

## Review Article

# Dermatologic manifestations in patients of renal disease on hemodialysis

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**Abstract** Chronic renal failure (CRF) is recognized as a significant medical problem in our part of the world. It refers to an irreversible deterioration in renal function which classically develops over a period of years. The disorder has five stages and the stage 5, also called end stage renal failure (ESRF), is a severe illness and requires some form of renal replacement therapy (dialysis or renal transplant). Cutaneous and mucosal changes are a common finding in patients of ESRF and on long-term hemodialysis and can vary from each patient population to another. The commonly seen dermatologic manifestations associated with ESRF are xerosis, pruritus, pallor, fungal, bacterial and viral infections, xerostomia, scalp hair loss, nail changes like half-and-half nails and splinter hemorrhages. The cutaneous manifestations related to hemodialysis are skin infections, arteriovenous shunt dermatitis, gynecomastia, bullous disease of dialysis etc. The present review does not highlight cutaneous changes of diseases associated with the development of ESRF but it familiarizes clinicians about the dermatologic changes in patients with chronic renal failure (CRF) undergoing hemodialysis.

### **Key words**

Chronic renal failure, hemodialysis, xerosis, xerostomia

## **Introduction**

Chronic renal failure (CRF) is a progressive loss of renal function over a period of months or years through five stages.<sup>1,2</sup> Each stage is a progression through an abnormally low and deteriorating glomerular filtration rate, which is usually determined indirectly by the serum creatinine level.<sup>1,2</sup> All individuals with either kidney damage or a glomerular filtration rate (GFR) <60 ml/min/1.73 m<sup>2</sup> for three months are classified as having chronic renal disease.<sup>1,2</sup>

The incidence of chronic kidney disease is higher in Indo-Asians than in the European population.<sup>3</sup> The number of patients with end-stage renal failure (ESRF) in Pakistan is continuously increasing with an estimated

annual incidence of about 100 per million population.<sup>4</sup> The effects of chronic kidney disease are complex as it causes dysfunction of multiple organs.<sup>5</sup> Hemodialysis is one of the therapeutic modalities which can improve the quality of life in these patients.<sup>5</sup> It has been found that 50-100% patients with ESRF have at least one associated cutaneous change.<sup>5,7</sup> The dermatologic findings can precede or follow the initiation of hemodialysis treatment and there are more chances to develop newer skin changes with this therapeutic modality as it increases the life expectancy of CRF patients.<sup>5,7</sup>

It is very difficult to limit any particular cutaneous manifestation to either CRF or hemodialysis alone because many of them are associated with both of these situations. The present review is aimed to reflect the frequency of different dermatologic changes including those of mucous membrane, hair and nails in patients of CRF on hemodialysis with pathogenesis and management.

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## **Cutaneous, mucosal, nail and hair manifestations**

The cutaneous, mucosal, nail and hair changes in CRF patients may also depend on the climatic conditions of the region, race and socioeconomic conditions of patients, accuracy of diagnosis and the light of environment in which cutaneous examination have been done.<sup>5</sup> Prophylactic and remedial measures can be adopted to prevent few of these skin manifestations.

### **A. Cutaneous changes**

#### **1. Xerosis**

Xerosis is the most common cutaneous abnormality seen in these patients.<sup>7</sup> The intensity varies from mild to severe.<sup>7</sup> It is predominantly seen over the extensor surfaces of forearms, legs and thighs.<sup>7</sup> A reduction in the size of eccrine sweat glands may be contributory, although high dose diuretic regimens are also implicated in the pathogenesis.<sup>7,8</sup> Hypervitaminosis A is common in the dialysis patient and also has been implicated as an etiologic agent.<sup>6</sup> Xerosis is severe in diabetics.<sup>7</sup> In some of the patients, acquired ichthyosis has been noted.<sup>6</sup> It has also been seen that some patients have associated keratosis pilaris-like lesions.<sup>7</sup> Xerosis is found to be worsened in some patients, improved in few and unchanged in a lot of patients on hemodialysis.<sup>7</sup> Emollients can be applied for xerosis.<sup>6,7</sup>

#### **2. Pruritus**

Pruritus, observed in many cases, is an early finding that leads to an increased morbidity of these patients.<sup>5,9-11</sup> It may be episodic or constant, localized or generalized, and mild to severe in intensity.<sup>6,9</sup> When localized, the forearms and upper back are predominately affected.<sup>6</sup> It has no consistent association with age, sex, race, or the precipitating disease.<sup>6,9</sup> Cutaneous manifestations of pruritus include excoriations, prurigo nodularis and lichen

simplex chronicus.<sup>6</sup> The exact cause of pruritus in CRF is unknown<sup>10</sup> but it is thought to be associated with uremia.<sup>11</sup> Since pruritus is not seen with acute renal failure, changes in blood urea nitrogen and creatinine are not solely responsible for this symptom.<sup>6,8</sup> However, slowly accumulated or deposited pruritogens, of as yet uncertain nature, are the likely cause.<sup>7,8</sup> It has also been associated with the degree of renal insufficiency (urine output of <500 ml), secondary hyperparathyroidism, xerosis, increased serum levels of magnesium, calcium, aluminium, phosphate and histamine, uremic sensory neuropathy, abnormal fatty acid metabolism, hypervitaminosis A and iron deficiency anaemia.<sup>6,7,9,11</sup> The increased serum histamine level seen in CRF patients on hemodialysis is due to allergic sensitization to various dialyzer membrane components and impaired renal excretion of histamine.<sup>7</sup> Pruritus is found to be severe in diabetic patients.<sup>7</sup> Hemodialysis can initiate the symptom as well as improve it.<sup>5,7,8</sup> Hemodialysis therapy is also useful as it lowers the magnesium concentration.<sup>6,8</sup> Pruritus improves after kidney transplantation with the restoration of renal function.<sup>9</sup> Ultraviolet (UV) B phototherapy is an effective treatment modality and may have a prolonged benefit as it reduces vitamin A and phosphorus levels in skin.<sup>8</sup> UVA (without psoralen) has been reported nearly as effective.<sup>8,10,11</sup> Erythropoietin therapy can alleviate pruritus in some cases.<sup>1,7</sup>

Topical therapeutic options, which are inconsistently helpful, include emollients to alleviate xerosis and topical capsaicin cream (0.025%).<sup>7</sup> Sedating antihistamines may provide temporary relief while non-sedating antihistamines and topical steroids are not usually helpful.<sup>6,10,11</sup> Oral cholestyramine and activated charcoal are found to be effective.<sup>6,7,8</sup> Some clinical studies have suggested that the opioid antagonist, naltrexone is reported to reduce severe intractable pruritus in

hemodialysis patients.<sup>6,7,11</sup> Recently, low dose gabapentin therapy has been found to be beneficial.<sup>7,10,11</sup> Subtotal parathyroidectomy may be useful.<sup>6,8</sup> It has been mentioned in many studies that pruritus disappears after transplantation.<sup>6,7,9</sup>

### 3. Pigmentary changes

Pigmentary changes are seen in patients of CRF.<sup>5,7</sup> Hyperpigmentation is of two types, the first one is brownish-black while the second type is of yellowish colour.<sup>5,7</sup> The diffuse brownish-black hyperpigmentation on sun-exposed areas can be attributed to retention of chromogens and deposition of melanin in the basal layer and superficial dermis due to failure of the kidneys to excrete beta-melanocyte-stimulating hormone ( $\beta$ -MSH).<sup>6-8</sup> Hyperpigmented macules on the palms and soles have been reported by Pico *et al* and are also attributed to increased circulating  $\beta$ -MSH.<sup>7</sup> A yellowish discoloration of the skin has been noticed in 40% of patients in various studies.<sup>7</sup> It has been attributed to the accumulation of carotenoids and nitrogenous pigments (urochromes) in the skin.<sup>6,7</sup> Sunscreens, sun avoidance measures and clothing are advised for these pigmentary changes.

### 4. Pallor

Pallor of skin due to anaemia is seen in most of the patients.<sup>6,7</sup> It is an early and common sign in renal failure resulting from reduced erythropoiesis and increased haemolysis.<sup>7,8</sup> The use of erythropoietin can reduce the pallor.<sup>6</sup>

### 5. Perforating disorders

Perforating disorders of renal disease or acquired perforating disorders (APD); the term has been used to describe the hyperpigmented papules, up to 1 cm in diameter, with a central keratinous plug in patients of CRF.<sup>8,12</sup> The condition appears to be distinct from the four primary perforating disorders like perforating

folliculitis, Kyrle's disease, reactive perforating collagenosis and elastosis perforans serpiginosa.<sup>12</sup> APD has been reported to occur in 10-17% of patients on hemodialysis.<sup>7,12</sup> The exclusive feature of the perforating disorders is the trans-epidermal elimination of altered dermal substances.<sup>7</sup> The changes are significantly more prevalent in diabetic patients and the association has been confirmed by many studies.<sup>5,7</sup> Trauma to skin in patients with pruritus secondary to CRF could be the inciting agent in producing these lesions.<sup>5,7</sup> The condition seems to have a higher incidence in Afro-Caribbean.<sup>8</sup> The extensor surfaces of the limbs are more commonly affected but the trunk and face may be involved.<sup>8</sup> Topical and intralesional steroids, topical and systemic retinoids, cryotherapy, and ultraviolet light may be helpful.<sup>12</sup>

### 6. Purpura and ecchymoses

Purpura and ecchymoses are also noted in these patients.<sup>5,7,12</sup> Easy bruising is reported in a study in which Singh observed these changes in 20% of CRF patients not on dialysis.<sup>7</sup> Defects in primary hemostasis like increased vascular fragility, abnormal platelet function and the use of heparin during dialysis are the main causes of abnormal bleeding in these patients.<sup>7</sup> Purpura is also seen due to a mild thrombocytopenia.<sup>8</sup> Dialysis treatment partially corrects these changes.<sup>1,8</sup>

### 7. Cutaneous infections

Cutaneous infections seen in CRF patients are fungal, bacterial and viral in origin.<sup>7</sup> The patients are more susceptible to infections due to impaired cellular and humoral immunity.<sup>13</sup> The common fungal infection seen among CRF patients is onychomycosis, more prevalent in the diabetic group.<sup>7</sup> Tinea pedis is also reported to be common.<sup>7</sup> Pityriasis versicolor is seen in some patients.<sup>7</sup> Bacterial infections are common in diabetics.<sup>7</sup> The viral infections include warts, herpes simplex and

herpes zoster.<sup>6,7</sup> Prompt recognition and treatment of these infections is essential to reduce the morbidity of these patients.

### **8. Uremic frost**

In the pre-dialysis era, uremic frost was a frequent dermatologic finding.<sup>6</sup> All the patients, who exhibit uremic frost, have a blood urea nitrogen level of more than 250-300 mg/dl.<sup>6</sup> The concentration of urea in sweat is increased and, after evaporation, there is a deposition of urea crystals on the skin surface.<sup>6,7</sup> It consists of a white or yellowish coating on the beard area and other parts of the face, neck and trunk.<sup>7</sup> It is due to eccrine deposition of urea crystals on the skin surface of patients with severe uremia.<sup>6,7</sup> The condition is rarely seen now a days because of early intervention and hemodialysis treatment.<sup>6,7</sup>

### **9. Calcification and calciphylaxis**

Metastatic skin calcification is a rare phenomenon in uremic patients but occurs from secondary or tertiary hyperparathyroidism.<sup>8</sup> There is abnormally elevated level of parathyroid hormone (PTH) which may trigger the deposition of crystalline calcium pyrophosphate in the dermis, subcutaneous fat, or arterial walls.<sup>7,12</sup> The calcium deposits are identical to calcinosis cutis in other skin disorders like CREST syndrome.<sup>12</sup> The condition usually presents as papular or nodular cutaneous lesions around large joints or flexural sites.<sup>8</sup> The involved skin may ulcerate without livedo or ischemic pain.<sup>12</sup> Occasionally, a syndrome called calciphylaxis has been reported in CRF patients due to acute thrombosis of calcified vessels.<sup>7,12</sup> This produces violaceous mottling of the skin that are acutely painful due to ischemia.<sup>14</sup> Surrounding tissue may be inflamed with cellulitis.<sup>14</sup> Lesions often progress to necrosis and gangrene.<sup>12,14</sup> The condition is associated with a high mortality, particularly when the skin of the trunk is

involved.<sup>12</sup> PTH is usually markedly elevated.<sup>12</sup> The serum calcium and phosphate levels, and the calcium-phosphate product, are frequently only minimally elevated.<sup>12</sup> Treatment of calciphylaxis includes analgesia, debridement of gangrenous tissue and parathyroidectomy.<sup>12</sup>

### **10. Cancerous and precancerous lesions**

These are also seen in these patients because of immunosuppression.<sup>7,12</sup> Basal cell carcinoma is the commonest tumour seen followed by multiple actinic keratoses on sun-exposed areas progressing to squamous cell carcinoma.<sup>7,12</sup>

### **11. Nephrogenic fibrosing dermopathy (NFD)**

NFD is seen in a few patients resembling scleromyxoedema.<sup>7,8,12</sup> It is characterized by the progressive development of erythematous, indurated dermal plaques with mild itching on the arms and legs, sparing the head and neck.<sup>7,12</sup> Nodules and contractures can be seen in patients with disease of long duration.<sup>8</sup> There is no associated plasma cell dyscrasia in NFD in contrast to scleromyxoedema.<sup>8</sup> Histology shows proliferation of fibroblasts in the dermis and subcutaneous septae, accompanied by an increased collagen and mucin deposition.<sup>7,8,12</sup> There is no effective therapy for this condition.<sup>7</sup>

### **12. Other changes**

Wound healing is delayed in CRF patients and they are more susceptible to pressure sores.<sup>8</sup> Arteriovenous shunts are also observed in patients on long term hemodialysis.<sup>8</sup> Uremic neuropathy is another sign, predominantly sensorimotor, noted in 60% patients of chronic renal failure or on long term hemodialysis.<sup>8</sup> Neurotic excoriations are also found in these patients.<sup>5</sup> Amitriptyline and gabapentin may be useful.<sup>1,8</sup> The condition may also improve or even resolve once dialysis is established.<sup>1</sup> There is an increased frequency of drug reactions seen in CRF patients due to the

administration of multiple drugs and prolonged half-life of each medication.<sup>7</sup> Prurigo nodularis, vitiligo, melasma, hyperkeratosis and fissures on the soles, papular urticaria, chronic dermatitis of leg, seborrheic dermatitis of the scalp, varicose eczema and Schamberg's disease are reported but their association with CRF cannot be assured definitely.<sup>7</sup>

### **B. Mucosal changes**

Oral mucosal changes have been reported in most of the patients with CRF.<sup>5,7</sup> Xerostomia is the most common oral finding followed by macroglossia, scrotal tongue, furred tongue, gingivitis, ulcerative stomatitis, angular cheilitis and uremic breath.<sup>5,7</sup> Xerostomia is attributed to mouth breathing and dehydration.<sup>7</sup> Macroglossia with teeth marking (tongue sign of uremia) is the finding first described by Mathew in 92% of patients with CRF.<sup>7</sup> Ulcerative stomatitis is reported to occur in patients with blood urea levels greater than 150 mg/100 ml.<sup>7</sup> This can be attributed to poor oral hygiene of the patients.<sup>7</sup> Angular cheilitis and coated tongue are seen in few patients.<sup>7</sup> Some of the patients have uremic fetor which is an ammoniacal odour caused by a high concentration of urea in the saliva and its breakdown to ammonia.<sup>7</sup> This can be associated with an increased predialysis blood urea level (more than 200 mg%).<sup>7</sup> Some of the studies show that, in addition to the increased urea, there are fewer fungiform taste buds that contribute to the impairment of taste in these patients.<sup>7</sup> Good oral hygiene and nutritional supplementation are advised in these patients to prevent oral mucosal changes.<sup>7</sup>

### **C. Nail changes**

Increased nail pigmentation, usually confined to the distal aspect, occurs in a proportion of patients.<sup>8</sup> This distal brownish colour, combined with a proximal white zone gives rise to the 'half-and-half' nails (Lindsay's nails), a distinctive condition more commonly

seen in fingernails (the colour does not fade with pressure).<sup>6,8</sup> The change is significantly more prevalent in diabetic patients.<sup>7</sup> Fungal nail infections are also found in CRF patients. Other nail changes observed are leukonychia, koilonychia, subungual hyperkeratosis, onycholysis, Mees' lines, Muehrcke's lines, Beau's lines and splinter hemorrhages.<sup>5,7</sup> The colour changes noted in half-and-half nails disappear several months after successful renal transplantation.<sup>6</sup>

### **D. Hair changes**

The most common hair disorder is diffuse hair loss of scalp.<sup>5,7</sup> The alopecia may be related to telogen effluvium associated with severity of illness, xerosis, pruritus or due to drugs (heparin, anti-hypertensives, lipid-lowering) used in these patients.<sup>5,6</sup> Sparse body hair, discoloration and dryness of hair are other changes seen in patients of CRF.<sup>5,7</sup> Dry and lustreless hair are due to a decreased secretion of sebum.<sup>7</sup> Various studies have reported 10-30% hair changes in CRF patients not on dialysis.<sup>7</sup> Nutritional supplementation is very much required along with treatment of xerosis and pruritus to prevent hair loss.<sup>5-7</sup>

### **Cutaneous findings related to hemodialysis treatment**

Therapeutic interventions in the presence of ESRF may precipitate certain cutaneous infections.<sup>13,14</sup> Bencini *et al.* have reported the incidence of fungal infection in patients undergoing hemodialysis to be 67%.<sup>7</sup> Cutaneous complications originating due to arteriovenous shunt include infection, phlebitis and hematoma.<sup>8,12,13</sup> However, arteriovenous shunt dermatitis (both irritant and allergic) may also develop.<sup>7,12</sup> Vascular complications of arteriovenous fistula construction include digital ischemia and aneurysm formation.<sup>6,7,8</sup> Gynecomastia is the finding noted especially in cases who are on hemodialysis and may be reversed by a low phosphorus diet and

aluminium hydroxide gel.<sup>8,15</sup> The venous hypertension syndrome and pseudo-Kaposi's sarcoma can also be seen.<sup>7,8</sup> Keratotic pits of palms and soles are also seen in patients on hemodialysis.<sup>7,12</sup> Acute diffuse alopecia following a few weeks of dialysis is reported in a few patients.<sup>6</sup> The entity so called bullous disease of dialysis, metabolically distinct from PCT, is also related to hemodialysis because plasma porphyrins are poorly dialyzed and are mildly to moderately elevated in most patients.<sup>6,12</sup> True porphyria cutanea tarda (PCT) can occur because these patients have uremia-related anemia and need excessive blood transfusions which may result in considerable iron overload, contributing significantly to its development.<sup>6,12</sup> Erythropoietin has decreased the incidence of PCT by reducing the number of transfusions in CRF patients on hemodialysis.<sup>6</sup> Desferoxamine may reduce serum porphyrin levels in some patients while others may need renal transplantation to achieve complete resolution of the problem.<sup>12</sup>

## Conclusion

Considering the diversity of dermatoses associated with CRF, a clinician should be highly vigilant while examining patients presenting with aforementioned skin disorders. At times, these dermatologic findings may even precede any clinical or biochemical evidence of CRF. Moreover, the early recognition and treatment of cutaneous signs can relieve suffering and decrease morbidity of these patients.

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