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 (calcinosus 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.
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; Raisisifar 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; Raisisifar et al., 2018). Typically, patients with ESRD have at least one skin problem, which can significantly lower patients’ quality of life and 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 (Raisisifar 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 management of 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 patients than 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 (Raisisifar et al., 2018).
Table 1. Cutaneous specific and nonspecific manifestations of ESRD

<table>
<thead>
<tr>
<th>Specific Manifestations</th>
<th>Nonspecific Manifestations</th>
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<tbody>
<tr>
<td>Acquired perforating disorder:</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Reactive perforating collagenaosity</td>
<td>Xerosis</td>
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<tr>
<td>Perforating folliculitis</td>
<td>Pigmentation disorders:</td>
</tr>
<tr>
<td>Elastosis perforans serpiginosa</td>
<td>Pallor, hyperpigmentation, yellowing skin</td>
</tr>
<tr>
<td>Kyrle disease</td>
<td>Nail disorders:</td>
</tr>
<tr>
<td>Calcifying disorders:</td>
<td>Half-and-half nails (Lindsay's nails), koilonychia,</td>
</tr>
<tr>
<td>Metastatic calcification (calcinosi cutis, calciphylaxis)</td>
<td>subungual hyperkeratosis, onycholysis, Mees' lines</td>
</tr>
<tr>
<td>Bullous dermatoses:</td>
<td>Hair disorders:</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Sparse (minimal) body hair, diffuse alopecia, dry</td>
</tr>
<tr>
<td>Pseudoporphyria</td>
<td>lusterless hair</td>
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<tr>
<td>Nephrogenic systemic fibrosis</td>
<td>Purpura</td>
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<td></td>
<td>Oral mucosa changes:</td>
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<tr>
<td></td>
<td>Coated tongue, xerostomia, macroglossia</td>
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<tr>
<td></td>
<td>Skin infections (fungi, bacteria, and viruses)</td>
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<tr>
<td></td>
<td>Other skin manifestations</td>
</tr>
<tr>
<td></td>
<td>Acrochordon, prurigo nodularis, ichthyosis</td>
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Source: (Galperin, Cronin, and Leslie, 2014; Charu and Anshul, 2020; Malik, 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 collagenaosity (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 to characterize 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 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,
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 of APD. 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 areawith 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.
(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 (Sabbán, 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: | IntraleSIONal triamcinolone |
| | Hydroxyzine | |
| | Fexofenadine | |
| | Doxepin | |
| Retinoid | Isotretinoin | Narrow-band ultraviolet B (NB-UVB) |
| Cantharidin | Allopurinol 100 mg | Photodynamic therapy (PDT) with 5-amino-levulinic acid |
| | Acitretin | Cryotherapy with liquid nitrogen |
| | Doxycycline 100mg | |
| | Minocycline 100 – 200 mg | |

*Source: (Galperin, Cronin, and Leslie, 2014)*
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). Porphyrin cutanea 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).
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 approach 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)](image-url)
Calcineurin inhibitors are initiated and adjusted to keep serum creatinine levels (SCT) within the therapeutic range (0.6–1.2 mg/dL) and reduce the risk of allograft rejection. The main goal of immunosuppressive therapy is to preserve kidney function while minimizing the risk of adverse effects. Treatment duration varies based on the patient's condition and response to therapy. The efficacy and safety of calcineurin inhibitors have been evaluated in numerous studies, demonstrating their effectiveness in managing transplant rejection and their impact on graft survival.

In conclusion, calcineurin inhibitors remain a cornerstone therapy in transplant nephrology. Research continues to explore innovative strategies and improve the efficacy and safety of these medications to optimize outcomes for transplant patients.
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 rapidly progressive 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).
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 decreased inflammatory 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)-x, psoralen therapy and ultraviolet A (PUVA), and kidney transplant (Kuypers, 2009; Maiberger and Nunley, 2017).

### NONSPECIFIC 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...
Tidak ada data pasti tentang kejadian diabetes insipidus pada pasien dengan cedera otak traumatis dan 500.000 insiden gangguan neurologis permanen. Sekitar 85% kematian terjadi dalam 2 minggu. Cedera otak berat traumatis adalah cedera fatal, dengan tingkat kematian hingga 50%. Sekitar 1,5 juta orang mengalami cedera otak berat di Amerika Serikat. Terdapat lebih dari 50.000 kematian.

ABSTRACT

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Adibah Zahra 1, Farindira Vesti Rahmasari 2,3, Gina Puspita 4, Kanti Ratnaningrum 5, Tri Wulandari 6 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, ondancentreone, 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 itching in 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).
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

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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Information</th>
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<tbody>
<tr>
<td>Optimize dialysate</td>
<td>Correct electrolyte imbalance</td>
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<tr>
<td>Emollients</td>
<td>10% urea and dexamphenol lotion</td>
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<td></td>
<td>Sericin cream 8% 2 times daily</td>
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<tr>
<td>Mast cell stabilizer</td>
<td>Cromolyn sodium 4% cream daily</td>
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<td></td>
<td>Cromolyn 135 mg 3 times daily orally</td>
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<tr>
<td>Capsaicin</td>
<td>Capsaicin 0.025% ointment</td>
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<tr>
<td>Topical analgetic</td>
<td>Pramoxine 1% lotion 2 times daily</td>
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<tr>
<td>Antihistamine</td>
<td>Hydroxyzine 10-25mg 2-4 times daily orally</td>
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<tr>
<td>Anticonvulsant</td>
<td>Gabapentin 100-300 mg 3 times a week orally after each dialysis session</td>
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<td>Gabapentin 400 mg 2 times a week orally everyafter each dialysis session</td>
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<tr>
<td>Opioid antagonist</td>
<td>Nalfurafin 5 g intravenous 3 times a week after each hemodialysis session</td>
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<td>Sertraline</td>
<td>50 mg/day orally</td>
</tr>
<tr>
<td>Narrow-band UVB (NB-UVB)</td>
<td>3 times a week, all over the body</td>
</tr>
</tbody>
</table>
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 resulting in 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 (Raièsifar et al., 2018). Using sunscreens and avoiding sun exposure can minimize changes in the skin pigmentation of ESRD patients.

**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...
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.
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 infections at 5.38% (Charu and Anshul, 2020). Onychomycosis is common in ESRD patients 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
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 peripheral neuropathy (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.

REFERENCES


Keywords:
Tidak ada data pasti tentang kejadian diabetes insipidus pada pasien dengan cedera otak traumatis.

Correspondence:

Keywords:


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Case Report

Tidak ada data pasti tentang kejadian diabetes insipidus pada pasien dengan cedera otak traumatis

Keywords:

1) Diabetes insipidus, brain injury,
2) Staff Department of Anesthesiology and Reanimation of RSUD Dr. Soetomo, Medical Faculty of Airlangga University.

ABSTRACT

Traumatic severe brain injury is a fatal injury, with a mortality rate of up to 50%. About 1.5 million people experience severe brain injury in the United States. There are more than 50,000 deaths and 500,000 incidents of brain injury in Indonesia. About 250,000 people suffer from severe brain injury in the United States. There are over one million brain injuries in the United States. There are over 50,000 deaths and 500,000 incidents of brain injury in Indonesia. About 1.5 million people experience severe brain injury in the United States. There are more than 50,000 deaths and 500,000 incidents of brain injury in Indonesia. About 250,000 people suffer from severe brain injury in the United States.

In this case report, a male, 45 years old, was taken to the Emergency Installation (IRD) after experiencing a traffic accident 12 hours before being hospitalized. After surgery, the signs of diabetes insipidus were presented by polyuria of 300 cc/hour urine production and 149 mmol/l. The patient did not show any improvements. The patient passed away in the ICU on the 5th day of treatment.


