most commonly)
- Ulcerated papules symmetrically distributed to extensor extremities or buttocks

MPA
- Nodules
- Necrotic ulcers

EGPA
- Erythema[a]
- Urticarial plaques
- Palpable purpura[b]
- Retiform purpura[b]
- Ecchymoses
- Livedo racemosa
- Necrotic lesions
- Tender subcutaneous nodules

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.
[a]Erythema associated with the above findings may present more subtly in darker skin tones.
[b]Petechiae and purpura will appear deep red, violaceous, or deep brown in darker skin tones; similar lesions can present as bright or deep red, maroon, or violaceous in light skin tones.

Purpura can be complicated by associated cutaneous ulcers, increasing the risk for secondary infections. The characteristic histopathology of palpable purpura is leukocytoclastic vasculitis. Additional cutaneous manifestations seen in CV include dermal nodules, livedo reticularis, ecchymoses, digital necrosis, and Raynaud's phenomenon.

In darker skin colors, the purpura may take on deeper red, violaceous, or brownish hues, and the lesions may appear bright red, deep red, maroon, or violaceous in lighter skin tones. Shades of red will be more appreciable in livedo reticularis of lighter skin tones, and violaceous and brown hues may be more apparent in darker skin tones. It is also important to note in darker skin tones that dusky violaceous patches, associated vesicles or bullae, and dark brown to black focal colors may indicate epidermal necrosis preceding ulcer formation. The subtle presentation findings mentioned previously underscore the importance of ample lighting and careful physical examination.

Skin lesions are present in 100% of HSP cases. These lesions arise secondary to perivascular inflammatory infiltrate and to extravasation of erythrocytes from damaged vessel walls. The round, oval, and retiform patterns observed are secondary to the anatomical arrangement of damaged vessels, and the predilection for the lower legs is likely secondary to gravity-related slower blood flow contributing to enhanced IgA immune complex deposition. In severe cases, cutaneous hemorrhagic blisters and necrosis may be seen secondary to complete vessel destruction or inflammation-related thrombosis. These extensive cutaneous manifestations are more commonly observed in adults than in children.

HSP is characterized by the classic triad of palpable purpura, joint pain, and gastrointestinal complaints. In adults, kidney disease is more likely to occur when there are skin lesions above the waist. The symptoms may present slowly over days to weeks in a variable order, but purpura and joint pain are the most common initial symptoms. Generalized symptoms of inflammation are also frequently present, including mild fever, malaise, and fatigue. Diagnosis is based upon clinical criteria.

The diagnosis of AAV is based on clinical features and laboratory and characteristic histological findings. Because of the risk for severe morbidity and mortality associated with vasculitis, clinicians should maintain a high index of suspicion when patients present with constitutional symptoms in combination with organ dysfunction.

The diagnosis of cryoglobulinemic vasculitis should be considered in patients presenting with palpable purpura and risk factors for cryoglobulinemia, such as hepatitis C virus infection. The patient presented in Case 6 has cryoglobulinemic vasculitis, answer (b). Clues to the diagnosis are proteinuria, hematuria, and palpable purpura occurring in a patient with hypertension and kidney dysfunction in the setting of hepatitis C virus infection. The positive rheumatoid factor is further suggestive of cryoglobulinemia.

Pathophysiology

The incidence of AAV increases in the sixth and later decades of life, implying a role for age-related changes and cumulative environmental factors in the underlying disease pathophysiology. Although still incompletely understood, infection has also been implicated in triggering disease activity. Infection with *Staphylococcus aureus* has received special attention due to the increased rates of nasal carriage in patients with relapsing GPA.

Loss of immunologic T-cell and B-cell tolerance to 1 of 2 neutrophil proteins, PR3 or MPO, is the pathogenic hallmark underlying GPA and MPA development. The inciting cause for loss of tolerance is multifactorial: genetics, age, and environmental factors such as infection or inflammation have all been implicated. The loss of tolerance precedes AAV symptoms and leads to the development of ANCAs, autoantibodies that activate neutrophils. ANCA-activated neutrophils subsequently mobilize to susceptible microvascular beds, such as the lungs or kidneys, where they induce injury and release autoantigen for presentation to antigen-presenting cells. These autoantigens are then recognized by effector T cells, which further propagate inflammation, leading to endothelial tissue injury, fibrosis, and progressive loss of function.

Eosinophil dysfunction is implicated in the pathogenesis of EGPA. Eosinophil-mediated injury occurs through the release of granule proteins, which in turn stimulate the release of proinflammatory mediators in affected tissues.

The pathophysiology of cryoglobulinemic vasculitis is related to the presence of cryoglobulins, antibodies that

precipitate at low temperatures (<37°C) and dissolve once rewarmed. The formation and precipitation of cryoglobulin immune complexes cause microvessel injury and end-organ damage in multiple tissues, including the skin, through a complex, immune-regulated inflammatory process.

The underlying cause of HSP likely involves a complex interplay of immunologic, genetic, and environmental factors. While the exact mechanisms have yet to be elicited, known environmental triggers and characteristic IgA deposition suggest that HSP involves an IgA-mediated aberrant immune response to an antigen in a genetically susceptible individual. Several infectious triggers have been recognized, with upper respiratory tract infections preceding the majority of HSP cases. Preceding gastrointestinal tract infections are also possible. The commonly implicated pathogens include *Streptococcus* strains, parainfluenza virus, and human parvovirus B19. Drugs, toxins, and food sources are also possible triggers, especially in children. Although rare, HSP has also been associated with solid-organ malignancies, with tumors of the gastrointestinal tract, respiratory organs, and urinary tract most commonly implicated; this has primarily been reported in male adults around 60 years of age. Therefore, evaluation for occult malignancy should be pursued in adults who present with unexplained HSP.

Treatment

The treatment of AAV should occur in collaboration with a multidisciplinary team of specialists who have expertise in the complex care of vasculitis. Furthermore, careful assessment for concomitant infection, immunodeficiency, and other comorbidities should be carried out before initiation of treatment to prevent complications associated with immunosuppression.

The treatment of AAV may be stratified according to disease severity and subtype (GPA/MPA vs EGPA) and into 2 distinct phases: remission induction and remission maintenance with B-cell depleting therapies and other immune modulators.

The treatment of cryoglobulinemic vasculitis is aimed at the underlying cause of production of cryoglobulins. In the case of hepatitis C virus infection, antiviral therapy directed against the hepatitis C virus is the mainstay of therapy. Treatment with corticosteroids or cytotoxic therapies are sometimes needed in severe cases while the hepatitis C viral load is being contained. In cases of cryoglobulinemic vasculitis associated with lymphoproliferative disorder, treatment is directed at the underlying disorder.

Most cases of HSP are self-limited, requiring only supportive care. Such measures include adequate hydration, pain control, compression garments for leg edema, and surgical intervention for related complications such as intussusception. Wound care in consultation with dermatology may also be necessary in cases of skin necrosis and ulceration. When kidney involvement or skin vesiculation or ulceration is present, additional treatment measures may be indicated.

Although there have been no randomized trials to prove its efficacy, a number of case series have shown treatment with dapsone to result in healing of chronic purpuric skin lesions of HSP. In general, immunosuppressants and immunomodulators should be reserved for chronic, persistent, recurrent, or complicated cases. Additional studies are needed to determine the indications for systemic corticosteroids and to further assess the efficacy of steroid-sparing agents.

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