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Original Article

Cutaneous manifestations of end-stage renal disease

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ABSTRACT

Objectives: (1) To study the dermatological manifestations in patients with end-stage renal disease (ESRD) of diverse etiology and (2) to compare the dermatological manifestations in patients on conservative treatment and those receiving hemodialysis.

Materials and Methods: One hundred patients with ESRD who attended the nephrology/dermatology department of a tertiary care center were examined for dermatological manifestations.

Results: All the 100 patients evaluated had at least one cutaneous manifestation. Pallor was the most common cutaneous finding in our study (64%). Xerosis was observed in 61% and pruritus in 46%. Other common findings included diffuse hyperpigmentation (22%) and cutaneous infections (20%). Specific changes noted were acquired perforating dermatoses (7%) and nephrogenic systemic fibrosis (2%). Nail, oral mucosa, and hair were affected in 61%, 54%, and 29% cases, respectively. No significant association was noted between dermatological manifestations and modality of treatment. Comparison of serum calcium, serum phosphorus, and calcium-phosphate product was done with pruritus and a significant association was noted between pruritus and the serum levels of phosphate and calcium-phosphate product.

Limitations: Small sample size and the single center study design were the major limitations.

Conclusion: Dermatological manifestations are common among patients with ESRD. Early diagnosis and prompt management of the dermatological diseases may improve the quality of life of the affected.

Keywords: End-stage renal disease, Pruritus, Xerosis, Acquired perforating dermatoses, Nephrogenic systemic fibrosis

INTRODUCTION

Literature states that 50%–100% of patients with end-stage renal disease (ESRD) have at least one associated cutaneous change.[1] Cutaneous manifestations in renal failure are polymorphic and diverse. They may range from asymptomatic to life-threatening forms. They may occur before or after initiation of dialysis and can be divided into: Specific and non-specific.[2] Pruritus, xerosis, pigmentation disorders, and half and half nails (Lindsay's nails) are included under non-specific and acquired perforating disorders (APD), bullous dermatoses, calcifying disorders, and nephrogenic systemic fibrosis are included under specific manifestations of ESRD.[3]

MATERIALS AND METHODS

After obtaining institutional ethics committee approval, a descriptive study was conducted in consecutive 100 patients with ESRD (patients with irreversible decline in kidney function) of

diverse etiology who attended the nephrology or dermatology department of a tertiary referral center from March 2014 to August 2015. Individual study participant gave written informed consent.

A detailed clinical history, nature of onset and progression of cutaneous symptoms, history regarding renal disease, treatment history, history of any skin disease, and history of any comorbid condition were recorded. A detailed physical and dermatological examination was done in all cases. Dermatological manifestations observed were documented. Pruritus, xerosis, pigmentation disorders, and half and half nails (Lindsay's nails) were classified as non-specific and APDs, bullous dermatoses, calcifying disorders, and nephrogenic systemic fibrosis as specific manifestations of ESRD.[3]

Complete hemogram, urine microscopy, blood urea, serum creatinine, serum electrolytes, blood sugar, serum calcium, serum phosphate, liver function test and serology for infections due to human immunodeficiency virus, hepatitis C virus, and hepatitis B virus were done in all patients. Antinuclear antibody (ANA) and ANA profile were done when indicated. Skin biopsy was carried out when the diagnosis was doubtful.

Data were entered in Microsoft Excel and analyzed with SPSS version 16.0. We compared the dermatological manifestations in patients receiving conservative treatment with the same noted in patients on hemodialysis by Pearson's Chi-square test. $P < 0.05$ was considered as statistically significant.

RESULTS

The total number of patients included in this study were 100. Of the 100 patients, 72 (72%) were males and 28 (28%) were females (male to female ratio 2.6:1).

The age of the patients ranged from 13 years to 75 years. The youngest male and female patients were of 13 years and 22 years while the oldest were of 75 years and 74 years, respectively. Maximum number of patients belonged to 51–60 year age group. The mean age was 49.7 with a standard deviation of 13.9.

The most common etiology of ESRD [Table 1] was diabetic nephropathy (49 patients, 49%).

Of the 100 ESRD patients included in this study, 39 (39%) were on conservative management and 61 (61%) were on hemodialysis. All the study participants had at least one specific or non-specific dermatological manifestation of ESRD.

