

CUTANEOUS MANIFESTATIONS IN CHRONIC RENAL DISEASE – An observational study of skin changes, new findings, their association with hemodialysis, and their correlation with severity of CKD

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Abstract: Chronic Kidney Disease (CKD) is associated with various cutaneous abnormalities caused either by the disease or by treatment and can precede or follow initiation of dialysis, significantly impairing the quality of life in individuals. This study was undertaken to study the variety and prevalence of cutaneous manifestations in chronic renal disease, and their correlation with severity of CKD, and also to correlate variations in cutaneous changes with hemodialysis. 75 patients on CKD, including patients on hemodialysis, were examined for cutaneous changes. Creatinine clearance was calculated for staging of CKD. The common skin changes observed were xerosis (75%), hyperpigmentation (56%), pruritus (48%). Other changes seen were striae, purpurae, ecchymoses, Kyrle's disease, pyoderma, mucosal, hair and nail changes and other infections. One case of Calcinosis cutis was seen. There was a significant decrease in pruritus ($p=0.034$) and an increase in pallor ($p=0.001$) in dialysis patients compared to others. There was also a remarkable increase in the diversity of skin changes that correspond with severity of CKD ($p=0.044$). Black pigmentation of the tongue, not usually seen was observed in 41% of patients. With an almost 100% prevalence in CKD, early recognition of these skin manifestations and prompt initiation of treatment can dramatically alter their course and even detect underlying renal disease.

KEY WORDS – renal disease, cutaneous manifestations, hyperpigmentation

I. INTRODUCTION

Chronic renal failure is a pathophysiologic process with multiple etiologies, resulting in the inexorable attrition of nephron number and function, and frequently leading to end stage renal disease (ESRD). The skin is the most visible and easily accessible organ of the body, and is an important diagnostic window to diseases affecting internal organs, especially the renal system.^[1]

There are diverse ways in which the skin is affected by chronic kidney disease (CKD). Various specific and nonspecific skin abnormalities are observed in these patients, caused either by the disease or by treatment and is due to a host of factors ranging from metabolic disturbances to immunosuppressive drugs. The dermatologic complications can significantly impair the quality of life in certain individuals; therefore, early diagnosis and treatment can greatly reduce the associated morbidity .

The aim of this study was to document the prevalence of skin diseases that commonly occur in patients with CKD on medical treatment and dialysis, the effect of dialysis on the cutaneous manifestations and to observe if there is a correlation between the severity of CKD and the presence of skin changes.

II. MATERIALS AND METHODS:

In this prospective study, 75 consecutive patients with chronic renal disease (CKD), attending the Nephrology out-patient department and dialysis unit, over a period of 6 months, were examined for cutaneous manifestations of the disease. Patients of both sexes of any age group, with history of at least 6 months of chronic renal disease were included in this study.

Patients of known immunocompromised status, patients undergoing hemodialysis following renal transplant or those who had undergone peritoneal dialysis were excluded from the study.

After taking written and informed consent, a detailed clinical history including age, sex, underlying cause, medications, duration of renal disease and treatment, and duration of the present cutaneous illness was taken. A full cutaneous examination was done and investigations like serum urea, serum creatinine, Gram stain, KOH mount, bacterial culture and sensitivity, fungal culture and skin biopsy, were done where necessary, with informed consent.

Gomerular Filtration Rate(GFR) was calculated for each patient using Cockcroft – Gault formula and staging of severity of CKD was done accordingly. Staging of CKD was done according to **the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines as follows** ^[2]

Stage 1 - GFR > 90 ml/minute

Stage 2 - GFR 60-89 ml/minute

Stage 3 - GFR 30-59 ml/minute

Stage 4 – GFR 15-29 ml/minute

Stage 5 – GFR < 15 ml/minute

Collected data was analysed by frequency, percentage and Chi Square test and Fischer exact test.

III. RESULTS

The study included 75 patients with 48 males and 27 females. 58 of these patients were on hemodialysis. Most of the patients (23 of 75) were in the 51-60 age group, followed by 14 patients in 41- 50 age group. [Table 1]

Staging of CKD showed 56 patients in stage 5, 8 patients in stage 4, 9 patients in stage 3, and 1 each in stage 1 and stage 2.

