Cutaneous manifestations of acute kidney injury

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ABSTRACT

Acute kidney injury (AKI) is a common medical problem with a multitude of aetiologies. Prompt diagnosis and management is key in the prevention of complications. Cutaneous signs can often give diagnostic clues of underlying systemic diseases causing AKI.

This review summarises cutaneous findings of diseases causing AKI in adults. Knowledge of such cutaneous signs could lead to earlier diagnosis of underlying kidney disease and facilitate management strategies in a timely manner.

Acute interstitial nephritis, polyarteritis nodosa, Kawasaki’s disease, granulomatosis with polyangiitis (previously Wegener’s granulomatosis), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss syndrome), Henoch-Schonlein purpura, cryoglobulinaemia, Sjogren’s Syndrome, systemic sclerosis, nephrogenic systemic fibrosis, dermatomyositis, systemic lupus erythematosus, amyloidosis, and cholesterol embolisation syndrome were highlighted as diseases causing AKI with cutaneous manifestations.

Keywords: acute kidney injury, connective tissue, cutaneous, skin, vasculitis

INTRODUCTION

Acute kidney injury (AKI) is a common presentation to both inpatient and outpatient medical services and is defined as an increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours, or ≥1.5 times baseline within the prior seven days, or urine volume <0.5 mL/kg/hour for six hours. Causes of AKI are many and varied, and identifying the underlying aetiology is key to timely management and prevention of complications, including chronic kidney disease and end stage kidney disease. In clinical medicine, cutaneous manifestations can often reveal signs of systemic disease. In AKI, there are several aetiologies associated with dermatological changes which may give rise to diagnostic clues. AKI caused by such aetiologies can be directly due to the underlying disease
process or in cases of severe systemic disease, prerenal AKI. The aim of this review is to outline common dermatological manifestations associated with AKI, and how this can aid clinical diagnosis and management.

We performed a PubMed search in March 2021 using the search terms: kidney, skin, renal, cutaneous, AKI, nephrology, dermatological, dermatology, adult. We selected articles published between 2000-2020 and those that discussed dermatological and kidney manifestations. Severe dermatological diseases which cause AKI secondary to multiorgan failure, such as toxic epidermal necrolysis and toxic shock syndrome are not included in this review.

Acute interstitial nephritis

Acute interstitial nephritis (AIN) is characterised by inflammation within the renal interstitium, usually associated with AKI and urinary abnormalities. The majority of cases are drug-induced, but other causes include infective, idiopathic, or associated with systemic disease (e.g. systemic lupus erythematosus, sarcoidosis, Sjogren’s syndrome). The classical triad of AIN is fever, rash and eosinophilia – although this complete triad is present in less than 10% of cases. Notably, rash is thought to be present in around 20-30% of cases. The rash is typically a non-specific maculopapular or morbilliform exanthem, starting on the trunk before spreading to the limbs and neck. It may or may not be itchy. It is usually bilateral and symmetrical. Lesions tend to blanche with pressure but may be purpuric on the lower limbs. Whilst the rash is relatively non-specific on its own, in the context of AKI it should raise the suspicion of AIN.

Despite recognition amongst nephrologists, AIN-associated rash is poorly documented within the dermatological literature. The underlying process causing this phenomenon is unclear. Given that AIN is largely drug-induced and frequently associated with an eosinophilia, it would be reasonable to
speculate that the associated rash is simply a drug hypersensitivity rash, rather than an alternative process secondary to AIN.

AIN can be associated with Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome - a severe, systemic hypersensitivity drug reaction that typically manifests 2-8 weeks after initiation of the culprit medication.4 The cutaneous manifestations of DRESS include an urticated, papular exanthem, erythema multiforme-like reaction, morbilliform rash, and exfoliative rash (figure 1).6 One of the most useful clinical features to help distinguish DRESS from other diseases is facial oedema, which is present in around one third of cases.6 The most common medications known to cause DRESS are carbamazepine, allopurinol, sulfasalazine, phenobarbital, lamotrigine, and nevirapine.5 Although kidney involvement is more common in DRESS cases associated with allopurinol,7 there are reports following multiple classes of culprit drugs,7 suggesting AKI is secondary to disease association rather than direct drug effect.

Withdrawal of the medication is the most beneficial step in early management of AIN, and often leads to resolution of kidney function.8 Corticosteroid therapy can be considered depending on the clinical course following removal of medications. The only definitive diagnostic test for AIN is a kidney biopsy, which may be undertaken when the diagnosis is unclear and the kidney function has not improved despite cessation of suspected medications.

Vasculitis

The vasculitides are a diverse group of diseases characterised by inflammation and necrosis of blood vessel walls. Cutaneous and kidney manifestations of vasculitis are common. Diagnosis is often difficult given the non-specific nature of presentation, however patterns of skin disease may give rise to important diagnostic clues. Well-recognised vasculitides affecting the skin and kidney are polyarteritis nodosa, Kawasaki’s disease, Granulomatosis with polyangiitis (previously Wegener’s
granulomatosis), microscopic polyangiitis, Eosinophilic Granulomatosis with Polyangiitis (previously Churg-Strauss syndrome), Henoch-Schonlein purpura, and cryoglobulinaemia. However, the majority of vasculitides seen by dermatologists are not associated with kidney disease and often do not fit into any specific diagnosis or category of vasculitis. Findings have been summarised in Table 1.

**Polyarteritis nodosa (PAN)**

PAN is a necrotising vasculitis affecting small and medium vessels. Kidney involvement occurs in approximately half of cases secondary to disease of the renal, interlobar, and arcuate arteries. Importantly, skin involvement can be seen in around half of systemic PAN cases, most commonly on the legs and feet (figure 2). Manifestations include palpable purpura (reflecting small vessel vasculitis), tender subcutaneous nodules which may breakdown and ulcerate (reflecting medium vessel vasculitis), livedo reticularis, and digital ischaemia.

**Kawasaki’s Disease**

Kawasaki disease is the most common vasculitis in childhood and can occur rarely in adults. It affects medium-sized vessels. A recent study suggested almost a third of patients may have an associated AKI. Skin changes include morbilliform rash, erythema and oedema of acral surfaces with subsequent sheet-like desquamation that begins in the periangual region after 2-3 weeks. Other features include cheilitis, conjunctival injection, strawberry red tongue, mucosal and pharyngeal erythema and cervical lymphadenopathy. Petechial, vesicular or bullous skin changes are not usual and should prompt investigation for an alternative cause.
Granulomatosis with Polyangiitis (GPA), (previously Wegener’s granulomatosis)

This is a rare, necrotising granulomatous small/medium vessel vasculitis with a predilection for the airways, lungs, and the kidneys. More than 90% of patients present with involvement of the upper (sinusitis) or lower respiratory tract. Kidney involvement is common and is thought to be present in at least 80% of cases during the disease course. Cutaneous involvement occurs in around 50% of cases and has a similar clinical appearance to that of PAN – most commonly palpable purpura, but also papules, nodules and blistering as well as necrotic-ulcerative lesions on a background of livedo reticularis – all with a predilection for the lower limbs. Digital ischaemia can also occur, and rarely pyoderma gangrenosum-like ulcers. Oral involvement may also occur, in the form of non-specific ulcers or “so-called” strawberry gingivitis (named so due to reddish/purple gingival swelling with petechial haemorrhages). Positive ANCA (particularly c-ANCA/anti-PR3) has high specificity for the diagnosis of GPA. This contrasts with PAN, which is not associated with ANCA positivity.

Eosinophilic Granulomatosis with Polyangiitis (EGPA), (previously Churg-Strauss syndrome)

EGPA is a small/medium vessel granulomatous vasculitis belonging to the spectrum of ANCA-positive vasculitides (typically p-ANCA/MPO-ANCA). Despite this, less than half of patients are actually ANCA-positive. Kidney involvement occurs in 30-40% of cases and cutaneous involvement in 40-50%. Palpable purpura on the lower limbs and scalp are the most common findings (figure 4). Vesicles or pustules, livedo reticularis, urticarial lesions, and necrotic ulcers may also be seen. An erythema multiforme mimicking rash has also been described. Of note, kidney and cutaneous involvement are more common if ANCA is positive.
Microscopic polyangiitis

Microscopic polyangiitis is a small vessel non-granulomatous vasculitis typically associated with p-ANCA. It affects the kidneys causing a rapidly progressive glomerulonephritis in most cases. Skin lesions are seen in 30-60% and are the initial presenting feature in 15-30%. Lower limb palpable purpura is the most common finding, with livedo reticularis, nodules, urticarial lesions and ulceration with necrosis as other manifestations. Symmetrical, erythematous-violaceous papules, bullae or nodules may also be present.

Henoch-Schonlein Purpura (HSP)

HSP, also known as immunoglobulin A vasculitis, is a vasculitis that is characterised by IgA deposits in small vessels. It is more common in childhood, however can occur in adults. Kidney involvement due to IgA1 deposition in blood vessel walls and the renal mesangium is common and disease in adults is associated with more severe kidney disease. Cutaneous involvement occurs in nearly all cases. Symmetrical palpable purpura is the most common cutaneous feature and may be the presenting symptom in 50% of cases (figure 5 and 6). Extremities, buttocks and trunk are the most commonly involved sites. In adults, bullous lesions and necrotic ulcers may develop. Other clues to diagnosis include gastrointestinal tract symptoms – present in around 85% - including abdominal pain, colorectal bleeding, vomiting and diarrhoea.

Cryoglobulinaemia

Cryoglobulinaemia is the presence of cryoglobulins in the blood. Diagnosis is strongly associated with underlying chronic viral hepatitis, monoclonal gammopathies and connective tissue disease. Although asymptomatic in most cases, cryoglobulinaemia can lead to immune complex tissue deposition and cryoglobulinaemic vasculitis. Kidney disease usually secondary to immune complex
disease occurs in around 25% of cases, usually due to subtypes 2 or 3 mixed cryoglobulinaemia. Skin involvement is seen in most cases of cryoglobulinaemic vasculitis, most commonly presenting in the form of palpable purpura on the extremities (coldest regions), but livedo reticularis, digital necrosis, cold urticaria, and nail fold changes can also be found. Skin biopsy may demonstrate dermal vessels plugged with homogenous eosinophilic material or typical vasculitic features (as below).

A diagnosis of acute cutaneous vasculitis can be made clinically, however skin biopsy may be required for a definitive diagnosis. If a biopsy is needed, early lesions should be targeted. Findings may include perivascular neutrophilic inflammation with necrosis of vessel walls, fibrinoid deposition around vessels, extravasation of RBCs (causing purpura) and leukocytoclasis (fragmented neutrophil nuclei).
| Diagnosis                                | Pathophysiology                                      | % Kidney Involvement | % Skin Involvement | Cutaneous features                              | Kidney features                                      |
|-----------------------------------------|------------------------------------------------------|----------------------|--------------------|--------------------------------------------------|------------------------------------------------------|
| **Polyarteritis nodosa (PAN)**          | Small / medium vessel vasculitis Not ANCA associated | 40%                  | 50%                | Legs and feet predominant                       | Necrotising arteritis of intra-renal arteries        |
| **Kawasaki’s Disease**                  | Medium vessel vasculitis                             | 33%                  | 68-98% periumgal desquamation | Morbilliform rash                             | Arteritis of intra-renal arteries – less necrotising than PAN |
| **Granulomatosis with Polyangiitis (GPA)** | Small / medium vessel vasculitis ANCA-associated     | 80%                  | 50%                | Similar to findings seen in PAN                  | Crescents glomerulonephritis                         |
| **Eosinophilic Granulomatosis with Polyangiitis (EGPA)** | Granulomatous                                        | 30-40%               | 40-50%             | Palpable purpura of legs and scalp              | Crescents glomerulonephritis                         |
|                                          |                                                      |                      |                    | Vesicles or pustules                            |                                                      |
|                                          |                                                      |                      |                    | Urticarial lesions                              |                                                      |
|                                          |                                                      |                      |                    | Necrotic ulcers                                 |                                                      |
| **Microscopic polyangiitis**            | Small vessel vasculitis ANCA-associated Non-granulomatous | Majority             | 30-60% (initial presentation in 15-30%) | Lower limb palpable purpura                    | Necrotising crescentsial glomerulonephritis          |
|                                          |                                                      |                      |                    | Livedo reticularis                              |                                                      |
|                                          |                                                      |                      |                    | Nodules, urticarial lesions                     |                                                      |
Connective Tissue Diseases

Certain autoimmune connective tissue diseases have both kidney and cutaneous manifestations which may aid clinical diagnosis, including Sjogren’s syndrome, systemic sclerosis, dermatomyositis and systemic lupus erythematosus (SLE).

Sjogren’s Syndrome

Primary Sjogren’s syndrome has been reported to affect the kidneys with variable occurrence – between 4 - 67%. Kidney manifestations include interstitial nephritis, type 1 (distal) and 2 (proximal) renal tubular acidosis, mild proteinuria, hyposthenuria, and glomerulonephritis. 24

Cutaneous features of primary Sjogren’s syndrome are common. Xerosis occurs in around 50%, which results in dry, rough skin which is often itchy. This also affects the mucosal and ocular surfaces. 25 Raynaud’s phenomenon occurs in around 30%. 25 A small vessel cutaneous vasculitis occurs in around 10%, which can present with purpura, maculopapular rash, urticaria, or cutaneous ulcers. 25 Histopathological findings are of a small vessel vasculitis, as discussed above. A
photosensitive annular erythema consistent with subacute cutaneous lupus erythematosus (SCLE) has been reported. Histology resembles SCLE with positivity for anti-Ro/anti-La antibodies.

Systemic Sclerosis (SSc)

SSc is a connective tissue disease characterised by deposition and overproduction of extracellular matrix proteins and collagen, resulting in tissue fibrosis. Kidney complications include scleroderma renal crisis, scleroderma normotensive renal crisis, and glomerulonephritis.

Cutaneous involvement is almost universal, and key to the diagnosis, as it stratifies the patient into having limited disease or diffuse disease – which are useful in determining clinical outcomes. In limited disease, cutaneous features are limited to the fingers, hands, and face. In diffuse disease, skin changes start peripherally, but gradually spread to involve the upper and lower limbs, and the trunk. Limited sclerosis tends to have a more insidious onset, with more prominent vascular complications such as pulmonary hypertension, renal crisis, and digital ulceration. Diffuse disease has more rapid onset accompanied by more severe early organ involvement.

Skin sclerosis is the cardinal feature that usually develops first. Skin becomes thickened and tight, first around the fingers (figure 7) but often involving the face. Digital ulceration often occurs as a result of vascular insufficiency. Typical facial features are a beak-shaped nose and microstomia. As the skin hardens, facial expressions become reduced. Raynaud’s phenomenon affects nearly all patients with SSc. Other skin changes include telangiectasia, hyperpigmentation of thickened skin, cutaneous calcification, and dry skin.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis a rare disorder in which patients present with scleroderma-like skin lesions in the presence of reduced kidney function (eGFR less than 30 mL/min), potentially
resembling systemic sclerosis. The underlying pathophysiology remains unknown, however all patients have either moderate to severe chronic kidney disease or AKI (highest risk patients are those undergoing peritoneal dialysis), and there is a strong association with gadolinium based contrast agents (GBCAs). The most commonly affected site is the skin, followed by muscle. Presentation occurs approximately 2-10 weeks following GBCA exposure. Typical cutaneous features are symmetrical, erythematous papules/nodules affecting the distal upper and lower limbs (figure 8). Acutely, the limbs may be oedematous or have a peau d’orange appearance. The face is usually spared. The lesions may then coalesce to form indurated plaques. Later skin changes include thickened and hardened areas of skin with hyperpigmentation. Involvement of muscles and deeper tissues results in limb pain, contractures, and loss of mobility. Diaphragmatic involvement can lead to respiratory failure and death. Skin biopsy of involved sites is the gold standard for diagnosis. Immunohistochemistry shows abundant CD34+ dermal dendritic cells, and light microscopy ranges from subtle proliferation of spindle-shaped fibrocytes to a thickened fibrosed dermis with long dendritic processes.

Dermatomyositis

Dermatomyositis is an autoimmune disease characterised by a proximal myopathy, violaceous cutaneous eruption, and the presence of autoantibodies. Mechanisms of kidney injury are varied and include rhabdomyolysis secondary to myoglobin release leading to acute tubular necrosis, interstitial nephritis, minimal change disease, and focal segmental glomerulosclerosis. Correct evaluation of cutaneous signs can lead to timely diagnosis. The most common and highly diagnostic skin signs are the heliotrope rash (periorbital oedema often with erythema, (figure 9a)), Gottron papules (papules and plaques over the small joints of the hands, (figure 9b)) and Gottron’s sign (erythema over the back of the hands, elbows and knees). Other less specific and less common changes include facial erythema (figure 9a), mechanics hands (hyperkeratosis and fissuring of the
hands), photosensitive rash involving the neck and chest, shawl sign (symmetrical violaceous erythema of the back, shoulders, chest and neck, (figure 9c)), ragged cuticles (figure 9d) with telangiectasias of the proximal nail folds (figure 9e and 9f), flagellate erythema (linear erythematous streaks, (figure 9g)), Raynaud’s phenomenon, vesicles/bullae, purpura, and calcinosis cutis.  

**Systemic Lupus Erythematosus (SLE)**

SLE is a complex, multisystem autoimmune disease with a variety of potential clinical manifestations. Involvement of the kidneys is commonly seen during the disease course and is associated with poorer prognosis. The spectrum of kidney disease is wide, as summarised by the International Society of Nephrology.

The skin is the second most commonly affected organ, after articular involvement. Cutaneous involvement is seen in 80% of cases and can occur throughout the disease course, with 20% of patients presenting with cutaneous disease. Cutaneous manifestations are typically described as LE specific and LE non-specific. Specific lesions are termed “cutaneous lupus erythematosus” (CLE) and can be subdivided into acute CLE, subacute CLE, and chronic CLE.

Acute CLE is almost always associated with systemic disease. The most common manifestation is the classical malar or butterfly violaceous rash (tends to spare nasolabial folds) with accompanying oedema. It is usually photosensitive. Less commonly, a photosensitive maculopapular rash may be present.

Subacute CLE usually presents with a photosensitive rash in sun exposed areas. It tends to present as flat, scaly patches, often in a network pattern, and be annular (ring-shaped) and polycyclic (abutting and circular).

Chronic CLE most commonly manifests as discoid lupus erythematosus (DLE) (figure 10). It is localized above the head and neck in 60-80%, with the remaining 20-40% being generalized (lesions
both above and below neck). The typical lesion is a macular or papular lesion with scale which develops into a larger discoid plaque healing with an atrophic, hyperpigmented scar (figure 10). If the scalp is involved, scarring alopecia may occur. The oral, genital, nasal and conjunctival mucosal surfaces are often involved.

Rarer forms of chronic CLE include CLE hypertrophicus (solitary, verrucous, hypertrophic lesions) and CLE profundus (a panniculitis). LE non-specific lesions include Raynaud’s phenomenon, non-scarring alopecia, cutaneous vasculitis, and livedo reticularis.

**Amyloidosis**

Amyloidoses are a group of conditions that cause progressive end organ damage due to insoluble fibril deposition in extracellularly tissues. Kidney and cutaneous involvement commonly occurs in systemic amyloidosis, in particular AL (primary) and hereditary forms. Although kidney disease occurs in AA amyloidosis (secondary to chronic inflammatory diseases), cutaneous involvement is rare.

Without treatment, amyloidosis-related kidney disease (amyloid nephropathy) usually progresses to end stage kidney disease. Diagnosis usually requires histological confirmation of the presence of amyloid deposits using Congo red dye staining and bright apple-green birefringence under polarisation. Amyloid deposits can be deposited within many tissues amenable to biopsy including kidney, GI tract, skin and fat.

Cutaneous amyloidosis occurs when amyloid-like proteins are deposited directly within the dermis. Most common cutaneous features are purpura, petechiae and ecchymoses secondary to intracutaneous haemorrhage when vessels are infiltrated by amyloid (figure 11). Waxy papules, plaques or nodules can occur around the eyelids, neck, groin and anogenital area. Nail dystrophy
and diffuse alopecia can also occur. Macroglossia occurs in 10-20% of primary systemic amyloidosis.\textsuperscript{39}

Localised primary amyloidosis is a separate entity to systemic amyloidosis as discussed above, causing cutaneous disease without kidney involvement. Further detail will not be explored within this review due to the absence of kidney disease.

**Cholesterol Embolisation Syndrome**

Cholesterol embolisation syndrome (CES) is a disease caused by showering of cholesterol crystals from fractured atherosclerotic plaques of the aorta and its major branches to distal sites, leading to vascular occlusion and subsequent multi-organ damage.\textsuperscript{40} It is usually iatrogenic secondary to intervention within the major vessels, such as angiography or cardiac/aortic surgery, but can occur spontaneously. Kidney involvement occurs in around 50% of cases of CES, and renal artery atheroembolism can lead to acute, subacute or chronic kidney disease.\textsuperscript{41}

Cutaneous findings are seen in between 35-96% cases, however the highest rates of cutaneous involvement are seen in those who also have kidney involvement.\textsuperscript{41} The most common findings are livedo reticularis (49%), digital gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%), and purpura (9%).\textsuperscript{41} The lower legs are most often involved, however findings can spread to the trunk or upper limbs.

**COVID-19**

AKI is common in patients affected by COVID-19, particularly those in the intensive care unit. The pathophysiology behind this has not been fully uncovered but it is likely multifactorial and in keeping with AKI in critical illness.\textsuperscript{42} Following a Spanish study of 375 COVID-19 patients, cutaneous lesions have been characterised into five subtypes: maculopapular eruptions occurring most commonly
(47%), acral erythema with vesicles or pustules (pseudo-chilblains) (19%), urticarial lesions (19%), vesicular eruptions (9%) and livedo or necrosis (6%).

CONCLUSION

Although not an exhaustive list, we have highlighted key cutaneous manifestations of important disease processes which cause AKI. Alternative, and possibly co-existing, causes for AKI in these patients should not be overlooked, for example, prerenal and postrenal causes. Knowledge of the clinical features discussed is essential as it may aid in diagnosis, investigation, and management in a timelier fashion – helping to prevent long-term renal and extra-renal complications.

PATIENT CONSENT

Informed written consent has been obtained for all images or where consent was not possible, images have been sufficiently anonymised.

CONFLICT OF INTEREST STATEMENT

None declared.

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**Figure 1.** Urticated exanthem with targetoid lesions and associated facial swelling in a patient with DRESS syndrome.
Figure 2. Purpuric livedoid rash of the lower limbs occurring in polyarteritis nodosa.
Figure 3. Granulomatous nodular rash of the back occurring in GPA.
Figure 4. Palpable purpuric rash of the lower limbs in EGPA.
Figure 5. Bilateral palpable purpuric rash in HSP with secondary leg oedema.
Figure 6. Palpable purpuric rash and haemorrhagic bullae involving predominantly the lower limbs in HSP.
Figure 7. Sclerotic (thickened, tight) skin of the arms and sclerodactyly in a patient with systemic sclerosis.
Figure 8. Nephrogenic systemic fibrosis. Swollen, fibrotic digits with flexion contractures and prominent sclerotic nodules associated with the palmar aponeurosis. Woody induration and skin thickening extending to the forearms.
Figure 9: Typical cutaneous features of dermatomyositis.

Figure 9a. Heliotrope rash and facial erythema.
Figure 9b. Gottron’s papules of the dorsal aspect of the hands.
Figure 9c. Symmetrical erythema of the back, shoulders, chest and neck, known as the “shawl sign”.
Figure 9d. Ragged cuticles.
Figure 9e and 9f. Dilated capillary loops and telangiectasia, including visualisation under dermoscopy.
Figure 9e and 9f. Dilated capillary loops and telangiectasia, including visualisation under dermoscopy.
Figure 9g. Linear erythematous streaks of the back known as flagellate erythema.
Figure 10. Discoid lupus erythematosus. Ro-antibody positive patient with longstanding treatment-resistant DLE. Well defined symmetrical erythematous facial plaques with hypo and hyper-pigmented scarring.
Figure 11. Periorbital ecchymoses in a patient with cutaneous amyloidosis.
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