Pallor was noted in 64 patients (64%). Hemoglobin ranged from 5 g% to 11.8 g%. It was seen in 18 out of 39 patients (46.2%) on conservative treatment and 46 out of 61 patients (75.4%) on hemodialysis. The difference was not significant.

Xerosis was seen in 61 cases (61%). Eighteen out of the 39 patients (46.2%) on conservative treatment and 43 out of 61 patients (70.5%) on hemodialysis had xerosis. The difference was not significant.

Forty-six patients (46%) complained of pruritus, of which 29 (63%) were males and 17 (37%) were females. Twenty-nine of 72 males (40.3%) and 17 of the 28 females (60.7%) had pruritus. The difference was not statistically significant. Eighteen (46.2%) out of the 39 patients on conservative treatment and 28 (45.9%) out of the 61 patients on hemodialysis had pruritus. The difference was not significant.

Out of 46 patients with pruritus, 35 (76%) had generalized and 11 (24%) had localized pruritus.

Among the 35 patients who manifested generalized pruritus, 23 (23/35, 65.7%) were on hemodialysis and 12 (12/35, 34.3%) were receiving conservative treatment. Among the 11 patients who showed localized pruritus, five (5/11, 45.5%) were on hemodialysis and six (6/11, 54.5%) were on conservative treatment. No significant difference was noted.

We compared the values of serum calcium, serum phosphate, and calcium-phosphate product in patients with and without pruritus. We found a significant association of pruritus with hyperphosphatemia and calcium-phosphate product [Table 2].

Among patients with pruritus, 80.4% had elevated serum phosphate while 57.4% of those without pruritus showed elevated serum phosphate and this was statistically significant ($P = 0.02$).

Table 1: Etiology of end-stage renal disease in study participants.

Cause	Number of patients (% of total) *n*=100
Diabetic nephropathy	49 (49)
Chronic tubulointerstitial nephritis	11 (11)
Chronic glomerulonephritis	10 (10)
Ischemic renal failure	7 (7)
Ig A nephropathy	5 (5)
Nephrotic syndrome	5 (5)
Lupus nephritis	4 (4)
Obstructive nephropathy	4 (4)
Hypertensive nephrosclerosis	2 (2)
Autosomal dominant polycystic kidney disease	2 (2)
Pauci-immune vasculitis	1 (1)

Table 2: Relation of pruritus with serum phosphate levels in patients with end-stage renal disease.

Serum phosphate level	Without pruritus (*n*=54) (%)	With pruritus (*n*=46) (%)	Total (*n*=100)
Normal	23 (42.6)	9 (19.6)	32
Elevated	31 (57.4)	37 (80.4)	68

Among the 46 patients with pruritus, only 19.6% (9/46) showed elevated serum calcium while 7.4% (4/54) of those without pruritus had elevated serum calcium. No significant association was noted between pruritus and raised serum calcium ($P = 0.07$).

Among the 46 patients with pruritus, 69.5% (32/46) had calcium-phosphate product >55 while only 13 out of the 54 (24%) patients without pruritus had calcium-phosphate product >55. The difference was significant ($P < 0.001$).

Diffuse hyperpigmentation in sun exposed areas was noted in 22 patients (22%). Six out of 39 patients (15.4%) on conservative treatment and 16 out of 61 patients (26.2%) on hemodialysis had pigmentary changes. No significant difference was noted.

APD was seen in seven patients (7%). Clinically, all of them manifested pruritic keratotic papules with central keratin filled crater mainly on the extensor aspect of extremities and trunk, suggestive of Kyrle's disease [Figure 1]. Histopathological confirmation was done in one patient [Figure 2]. Four patients showed Koebnerization. Four out of the 39 patients (10.3%) on conservative treatment and three out of the 61 patients (4.9%) on hemodialysis had APD. No significant association was noted between APD and modality of the treatment for ESRD.

All the seven patients with APD had diabetes mellitus. Seven of the 59 study participants (11.9%) with diabetes mellitus showed APD, whereas none of the 41 cases without diabetes mellitus manifested APD. The difference was significant ($P = 0.02$).

Nephrogenic systemic fibrosis was seen in two patients (2%); both had diabetes and were on hemodialysis. Both of them showed involvement of the lower limbs alone [Figure 3]. Histopathological confirmation was available in one patient [Figure 4]. No significant association was noted between nephrogenic systemic fibrosis and the modality of treatment.

Thirty-three patients (33%) had pedal edema and one (1%) each showed purpura and ecchymosis, respectively.

Nail changes were noted in 61 patients (61%). Twenty-two of 39 patients (56.4%) on conservative treatment and 39/61 patients (63.9%) on hemodialysis showed nail changes [Table 3]. There was no significant difference.

Half and half nails were seen in three cases (3%) and all were receiving hemodialysis (3/61, 4.9%). This was not significant.

Hair changes were observed in 29 patients (29%). Dry luster less hair was observed in 23 patients (23%), telogen effluvium in 15 patients (15%), and sparse body hair in six patients (6%). Lupus hair was observed in three patients (3%) with lupus nephritis.

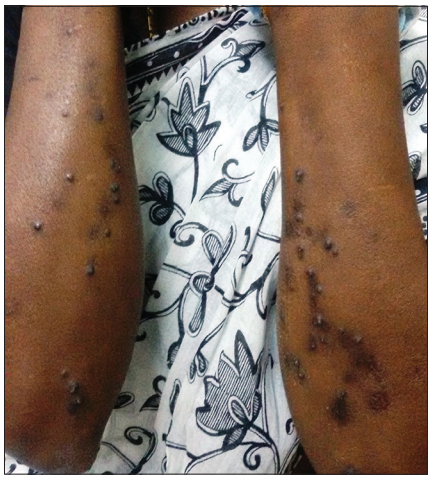

Figure 1: Keratotic papules with central keratin filled crater mainly on the extensor aspect of extremities in a patient with end stage renal disease (Kyrle's disease).

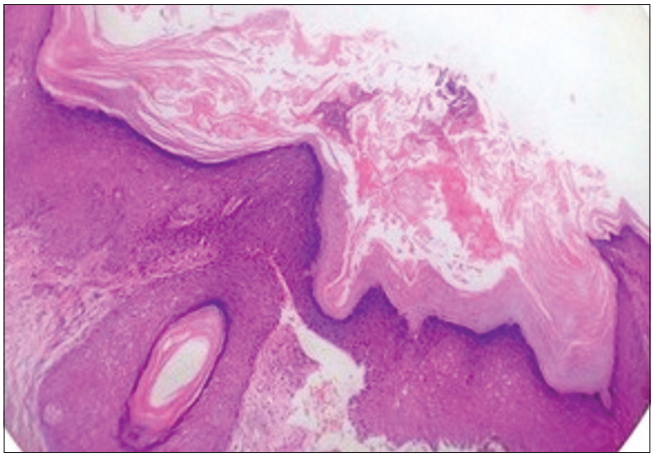

Figure 2: Skin biopsy from a patient with Kyrle's disease showing transepidermal elimination of keratotic material (H and E, ×40).

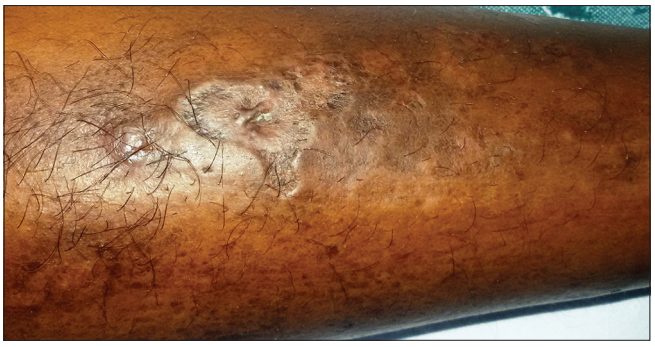

Figure 3: Indurated plaque of nephrogenic systemic fibrosis in a patient with end-stage renal disease.

Hair changes were seen in five (12.8%), out of the 39 patients on conservative treatment, and in 24 (39%) out of the 61 patients on hemodialysis. The difference was significant ($P = 0.01$).

Table 3: Nail changes.

Nail changes	Number of patients (% of total)
Longitudinal ridging	28 (28)
Leukonychia	21 (21)
Nail dystrophy	12 (12)
Onycholysis	10 (10)
Nail pigmentation	5 (5)
Beau's lines	5 (5)
Pitting	3 (3)
Subungual hyperkeratosis	3 (3)
Half and half nail	3 (3)
Clubbing	1 (1)
Yellowish discoloration	1 (1)

Oral mucosal changes observed among study participants were glossitis (32, 32%), cheilitis (11, 11%), hyperpigmentation of oral mucosa (13, 13%), macroglossia (7, 7%) [Figure 5], and xerostomia (3, 3%).

Other cutaneous manifestations documented in study participants included folliculitis (4, 4%), furuncle (1, 1%), tinea corporis (7, 7%), tinea versicolor (4, 4%), candidal intertrigo (3 3%), verruca vulgaris (1, 1%), diabetic shin spots (5, 5%), psoriasis (3, 3%), peripheral occlusive vascular disease (3, 3%), nummular eczema (2, 2%), asteatotic eczema (1, 1%), contact dermatitis (1, 1%), photodermatitis (1, 1%), lichen planus (1, 1%), phrynoderma (1, 1%), seborrheic keratosis (1, 1%), malar rash (1, 1%), and subacute cutaneous lupus erythematosus (1, 1%). No cases of adverse drug reactions were noted in the study.

DISCUSSION

Dermatological manifestations in ESRD are varied and can impair the quality of life. Prompt diagnosis may help to ensure treatment which, in turn, can reduce the disease associated morbidity.

Diabetes mellitus documented as the most common cause of ESRD by us, was consistent with the literature.[4]

Pico *et al.* had reported at least one dermatological alteration in all his study participants with ESRD, which was comparable to our observation.[5] Sixty-four percentage of the study population manifesting pallor was consistent with existing literature**.** Erythropoietin deficiency and anemia associated with the chronicity of the disease contribute to the pallor.[3]

The frequency of 61% noted for xerosis by us fell between the 50% and 85% reported by others.[3,6] Contrary to the observation of xerosis being more common in those who have not started dialysis, we observed a higher frequency of the former in those on hemodialysis (46.2% on conservative treatment and 70.5% on hemodialysis).[6] The xerosis is attributed to atrophy of sweat glands and sebaceous glands and loss of integrity of stratum corneum due to reduced water content. These changes cause premature skin aging in ESRD.[7] Alteration of Vitamin A metabolism and use of diuretics have also been implicated in the dryness of skin in ESRD.[8,9]

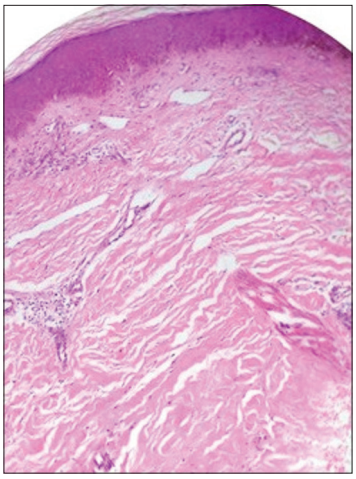

Figure 4: Skin biopsy from a patient with nephrogenic systemic fibrosis showing thickened collagen bundles in reticular dermis (H and E, ×40).

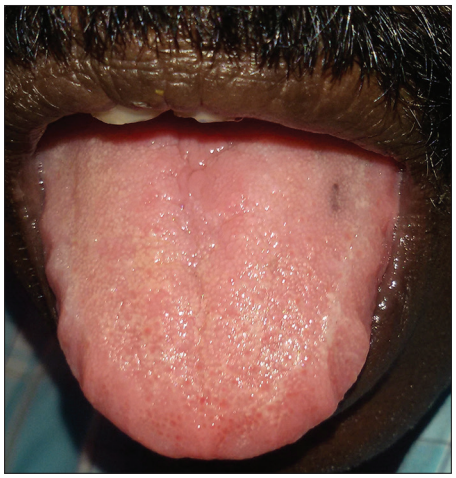

Figure 5: Macroglossia in a patient with end-stage renal disease.

Pruritus is considered as one of the difficult to treat manifestations of ESRD and renal transplant is suggested as the definite treatment.[3] The male predominance for pruritus was observed by Masmoudi *et al.*[2] This was contradictory to our finding of pruritus in 40.3% of males and 60.7% of females. However, a statistically significant association between pruritus and gender was not seen.

The frequency of pruritus noted by us (46%) was concordant to the reported frequency of 40%–90%.[10] Uremic and neuropathic causes are suggested as the underlying

mechanisms while a role for secondary hyperparathyroidism is also postulated.[3]

Certain studies found an improvement in pruritus in ESRD following aggressive hemodialysis.[3] In our study, the frequency of pruritus was comparable in patients receiving dialysis and those on conservative treatment. Falodun *et al*. noted a higher frequency of pruritus in those on hemodialysis.[11] Comparable frequency of pruritus noted in patients on hemodialysis and those on conservative treatment (by us) and a higher frequency of pruritus in those on hemodialysis by certain others may be explained by the hypersensitivity to components of extracorporeal circuit of dialysis unit. Comparison of serum calcium, serum phosphorus, and calcium-phosphate product were done with pruritus and a significant association was noted between pruritus and levels of serum phosphate and calcium-phosphate product. In another study with large sample size, independent and strong relationships were noted between pruritus and elevated levels of serum phosphorus, serum calcium, and serum calcium phosphorus product.[12]

Although it is suggested that the degree of pigmentation in patients with ESRD is directly related to the duration of dialysis, we did not find any significant difference in the frequency of hyperpigmentation in patients on hemodialysis and those on conservative treatment.[3] The frequency of hyperpigmentation observed in the study was comparable to the literature.[13] Diffuse hyperpigmentation on sun exposed areas, as noted by us is attributed to an increase in melanin in the basal layer and superficial dermis due to the failure of the kidneys to excrete beta-melanocyte stimulating hormone.[14]

Kyrle's disease is seen in 2%–11% of patients on dialysis as per literature.[3] We found a higher proportion of ESRD patients on conservative treatment manifesting the same (10.3% in those on conservative treatment and 4.9% in those on hemodialysis). All seven patients (irrespective of whether they were on hemodialysis or not) with Kyrle's disease being diabetics could be attributed to the former being a manifestation of diabetes mellitus itself.[15]

Both patients with nephrogenic systemic fibrosis belonging to hemodialysis group were as reported by others.[3] Exposure to certain gadolinium based contrast agents, vascular injury and metabolic acidosis are said to be associated with the development of nephrogenic systemic fibrosis.[16-18] Erythropoietin, through its ability to promote endothelial cell proliferation and augmentation of fibrin, could play a role in the pathogenesis of nephrogenic systemic fibrosis.[18]

The frequency of half and half nails (3%) noted by us was lower than the 20% reported by others.[3]

Glossitis and cheilitis in ESRD may be attributed to nutritional deficiency diseases such as riboflavin deficiency, iron deficiency anemia, and zinc deficiency.[19] Teeth indentation with macroglossia was first reported in 1986 by Mathew *et al*. in 92% patients with chronic renal failure.[20] Udayakumar *et al*. had reported macroglossia in 35% cases.[1] Thomas *et al*. documented macroglossia in 9.09% cases alone and this was comparable to our findings (7%).[19] Xerostomia in ESRD is attributed to dehydration and mouth breathing.[21]

Cutaneous infections were seen in 20% of cases in our study. According to Avermaete *et al*., skin infections occur more often among chronic renal failure patients.[22] Depressed neutrophil function, impaired phagocytosis, decreased T and B lymphocyte function, and reduced natural killer cell activity are believed to play a role.[8]

Purpura and ecchymosis were seen in 1% each. Defects in primary hemostasis such as increased vascular fragility and abnormal platelet function, and the use of heparin during dialysis are considered as the main causes for abnormal bleeding in these patients.[1]

Absence of calcinosis cutis, calciphylaxis and bullous dermatoses in our study was contrary to literature.[3]

Limitations

Small sample size and the single center study design were the major limitations.

CONCLUSION

Skin manifestations are common in patients with ESRD. All the 100 patients studied showed at least one cutaneous manifestation. In our study pallor, xerosis, pruritus, and hyperpigmentation were the most common findings. Specific findings such as Kyrle's disease and nephrogenic systemic fibrosis were also observed. Awareness and recognition of the these cutaneous features of end stage renal disease are important and patients presenting with these features should be evaluated. An inter-disciplinary approach involving dermatologists and nephrologists is essential to improve the quality of life of patients with ESRD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

Dr Kunjumani Sobhanakumari is on the editorial board of the Journal.

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