The etiology of CKD in this study showed that hypertensive nephropathy was the cause of CKD in 34 patients followed by diabetic nephropathy (18), nephrotic syndrome (2), IgA nephropathy (2), drug induced CKD (4), obstruction(renal stones, tumors) (4), snake bite (1), post streptococcal glomerulonephritis(3), sepsis (4), chronic glomerulonephritis (1), PNET (1), rhabdomyosarcoma metastasizing to kidney(1). [Table 2]

Xerosis was the most common cutaneous abnormality (75%), which is comparable with other studies, and seen mainly in patients who were on maintenance hemodialysis (59%)[Figure 1a, 1b].

Ichthyotic skin changes of varying degree were observed in 50 of 75 patients (66.7%). Senile atrophy was present in most patients above 60 years of age.^[3]

Hyperpigmentation of skin, more marked in sun- exposed parts of body, such as the face, upper back, arms and legs, was seen in 42/75 patients (56%) with 71% of these patients being on hemodialysis[Figure 2]. Similar results were seen in studies done by Nunley et al. and Pico et al.^[4,5]

Yellowish discolouration of skin was seen in 3 patients of our study (0.04%)[Figure 1b].

Hypopigmentation in the form of Idiopathic guttate hypomelanosis was seen in 5 patients, over the extremities.

Pruritus :

Generalised pruritus was recorded in 36 patients in our study (48%) and was comparable to various other studies. There was a significant decrease in pruritus of CKD patients on dialysis as compared to those who were not, with 71% of non-dialysed CKD patients and only 41% of dialysis patients having pruritus ($p = 0.034$).

Pallor :

Pallor of both skin and nails was seen in 81% of patients of which 93% were on dialysis ($p = 0.0001$). Pallor was more common in females than males, with 19/27 females with Hb < 10g/dl. These findings correlate well with other studies.

Purpura and ecchymoses were seen on the extremities of 6 patients, of whom 4 were on hemodialysis.

Kyrle's disease was seen in 3 patients as hyperkeratotic lesions on the skin, and was confirmed by histopathological examination. 1 case of Calcinosis cutis was seen, which is a rare finding in CKD.

Mucosal changes : 31 of 75 patients (41%) had black pigmentation of the tongue, a finding not specifically mentioned finding in CKD but seen in a large number of patients in our study, often preceding the diagnosis of CKD in these patients [Figure 3].

Other mucosal changes seen were teeth indentation marks on the tongue (tongue sign of uremia) in 7 patients, xerostomia, macroglossia and balding of the tongue.

Nail changes

Pallor was seen in majority of patients on dialysis. Other nail changes observed were, Lindsay's nails (half and half nails) seen in 25 patients (33.3%)[Figure 4a, 4b]. Other nail changes included onycholysis (14.6%), onychomycosis (10.6%), and Mee's lines (16%). Beau's lines (4%), koilonychia (12%), subungual hyperkeratosis (9.3%), brown nail bed arc (4%), Splinter hemorrhage (5.3%) and hyperpigmented nails. [Table 3]

Hair changes

Diffuse hairfall and thinning of hair was seen commonly in severe CKD and initial stages of dialysis, with decrease in hairfall as dialysis was continued. Loss of body hair was also seen.

Infections such as carbuncles, furunculosis, dermatophytic infections, onychomycosis,etc. were seen in 15 patients.

The severity and number of cutaneous manifestations in patients in this study, was significantly seen to increase with duration and severity of CKD ($p = 0.044$). A comparison of the cutaneous manifestations seen in CKD patients requiring and not requiring dialysis, and variations seen are described in Table 4.

Other non-specific findings seen in these patients included eczema such as polymorphic light eruptions, seborrhoeic keratosis, atopic dermatitis and seborrhoeic dermatitis. Vasculitis was seen in one patient and erythroderma was seen in a patient who had previous history of psoriasis.



Figure 1a: Xerosis



Figure 1b: Xerosis with yellowish discolouration of skin



Figure 2: Hyperpigmentation over sun exposed areas



Figure 3 : Blackish pigmentation of mucosa



Figure 4 a and 4b : Nail changes – Hyperpigmentation and Lindsay's nails

IV. DISCUSSION

Chronic kidney disease (CKD) is a progressive loss of kidney function over a period of months or years through five stages. The number of patients with end-stage renal disease (ESRD) in India is increasing.

Dermatologic abnormalities are common in chronic kidney disease (CKD) and range from the nearly universal xerosis and pruritus to uncommon conditions such as hyperpigmentation of exposed areas, purpuric skin changes, acquired perforating dermatosis, and nail abnormalities.^[6] In a study by Pico *et al.*, all patients with CKD had one or more skin manifestations.^[4] This study was conducted to determine the prevalence of cutaneous abnormalities in stable and dialysis-dependent CKD patients.

Cutaneous examination of patients with ESRD has shown that almost all patients have at least 1 dermatologic condition. This may be expected, because most patients with ESRD have an underlying disease process with cutaneous manifestations, along with uremia and conditions associated with renal replacement therapy or renal transplantation.^[5]

Causes:

Hypertension and Diabetes mellitus have been seen to be responsible for close to 50% of new cases of ESRD. Cystic/hereditary kidney diseases were the next most common causes. The remaining causes of ESRD included vasculitis, infectious or rheumatologic disease, interstitial nephritis, tumors, cholesterol emboli, and systemic amyloidosis. Infectious causes of glomerulonephritis included streptococcal infections, human immunodeficiency virus (HIV), and hepatitis viruses, both hepatitis C (HCV) and hepatitis B (HBV).

Systemic lupus erythematosus (SLE) has been the most commonly reported rheumatologic cause of ESRD. Polyarteritis nodosa, Wegener granulomatosis, Henoch-Schönlein purpura, scleroderma, and otherwise nonspecified vasculitides also were reported to have caused ESRD.^[5]

Xerosis:

Xerosis was the most common cutaneous abnormality (75%), which is comparable with other studies.^[7-10] This abnormality was observed mainly in patients who were on maintenance hemodialysis (59%); this being similar to studies by Anderson *et al.*,^[11] who reported a high frequency of xerosis (50-70%) in dialysis patients

A reduction in the size and functional abnormality of eccrine sweat glands, causing epithelial dehydration may contribute to the development of xerosis. Clinical and histologic evaluations have shown an overall decrease in sweat volume in patients with uremia, as well as atrophy of sebaceous glands. Some patients may develop acquired ichthyosis.^[12,5] Dry, lusterless hair and sparse body hair could also be attributed to the decreased sebaceous activity.

High dosage of diuretics, and excessive ultrafiltration might also be responsible for the above manifestation. The water content in the stratum corneum does not correlate with severity of xerosis.^[13]

Hyperpigmentation:

Diffuse hyperpigmentation accentuated in sun-exposed areas, seen in many patients is characteristic of uraemic patients.^[14] Nunley *et al.*,^[5] reported that pigmentary alterations occurred in 25-70% of dialysis patients and increases over the duration of renal disease. An increase in melanin in the basal layer of the epidermis due to an increase in poorly dialyzable beta-melanocyte stimulating hormone can explain the pigmentation on sunexposed areas^[15] The intensity of melanin pigmentation increases with respect to the duration of end-stage renal disease.

A yellowish tinge of the skin was reported in 40% of patients by Pico *et al.*,^[4] but we encountered yellowish discoloration in only 3 (0.04%) patients, probably because of the dark complexion of Indians, which masks this finding. This has been explained by retained lipid soluble pigments such as lipochromes and carotenoids, deposited in the dermis and subcutaneous tissue.^[16]

Pruritus :

Pruritus is one of the most characteristic and troublesome symptoms of CKD. Generalised pruritus was recorded in 48% of patients in our study. It has been reported to be the **most common** cutaneous symptom in CRF, with a prevalence of 15%-49% in renal disease in various studies.^[17]

There are a number of proposed etiologies for pruritus in CKD including changes related to xerosis, uremia, calcium and phosphate dysregulation, mast cell proliferation with a concomitant increase in histamine levels, hormonal derangement and hypovitaminosis D.^[18,19] Parathyroid hormone and divalent ions (eg, calcium phosphate and magnesium ions) have been implicated, as is seen with severe secondary hyperparathyroidism but these findings lack consistent correlation.^[20, 21]

Dysfunction of the transmission of itch sensations with reduction in total number of skin nerve terminals has been described in dialysis patients.^[22] Pruritus may also be a manifestation of allergy against sensitizing compounds in the dialysis set up, e.g. Ethylene oxide.^[23]

Pallor/ anemia Anemia was a common problem seen, with hemoglobin levels of even less than 5 g/dl, more common in patients on maintenance hemodialysis. Before the widespread use of erythropoietin, pallor was common and was attributed to the significant anemia and is still seen commonly in Indian population.

Purpurae and ecchymoses Defects in primary hemostasis- such as increased vascular fragility, abnormal platelet function, and use of heparin during dialysis are the main causes of abnormal bleeding in these patients.^[24]

Acquired perforating disorders (APD) such as perforating folliculitis, