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LITERATURE REVIEW

Cutaneous manifestations in end-stage renal disease (ESRD)

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ABSTRACT

Skin can reflect systemic conditions due to abnormalities in internal organs, including kidney disorders. Cutaneous manifestations are common in patients with end-stage renal disease (ESRD). It can be severe and negatively impact a patient's quality of life. Clinicians can effectively manage ESRD by closely examining the patient's skin and nails, improving the patient's quality of life, and reducing mortality and morbidity. Clinicians can be more aware of ESRD by examining the patient's skin and nails closely so proper management can be performed and the patient's quality of life can be improved. This review aims to increase understanding of common cutaneous manifestations in ESRD for early recognition and better management. Cutaneous manifestations in ESRD are divided into specific and nonspecific manifestations. Specific manifestations include acquired perforating dermatosis (APD), bullous disease (porphyria cutanea tarda and pseudoporphyria), metastatic calcification (calcinosis cutis and calcific uremic arteriolopathy), and nephrogenic systemic fibrosis. Nonspecific manifestations include pruritus, xerosis, skin pigmentation changes, nail disorders, purpura, hair disorders, oral mucosal changes, skin infections, and other skin manifestations. These manifestations range from benign and asymptomatic to serious conditions that negatively impact life quality. In conclusion, Early detection and treatment of cutaneous manifestations in patients with ESRD are crucial for reducing morbidity and mortality and also improving patients' quality of life.

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INTRODUCTION

Skin is the largest organ that can reflect systemic conditions due to abnormalities in internal organs, including kidney disorders (Chanda, Chintagunta, and Arakkal, 2017). Skin disorders in chronic kidney disease (CKD) are common, with a prevalence of 50-100% (Chanda, Chintagunta, and Arakkal, 2017; Raspha *et al.*, 2018; Adejumo *et al.*, 2019). In the last several decades, the prevalence and incidence of chronic kidney disease (CKD) have increased. It has become a global health problem in developed and developing countries (Prodjosudjadi and Suhardjono, 2009; Adejumo *et al.*, 2019). The prevalence of CKD in Indonesia has increased by 1.8% from 2013 to 2018, with hypertension as the leading cause (Laporan Nasional RISKESDAS, 2018). The decline of kidney function in CKD is chronic and progressive, leading to end-stage renal disease (ESRD), which is defined as a state where the kidneys are unable to maintain life without dialysis or a permanent kidney transplant due to irreversible loss of renal (Prodjosudjadi and Suhardjono, 2009; Fauziyati, 2017; Raiesifar *et al.*, 2018). Diabetes mellitus (45%), hypertension (35%), and glomerulonephritis (4%) were the most frequent causes of renal dysfunction (Charu and Anshul, 2020). As a consequence of kidney function deterioration, kidney clearance will reduce, leading to elevated serum creatinine, uric acid, and urea (Rehman and Khan, 2020).

As ESRD increases, the incidence and prevalence of skin disorders associated with ESRD also increase (Kuypers, 2009; Raiesifar *et al.*, 2018). Typically, patients with ESRD have at least one skin problem, which can significantly lower patients' quality of lifeand worsen both mental and physical health. The skin disorders associated with ESRD could be due to the underlying etiology, the drugs used for therapy, or the consequence of ESRD itself (Chanda, Chintagunta, and Arakkal, 2017; Adejumo *et al.*, 2019). Those skin disorders also increase with hemodialysis (Raiesifar *et al.*, 2018). Chanda et al. reported clinical manifestations in the group that underwent hemodialysis were significantly higher than in the nondialysis group (Chanda, Chintagunta, and Arakkal, 2017). Hemodialysis can't work as effectively as normal kidneys. It can't replace endocrine function from the kidneys, resulting in an electrolyte imbalance and buildup of urea in the blood, leading to skin manifestations (Galperin, Cronin, and Leslie, 2014; Charu and Anshul, 2020). However, it is difficult to determine whether the cutaneous manifestations are caused by an underlying kidney disorder or due to hemodialysis because those two are related (Charu and Anshul, 2020).

Clinicians should be able to identify early abnormalities in the kidneys, thus, basic knowledge of common skin disorders in patients with ESRD is needed. Adequate managementof the various skin disorders in ESRD is expected to reduce the symptoms so that patients will have a better quality of life. Therefore, this review aims to increase understanding of common cutaneous manifestations in ESRD for early recognition and better management.

LITERATURE REVIEW

Cutaneous manifestations in ESRD can be distinguished into specific and nonspecific manifestations (Table 1). Nonspecific skin manifestations are more common in ESRD patientsthan specific skin manifestations (Charu and Anshul, 2020). Due to variations in race, ethnicity, socioeconomic status, geographic location, regional climate, and the accuracy and experience of the examiner, each skin manifestation's prevalence differed according to several studies (Raiesifar *et al.*, 2018).

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Table 1. Cutaneous specific and nonspecific manifestations of ESRD

Cutaneous Manifestations	
Specific	**Nonspesific**
Acquired perforating disorder: Reactive perforating collagenosis Perforating folliculitis Elastosis perforans serpiginosa Kyrle disease Calcifying disorders: Metastatic calcification (calcinosis cutis, calciphylaxis) Bullous dermatoses: Porphyria cutanea tarda Pseudoporphyria Nephrogenic systemic fibrosis	Pruritus Xerosis Pigmentation disorders: Pallor, hyperpigmentation, yellowing skin Nail disorders: Half-and-half nails (Lindsay's nails), koilonychia, subungual hyperkeratosis, onycholysis, Mees' lines Hair disorders: Sparse (minimal) body hair, diffuse alopecia, dry lusterless hair Purpura Oral mucosa changes: Coated tongue, xerostomia, macroglossia Skin infections (fungi, bacteria, and viruses) Other skin manifestations Acrochordon, prurigo nodularis, ichthyosis

Source: (Galperin, Cronin, and Leslie, 2014; Charu and Anshul, 2020; Malkud, Dyavannanavar, and Varala, 2020)

SPECIFIC MANIFESTATIONS

Acquired Perforating Dermatosis (APD)

Acquired perforating dermatosis (APD) is a varied group of skin conditions defined by the transepidermal elimination of collagen and elastic fibers, two components of the dermal connective tissue. There are four different types of this condition, each of which may be identified by the histological characteristics and the content of the material that is extruded through the dermis: reactive perforating collagenosis (RPC), perforating folliculitis (PF), elastosis perforans serpiginous (EPS), and Kyrle disease (Maiberger and Nunley, 2017; Forrestel and Micheletti, 2019; Garrido *et al.*, 2020). However, the term APD has been used tocharacterize perforating dermatoses that develop in adult patients with systemic disease because some patients can present with more than one type, and the pathologic examination frequently overlaps (Garrido *et al.*, 2020).

Diabetes mellitus (DM) and chronic kidney disease (CKD) patients are more likely to have acquired APD, but it has been reported to have an association with many other systemic disorders such as liver disease, thyroid disease, malignancy, and AIDS (Kuypers, 2009). It typically occurs following dialysis treatment. Acquired perforating dermatosis (APD) affects between 2% and 11% of patients who received dialysis therapy and it is more prevalent in patients between the fourth and fifth decades of life without preference for gender (Forrestel and Micheletti, 2019; Wang *et al.*, 2020).

Patients usually experience moderate to severe pruritus on the affected skin area accompanied by hyperpigmented domed-shaped papules (Figure 1A) or hyperkeratotic follicular nodules with clear borders and a central keratotic plug with umbilication and crusts. The predilection areas are commonly on the body and the surface of extensor limbs, especially inferior limbs,

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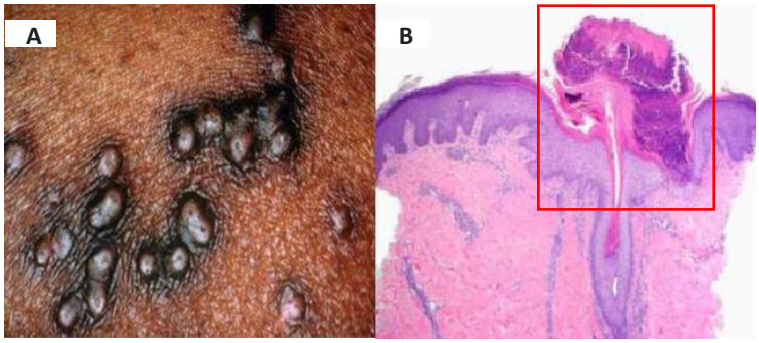

Figure 1. Acquired perforating dermatosis (APD). **(A)** A central keratotic plug is present in some clustered, hyperpigmented, dome-shaped nodules and coalescing plaques (Galperin, Cronin and Leslie, 2014). **(B)** A cup-shaped epidermal depression filled with parakeratosis and neutrophilic debris is visible upon histopathological examination. The epidermis is thinner and protrudes through this attenuated epidermis at the depression's base, where degraded collagen fibers are visible. (HE 20x magnification) (Source: (Galperin, Cronin, and Leslie, 2014).

and are often linearly distributed (Forrestel and Micheletti, 2019; Wang *et al.*, 2020). Koebnerization, the formation of lesions in traumatized skin areas, including scratching,is frequently found in APD patients (Galperin, Cronin, and Leslie, 2014).

The exact pathophysiology of APD is still unknown and probably multifactorial. It has been suggested that the following etiologies exist: (1) epidermal or dermal abnormalities caused by changes in collagen and elastic fibers, possibly a result of metabolic disorders caused by CKD; (2) micro deposition of byproducts, such as calcium, uric acid, and hydroxyapatite caused by CKD; (3) diabetic vasculopathy, which is a significant risk factor in diabetic patients.

A skin biopsy of the lesion region is frequently used to confirm the clinical diagnosis ofAPD. Transepidermal elimination of the dermal substrate, such as collagen, keratin, and elastin, which manifests as a cup-shaped invagination of the epidermis, is the characteristic histopathological feature of this disease (Figure 1B) (Galperin, Cronin and Leslie, 2014; Wang *et al.*, 2020). Dermoscopy can also be helpful in the diagnosis of APD. Shiny, white areaswith cellular debris and keratin in the center of the lesion that is associated with dilated hair follicle infundibulum are surrounded by a non-structured, grayish area caused by a mix of epidermal and dermal changes (Sabban, 2018).

Treatment of APD is often tricky and challenging because the lesions can persist, and chronic scarring can develop (Kuypers, 2009). Although APD can experience resolution spontaneously, and in some cases, the lesions could disappear within 6-8 weeks without therapy,some cases persist for more than 8 years (Wang *et al.*, 2020). There are no controlled studies or treatment guidelines for APD, the evidence-based support for treatment comes from small case series and individual case reports (Lukács, Schliemann, and Elsner, 2018; Garrido *et al.*, 2020). Treatment of underlying internal diseases should always be considered and aimed at improving pruritus and reducing skin lesions (Lukács, Schliemann, and Elsner, 2018).

Several treatments that are commonly used for APD are topical retinoids, topical steroids(class II-III corticosteroids), and UVB phototherapy

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(Lima *et al.*, 2017; Kim *et al.*, 2020). Intralesional triamcinolone can also be applied (Lima *et al.*, 2017). It has been suggested that combination therapy yields better results than monotherapy (Lukács, Schliemann and Elsner, 2018). Antihistamines to reduce itching and corticosteroids and/or topical keratolytic medications (retinoids, salicylic acid, urea) plus emollients are the first-line treatments for this skin condition (Sabban, 2018). Garrido et al. discovered that the most frequently prescribed initial treatment was antihistamines and topical steroids. However, only 37.8% of the patients experienced a full recovery; some of these patients also received systemic steroids, narrow-band ultraviolet B (NB-UVB), topical calcipotriol, and sirolimus (Garrido *et al.*, 2020). Systemic therapy and phototherapy, especially NB-UVB, should be considered in addition to topical treatment, depending on the patient's primary disease and general condition. Antihistamines can reduce itching, but they are not always effective in treating pruritus caused by APD (Lukács, Schliemann and Elsner, 2018). Acitretin, systemic steroids, and phototherapy are associated with the best outcome and should be considered in managing patients with disseminated lesions and severe pruritus, as well as in those who have a poor response to topical therapies (Garrido *et al.*, 2020). Oral retinoids (isotretinoin) are also indicated, if necessary, but they require special attention to the accumulation and side effects, such as teratogenic potential, mood changes, elevated liver enzyme levels, and allergic reactions. Isotretinoin acts as an anti-inflammatory and induction of cell apoptosis in APD (Kim *et al.*, 2020).

Some patients were treated with antibiotics (doxycycline or tetracycline) and allopurinol (Garrido *et al.*, 2020). Doxycycline and tetracycline have anti-inflammatory properties and potent inhibitory effects on leukocytes and matrix metalloproteinases (Gilbert *et al.*, 2021). Allopurinol may be helpful, according to a study by Lukács et al., but another study found that

Table 2. Therapies for acquired perforating dermatosis (APD)

Topical Therapy	Oral Therapy	Other Therapy
Steroids and/ or keratolytic: salicylic acid or urea	Antihistamines: Hydroxyzine Fexofenadine Doxepin	Intralesional triamcinolone
Retinoid	Isotretinoin	Narrow-band ultraviolet B (NB-UVB)
Cantharidin	Allopurinol 100 mg	Photodynamic therapy (PDT) with5-amino-levulinic acid
	Acitretin	Cryotherapy with liquid nitrogen
	Doxycycline 100mg Minocycline 100 – 200 mg	

Source: (Galperin, Cronin, and Leslie, 2014)

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Bullous Diseases

Bullous diseases in ESRD manifest as porphyria cutanea tarda (PCT) or pseudoporphyria. Patients with PCT and pseudoporphyria have vulnerable, sensitive skin, showing clinical signs of tense bullae, erosions, and crusts on the arms' extensor surfaces and the hand's dorsum surface. Bullae can also appear on the face, sometimes accompanied by hyperpigmentation on the face (sclerodermoid plaque) and hypertrichosis (Kuypers, 2009). Both conditions occur due to the build-up of photosensitive molecules on skin exposed to ultraviolet light, resulting in vesiculation and skin fragility in sun-exposed areas (Galperin, Cronin, and Leslie, 2014). The prevalence of PCT in ESRD patients ranges from 5% to 18% (Pallet *et al.*, 2018).

The activity of uroporphyrinogen decarboxylase (URO-D), an essential enzyme in heme synthesis, is decreased in ESRD as a result of the accumulation of urea in the blood due to decreased kidney function. It will lead to the accumulation of water-soluble uroporphyrin in plasma, liver, and skin (Galperin, Cronin, and Leslie, 2014; Pallet *et al.*, 2018). Furthermore, patients with ESRD have an impaired ability to excrete porphyrin through the kidneys, while hemodialysis is unable to eliminate porphyrin, photoreactive molecules that can absorb light energy and pass it on to the surrounding tissue, effectively. As a result, porphyrin levels in the blood will increase and manifest as PCT (Maiberger and Nunley, 2017). Porphyrins will also produce oxidative free radicals when exposed to ultraviolet light, resulting in lesions on the skin with manifestations such as PCT (Pallet *et al.*, 2018).

Iron also plays a vital role in developing PCT by inhibiting the action of the enzyme uroporphyrinogen decarboxylase (URO-D). High frequency of red blood cell transfusions to treat anemia in ESRD patients can cause an overload of iron in the blood as well as increase the risk of hepatitis C infection due to transfusion. Chronic hepatitis C infection will decrease hepcidin production by hepatocyte cells, which causes an increase in iron absorption from the digestive tract and iron overload. Administration of erythropoietin recombinants can reduce the need for red blood cell transfusions, decrease iron overload, and reduce the risk of transfusion-induced hepatitis C infection. High-flux membranes can significantly increase the clearance of porphyrin in plasma if standard hemodialysis cannot eliminate uroporphyrin (Pallet *et al.*, 2018). Porphyria cutenea tarda (PCT) rarely occurs in peritoneal dialysis, possibly because peritoneal dialysis provides greater clearance of large molecules (Galperin, Cronin, and Leslie, 2014).

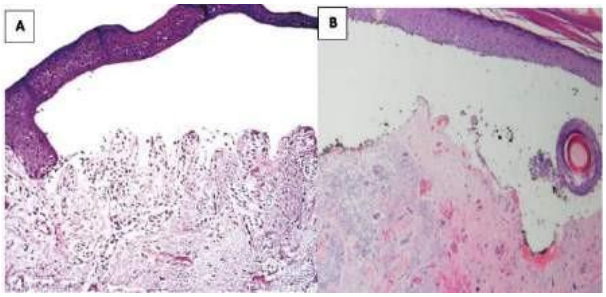

Figure 2. Histopathological features of PCT. **(A)** Non-inflammatory subepidermal bullae form a "*festooning*" pattern in the middle blood vessels of the papillary dermis (Source: Singal, 2019). **(B)** Fibrosis of the dermis and perivascular material hyalinization that is positive for PAS indicates immunoglobulin deposits and complement (Source: Wick, 2017).

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The diagnosis of PCT is determined by the urine or plasma porphyrin profile, which is dominated by uroporphyrin and heptacarboxyporphyrin (Pallet *et al.*, 2018). A skin biopsy examination is unnecessary to diagnose because the result is not specific. The histopathological features of PCT are subepidermal bullae with material deposits that are positive for periodic-acid schiff (PAS) staining around the blood vessels and the fine fibrillar material in the upper dermis and dermoepithelial junction (Anderson and Gou, 2019).

Avoiding triggering factors, including alcohol, smoking, hepatotoxic medicines, and sun exposure, also reducing iron overload, are a possible approaches to managing PCT (Galperin, Cronin and Leslie, 2014). Phlebotomy can also reduce iron levels in the liver, but most ESRD patients suffer from anemia and cannot tolerate phlebotomy, so giving erythropoietin would be better to reduce total iron stores in the body (Anderson and Gou, 2019). Another therapeutic option in cases with mild iron increase is hydroxychloroquine sulfate doses of 100-200 mg, given 2-3 times a week (Maiberger and Nunley, 2017).

Pseudoporphyria is similar to PCT clinically and histologically, without serum and urine porphyrin abnormalities (Galperin, Cronin, and Leslie, 2014). The pathophysiological pathway of pseudoporphyria is unknown, however excessive ultraviolet light exposure and the presence of uraemic toxins, together with photosensitizing drugs including naproxen, furosemide, tetracyclines, and amiodarone, seem to be the main contributors to its development (Pallet *et al.*, 2018). Hypertrichosis in pseudoporphyria is less common (Anderson and Gou, 2019). Management of pseudoporphyria involves discontinuing the suspected precipitating drug lesions, avoiding sun exposure, and administering the N-acetylcysteine, a metabolic precursor of glutathione (Galperin, Cronin, and Leslie, 2014).

Metastatic Calcification

The presence of abnormal calcium and/or phosphate metabolism in ESRD is a defining feature of metastatic calcification (Galperin, Cronin and Leslie, 2014; Anderson and Gou, 2019). Calcinosis cutis or calcific uremic arteriolopathy (calciphylaxis) could occur as the manifestation of metastatic calcification (Galperin, Cronin, and Leslie, 2014).

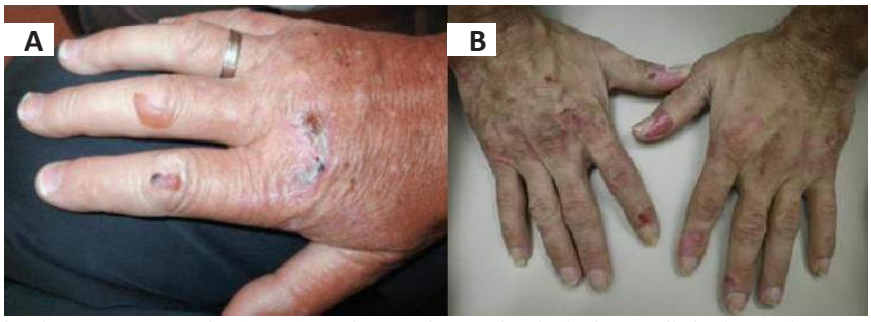

Figure 3. Porphyria cutanea tarda (PCT) and pseudoporphyria in hemodialysis patients. **(A)** Bullae can be seen in the dorsum surface of the hand of a patient with PCT (Source: Kuypers, 2009). **(B)** Pseudoporphyria is clinically difficult to distinguish with PCT (Source: Maiberger and Nunley, 2017)

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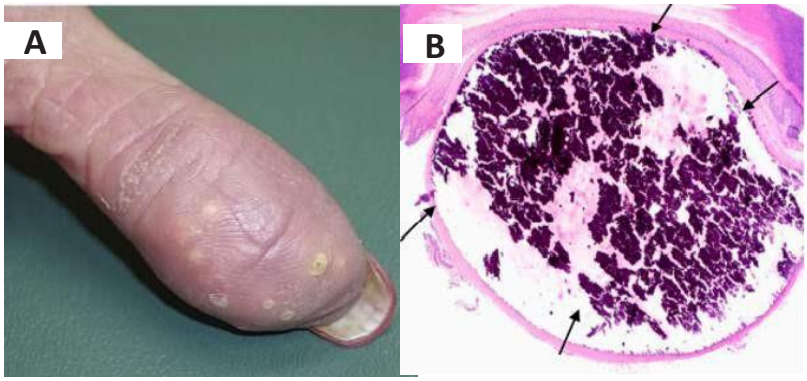

Figure 4. Calcinosis cutis. **(A)** Lesions are characterized by painful lesions on the distal fingertips (Source: Maiberger and Nunley, 2017) **(B)** Histopathology examination reveals a nodular deposit of basophilic refractile calcium in the dermis (black arrows). Minimal inflammation is present (Source: Galperin, Cronin and Leslie, 2014).

Calcinosis cutis

Cutaneous calcinosis is reported in 1% of patients with ESRD undergoing hemodialysis and is generally a late complication (Maiberger and Nunley, 2017). Hyperphosphatemia is a characteristic sign arising secondary to the reduction of phosphate clearance and inadequate phosphate clearance by hemodialysis (Galperin, Cronin, and Leslie, 2014). Clinically, patients manifest rock-hard papules, nodules, or plaques that are frequently found on the fingers and periarticular region and may secrete a white material through the epidermis. Periarticular lesions are usually asymptomatic, while knuckle lesions are usually painful. Phosphate levels in serum are associated with the quantity and size of the lesions. (Galperin, Cronin and Leslie, 2014; Maiberger and Nunley, 2017). A special stain can be used to identify calcium deposits. The histology examination reveals homogeneous blue material in the dermis, occasionally with foreign body giant cells (Maiberger and Nunley, 2017).

There is no gold standard therapy for cutaneous calcinosis. Normalized phosphate and calcium levels can cause lesion regression. Dietary phosphate restriction and phosphate binder may help lower serum phosphate levels. It is necessary to consider parathyroidectomy in somerefractory cases (Galperin, Cronin, and Leslie, 2014)

Calcific Uremic Arteriolopathy (Calciphylaxis)

Calcific uremic arteriolopathy, also known as calciphylaxis, is a painful ischemic vasculopathy of the skin and subcutaneous tissue that is potentially causing death. It is characterized by thrombosis and fibrosis of the small to moderate arteries and arterioles (Kuypers, 2009; Galperin, Cronin, and Leslie, 2014; Maiberger and Nunley, 2017). Calciphylaxis is a rare disease with a prevalence of 1-4% in patients with hemodialysis. The predilection of age is around 50 years old, usually between 69 and 72 years old. The mortality rate is 60-80%, with 5 years survival rate of 35%. Fatality often occurs secondary to sepsis and organ system failure (Kuypers, 2009; Galperin, Cronin and Leslie, 2014). The pathogenesis of calciphylaxis is still unclear. It is thought to be multifactorial due to metabolic factors, systemic inflammation, oxidative stress, and damage to the endothelium due to certain trigger factors (Maiberger and Nunley, 2017). Risk factors include local trauma, female gender, diabetes mellitus,

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Caucasian ethnicity, hypoalbuminemia, therapy with calcium salts, hypercalcemia, use of phosphate binders agents containing calcium, vitamin D therapy, hyperphosphatemia, the use of erythropoiesis-stimulating agents, warfarin, and iron supplementation. Other independent risk factors are obesity, liver disease, and systemic corticosteroids (Galperin, Cronin and Leslie, 2014; Maiberger and Nunley, 2017).

Calciphylaxis has a sudden onset characterized by the occurrence of unspecific violaceous mottling, skin lesions resembling livedo reticularis, or erythematous papules, nodules, or plaques commonly appear on the abdomen, buttocks, and thighs, which contain a lot of subcutaneous fat (Kuypers, 2009; Maiberger and Nunley, 2017). These lesions develop over a period of a few days or weeks into tender, subcutaneous, purpuric plaques and nodules, which thereafter develop into necrotic ulcers coated in eschars. Early clinical diagnosis in the non-ulcerative stage is crucial to improve the prognosis (Kuypers, 2009).

Histopathological examination can help establish the diagnosis; however, a skin biopsy needs to be done carefully because ulceration can develop and be difficult to heal. It shows vessel calcification in the small to medium-sized blood in the dermis and subcutis tissue **(Figure 5)**. Calcification occurs more precisely in the walls of the blood vessels in the media with extensive intima or subintima hyperplasia and fibrosis (Kuypers, 2009; Galperin, Cronin, and Leslie, 2014; Maiberger and Nunley, 2017)

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) is a fibrosing disease that resembles scleroderma and is associated to renal failure and hemodialysis. Although the etiology of the disease was found unclear initially, the etiology of nephrogenic systemic fibrosis is later associated with exposure to the contrast material gadolinium (Gd) used in radiological examination in patients with renal insufficiency. Gadolinium ion is very toxic to tissues (Galperin, Cronin and Leslie, 2014; Maiberger and Nunley, 2017). The clinical manifestations include skin thickening, progressive fibrosis, and pain with the involvement of various organs like the heart, lungs, liver, esophagus, duramater, testicles, and striated muscles (Kuypers, 2009). Early symptoms of NSF are thickening skin and tight sensation or indurated papules and plaques in the upper or lower limb and the trunk with discoloration of the skin to become bright red or dark, which is rapidlyprogressive and symmetrically distributed; sometimes it may be pruritic. Within a few days or

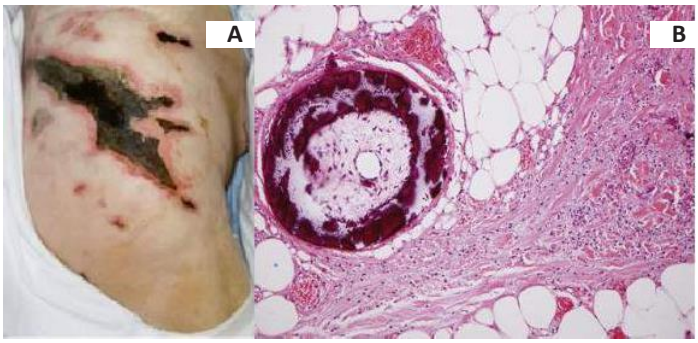

Figure 5. Calciphylaxis. **(A)** Deep ulceration in the upper thigh and eschar formation. **(B)** Histopathology of calciphylaxis typically demonstrates calcification within the media of small- and medium-sized arterioles with extensive intimal hyperplasia and fibrosis (Source: Sartori-Valinotti and Davis, 2015).

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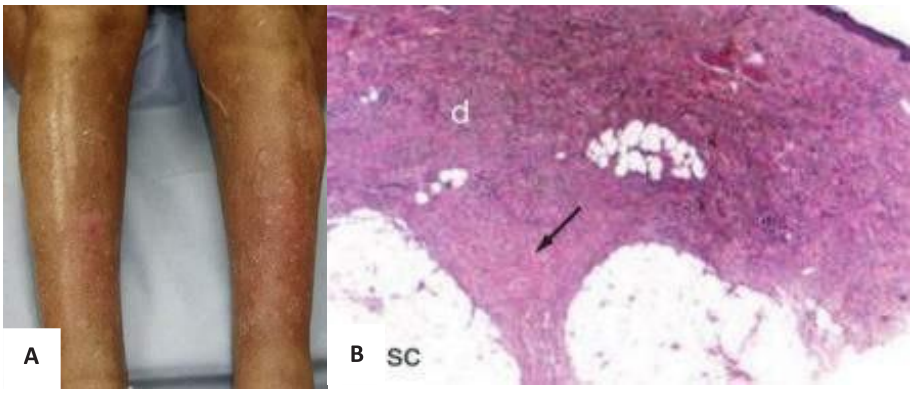

Figure 6. Nephrogenic systemic fibrosis. **(A)** Symmetric, indurated, hyperpigmented plaques on the bilateral legs (Maiberger and Nunley, 2017). **(B)** Dermal thickening is visible in the hematoxylin and eosin stain. The arrow shows a fibrotic septum that divides the subcutis's fat lobules (Kuypers, 2009).

progressively becomes a confluent erythematous lesion and thickening of the skin with a wood-like texture and brownish induration *peau d'orange* that may cause contractures and

immobilization. Patients usually complained about limbs that feel tight and painful, sometimes accompanied by pruritus and burning sensations or muscle weakness. It can lead to disability even if it does not always cause mortality (Kuypers, 2009; Maiberger and Nunley, 2017).

This disease is diagnosed based on the patient's history and physical examination; a skin biopsy is then used to confirm the diagnosis. Histopathological examination reveals thickening of the dermis and pathological alterations, such as proliferation of spindle cells with interstitial mucin deposits, thickened collagen bundles, and decreasedinflammatory cells. Additionally, histiocytes and dendritic cells are seen (Kuypers, 2009). Several studies have shown that there is no effective therapy available for NSF. Multiple treatments have been tried, such as corticosteroids, thalidomide, cyclophosphamide, cyclosporin, intravenous immunoglobulin, plasmapheresis, topical calcipotriene, interferon (IFN)-ɤ, psoralen therapy and ultraviolet A (PUVA), and kidney transplant (Kuypers, 2009; Maiberger and Nunley, 2017).

NONSPESIFIC MANIFESTATIONS

Pruritus

Pruritus is a common symptom of ESRD, also known as uremic pruritus. The term "uremic pruritus" refers to itching that is solely caused by renal illness and cannot be attributed to another concomitant condition (Galperin, Cronin, and Leslie, 2014; Verduzco and Shirazian, 2020). There are no significant differences between hemodialysis patients and non-hemodialysis patients (Raspha *et al.*, 2018; Charu and Anshul, 2020). The prevalence and intensity of uremic pruritus are not dependent on age, sex, ethnicity, and the duration of dialysis, although hemodialysis patients are more likely to experience it (Azimi, Lerner, and Elmariah, 2015). Uremic pruritus can be localized, generalized, episodic, or continuous (Galperin, Cronin, and Leslie, 2014; Charu

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and Anshul, 2020). Approximately 20-50% of patients have generalized pruritus. Local pruritus usually appears symmetrically on the extremities, head (especially vertex), back, and chest (Kuypers, 2009). Clinical manifestations of uremic pruritus are secondary changes in the skin, such as excoriation, lichenification, hyperpigmentation, and prurigo nodularis as a result of repeated scratching (Forrestel and Micheletti, 2019). Other causes of pruritus need to be excluded before making a diagnosis of uremic pruritus. The exact pathogenesis of uremic pruritus is unknown, but it might be multifactorial and related to the severity of xerosis (Galperin, Cronin, and Leslie, 2014). Additionally, it has been associated with inflammatory factors, vitamin A, parathyroid hormone, mast cell hyperplasia, high serum histamine, peripheral neuropathy, and mast cell hyperplasia (Raspha *et al.*, 2018).

The following criteria can help to diagnose uremic pruritus: (1) pruritus appearing immediately after dialysis or appearing at any time without being accompanied by other diseases that can actively trigger itching, (2) the patient had 3 or more episodes of itching in less than 2 weeks and symptoms occur several times a day with a duration of several minutes, and causing distress, (3) during six months, pruritus manifests in a regular pattern (Azimi, Lerner, and Elmariah, 2015).

Since there is no effective therapy for uremic pruritus other than kidney transplantation, it is difficult to manage. In general, improving dialysis effectiveness using the proper dialysis membranes and improving the patient's nutritional state are all part of managing uremic pruritus in hemodialysis patients (Kuypers, 2009). Itching has been reported to decrease when daily dialysate volume, time, and frequency increase (Azimi, Lerner, and Elmariah, 2015). In some circumstances, secondary hyperparathyroidism therapy and proper regulation of plasma calcium and phosphorus levels might alleviate the symptoms of pruritus (Kuypers, 2009).

Optimal therapy can be achieved by a combination of several therapies. Topical therapies for uremic pruritus include emollient, capsaicin cream, and tacrolimus. Regular application of emollients without scent and other additives to maintain the skin barrier's integrity, limit waterloss, and reduce exposure to environmental irritants are the main treatment for uremic pruritus (Azimi, Lerner, and Elmariah, 2015). There are several systemic treatments for uremic pruritus, including UV light, opioid receptor agonists and antagonists, gabapentin, antihistamines, cromolyn sodium (CS), immunomodulators, activated charcoal, cholestyramine, ondancentrone, and intravenous erythropoietin (Gnanaserkan *et al.*, 2020). Administration of cromolyn sodium (CS) orally (135 mg 3 times a day) and topical (4% cream) can reduce itchingin hemodialysis patients (Azimi, Lerner, and Elmariah, 2015).

Ultraviolet therapy is an effective therapy for uremic pruritus and is well tolerated. The mechanism of action is by reducing histaminergic factors in the patient's serum and vitamin A levels in the epidermis. The antipruritic effect of UV-B phototherapy that is given 3 times a week throughout the body(total 8-10 sessions) varies, but it can last several months (Kuypers, 2009; Galperin, Cronin, and Leslie, 2014; Gnanaserkan *et al.*, 2020).

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Table 3. Therapeutic approaches of uremic pruritus (Source: Galperin, Cronin and Leslie, 2014; Azimi, Lerner and Elmariah, 2015)

Therapy	Information
Optimize dialysate	Correct electrolyte imbalance
Emollients	10% urea and dexpanthenol lotion Sericin cream 8% 2 times daily
Mast cell stabilizer	Cromolyne sodium 4% cream daily Cromolyn 135 mg 3 times daily orally
Capsaicin	Capsaicin 0,025% ointment
Topical analgetic	Pramoxine 1% lotion 2 times daily
Antihistamine	Hydroxyzine 10-25mg 2-4 times daily orally
Anticonvulsant	Gabapentin 100-300 mg 3 times a week orally after each dialysis session, for a month Gabapentin 400 mg 2 times a week orally everyafter each dialysis session
Opioid antagonist	Nalfurafin 5 g intravenous 3 times a week after each hemodialysis session
Sertraline	50 mg/day orally
Narrow-band UVB (NB-UVB)	3 times a week, all over the body

Xerosis

Xerosis is a common skin disorder found in ESRD patients with a prevalence of 50-86%. Xerosis varies from mild to severe, especially on the extremities and back, sometimes accompanied by a rough scale. Severe xerosis can indicate that someone has ESRD and diabetes mellitus (Galperin, Cronin and Leslie, 2014; Gnanaserkan *et al.*, 2020). Skin dehydration, usage of diuretics, hypervitaminosis A, reduced sebum or sweat glands excretion, changes in skin barrier due to reduced lipids on the skin surface, malnutrition, and low use of moisturizers can contribute to the primary severity of xerosis. In contrast, the presence of external factors such as sun exposure, especially in tropical climates, and usage of detergents can aggravate the chronic dehydration that later causes xerosis (Raspha *et al.*, 2018; Malkud, Dyavannanavar, and Varala, 2020; Maskey, Kumar, and Shrestha, 2020). Reduced excretion of sweat glands in ESRD patients is due to reduced size and functional abnormalities of the eccrine duct (Sanai *et al.*, 2010; Charu and Anshul, 2020).

Emollient therapy alleviates abnormalities in xerosis, such as poor water binding, inadequate water transport to the stratum corneum, and skin barrier issues. A combination of substances with various functions, including humectants, lipid physiology, and natural moisturizing factors (NMF), is helpful in treating ESRD patients with xerosis (Wu *et al.*, 2015).

Skin Discoloration

One of the common skin symptoms seen in hemodialysis patients is skin discoloration, such as pallor, hyperpigmentation, and yellowing of the skin (Galperin, Cronin, and Leslie, 2014; Raiesifar *et al.*, 2018). Pallor in patients with Fitzpatrick's IV-V skin type is an essential clinical marker in ESRD patients who are anemic (Gnanaserkan *et al.*, 2020). The study by Charu et al. reported that 48% of ESRD patients undergoing hemodialysis experience

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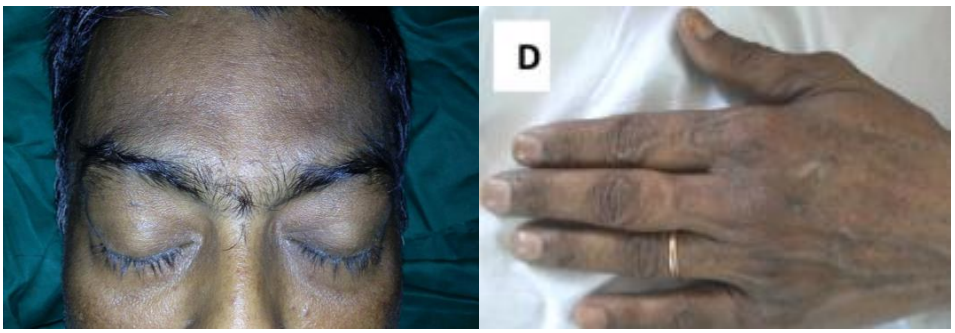

Figure 7. Skin discoloration in end-stage renal disease. Hyperpigmentation on the face (A) and dorsal of the hand (B). (Source: Mourad *et al.*, 2014; Levillard and Kambil, 2015)

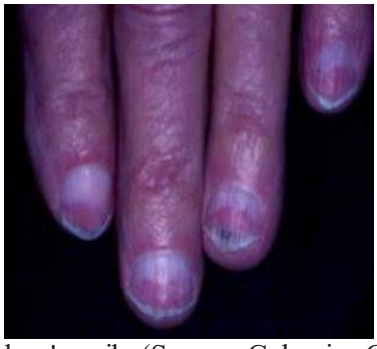

Figure 8. Half-and-half nails or Lindsay's nails (Source: Galperin, Cronin and Leslie, 2014)

hyperpigmentation. Tropical climate and light exposure to the sun can cause an increase in the prevalence of diffuse hyperpigmentation (Charu and Anshul, 2020).

Hyperpigmentation occurs due to increasing levels of β-melanocyte stimulating hormone (β-MSH), which cannot be excreted by the kidneys and is not dialyzed perfectly, thus resultingin increased melanin excess in the basal layer and superficial dermis (Galperin, Cronin, and Leslie, 2014; Raspha *et al.*, 2018; Charu and Anshul, 2020). Sung Ji Moon et al. reported a study that hyperpigmentation was significantly decreased in ESRD patients receiving high-flux hemodialysis (HFD) therapy. It was suggested from the study that enhanced removal of accumulated middle-molecular-weight (MMW) substances in ESRD patients by convection may reduce hyperpigmentation (Moon *et al.*, 2009). In addition, some patients also complain about yellowing skin in about 13-40% of patients due to lipid-soluble carotenoid deposits in the dermis or subcutis (Raspha *et al.*, 2018; Gnanaserkan *et al.*, 2020). Assessment of skin discoloration requires careful observation by the examiner's eye accurately and also the supportive environmental conditions such as room light intensity (Raiesifar *et al.*, 2018). Using sunscreens and avoiding sun exposure can minimize changes in the skin pigmentation of ESRDpatients.

Nail Changes

Half-and-half nails, also known as Lindsay's nails, account for 20% of nail abnormalities in ESRD, along with koilonychia (18%), subungual hyperkeratosis (14%), onycholysis (10%), Mees' line (7%), and splinter bleeding (5%) (Galperin, Cronin, and Leslie, 2014; Klionsky *et al.*, 2016). Half-and-half nails represent discoloration of the distal nail plate

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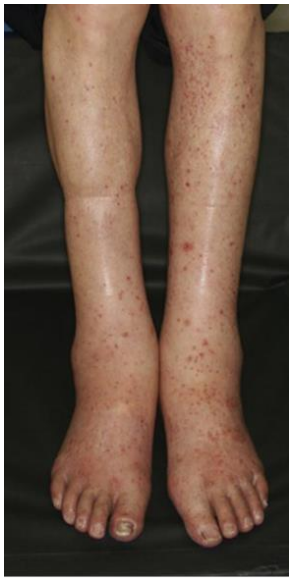

Figure 9. Purpura on the lower extremities in patient with renal failure (Source: Kamo *et al.*, 2019)

due to the increased capillary density of the nail bed (Raspha *et al.*, 2018). It manifests as colored nails,white in the proximal and red in the distal half of the nail, and the discoloration does not disappear with pressure (Shemer, Sakka, and Daniel, 2015; Gnanaserkan *et al.*, 2020). Half-and-half nails are more common in ESRD patients with diabetes mellitus (Gandimohan and Prabhakaran, 2019) but are not specific to ESRD. In addition, it has been found in cases of cirrhosis, Crohn's disease, Behcet's disease, and Kawasaki disease. The nail discoloration may fade after a successful kidney transplant, but hemodialysis will not help (Raja, 2021).

Purpura

Purpura is a condition of the presence of red or purple spots on the skin that are caused by spontaneous bleeding underneath the skin (Rahman *et al.*, 2020). The prevalence of purpura manifestation in ESRD was variable among many studies, between 8-20%. Gnanaserkan et al. reported that purpura prevalence in their study was about 8%, Baghel et al. reported 8,75%, Raspha et al reported 14,8%, and Rahman et al. reported 16,66%. The locations of the purpura were not mentioned in those studies. Increased blood vessel fragility, leakage of capillaries, and platelet dysfunction due to urea levels in the blood, as well as the use of anticoagulants for dialysis such as heparin, contribute to the appearance of purpura in ESRD patients (Raspha *et al.*, 2018; Charu and Anshul, 2020; Rahman *et al.*, 2020). In some cases, purpura can improve after dialysis (Galperin, Cronin and Leslie, 2014; Raiesifar *et al.*, 2018; Raspha *et al.*, 2018).

Hair disorder

Gandimohan et al. mentioned in their study of 100 patients with ESRD who undergo routine hemodialysis that common hair abnormalities found are sparse body hair (30 subjects), alopecia diffuse (11 subjects), and dry lusterless hair (16 subjects) resulting from reduced sebum secretion, while acute diffuse alopecia after several weeks of dialysis was reported in 3 persons (Gandimohan and Prabhakaran, 2019). There is still limited study to improve hair disorder in ESRD patients.

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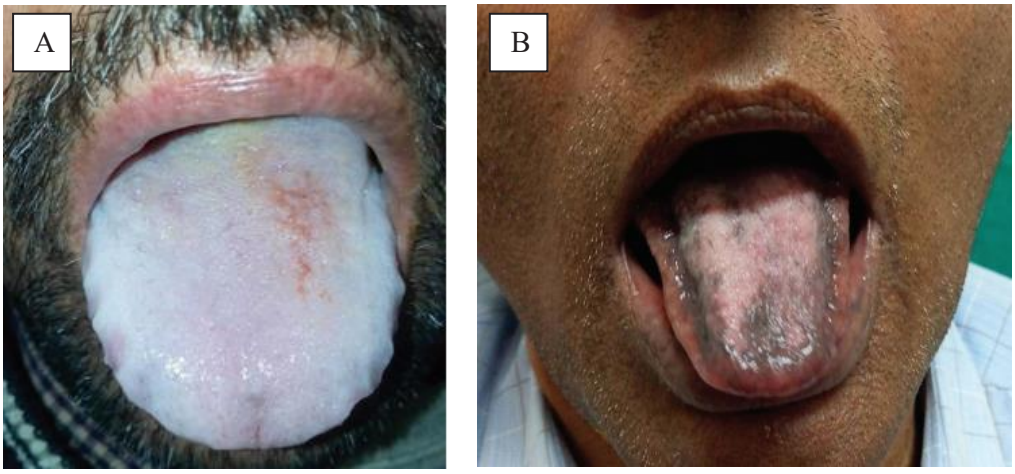

Figure 10. Oral mucosal change. (A) The characteristic "tongue sign of uremia" with macroglossia and white coated tongue. (B) Black pigmentation of tongue. (Source: Raspha *et al.*, 2018)

Oral mucosal change

A study by Charu et al. showed that 42.3% of ESRD patients had mucosal abnormalities, including coated tongue (11.6%), xerostomia (9.16%), macroglossia with bite marks and fissures on the tongue (7.5%), angular cheilitis (2.5%), and the hyperpigmented tongue (0.83%). The study by Raspha et al. showed that the most common mucosal abnormalities were coated tongue (14.8%) and xerostomia (12.3%), followed by macroglossia with bite marks (7.4%). Macroglossia is a characteristic sign of uremia in ESRD (Raspha *et al.*, 2018). Xerostomia occurs due to dehydration and mouth breathing, while glossitis and cheilitis occur due to a lack of nutrients such as riboflavin, iron, and zinc (Malkud, Dyavannanavar, and Varala, 2020). Overall, the presence of nutritional deficiencies, candidiasis, poor oral hygiene, smoking, alcohol consumption, dehydration, and mouth breathing can be trigger factors of mucosal changes in ESRD patients (Raspha *et al.*, 2018). The management should include maintaining oral hygiene to prevent oral mucosal changes and administration of appropriate nutritional supplementation.

Skin infections

Skin infections are common in patients with ESRD. A study by Muskay et al. reported that 31.5% of ESRD patients had viral, bacterial, and fungal infections (Galperin, Cronin and Leslie, 2014; Maskey, Kumar, and Shrestha, 2020). Abnormal cellular immunity in ESRD patients occurs as a result of decreased T lymphocyte cells, leading to an increased prevalence of infection (Maskey, Kumar, and Shrestha, 2020). Charu et al. reported that fungal infections occurred in 16.9% of ESRD patients, while bacterial infections were at 11.5% and viral infectionsat 5.38% (Charu and Anshul, 2020). Onychomycosis is common in ESRDpatients with diabetes mellitus (Galperin, Cronin, and Leslie, 2014; Gandimohan and Prabhakaran, 2019). Early identification of skin infection in ESRD leads to better management and prevents recurrence.

Other skin manifestations

Other clinical manifestations in ESRD patients are acrochordon, prurigo nodularis, ichthyosis, idiopathic guttate hypomelanosis, scabies, vitiligo, keratoderma plantaris, chronic eczema of the legs, gynecomastia and seborrheic

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dermatitis (Galperin, Cronin, and Leslie, 2014; Charu and Anshul, 2020). In addition, dermatitis due to arteriovenous (AV) shunts was reported in 8% of patients undergoing long-term hemodialysis. Perforating folliculitis is found in about 2.5% of diabetic patients who undergo hemodialysis. However, the pathogenesis remains unclear. Patients are at risk of developing foot ulcers and amputation due to peripheralneuropathy (Galperin, Cronin and Leslie, 2014).

CONCLUSIONS

Cutaneous manifestations in ESRD can be divided into specific and nonspecific skin manifestations. Clinicians must increase awareness of chronic kidney disease during physical examination, especially if specific skin manifestations are found. Understanding basic knowledge of the skin manifestations in ESRD may suggest clinicians identify the underlying renal abnormality early so that the patient can immediately get the right management and reduce skin complaints, thus increasing the patient's quality of life.Several managements to prevent the occurrence of further skin disorders in ESRD include using emollients for xerosis, using sunscreens and avoiding sun exposure to minimize changes in skin pigmentation and malignancy on the skin, maintaining oral hygiene to prevent oral mucosal changes, administration of appropriate nutritional supplementation, and identification of common fungal infections, such as onychomycosis. Early identification and proper management of various cutaneous manifestations in ESRD can reduce morbidity and mortality in ESRD patients, as well as improve the patient's quality of life.

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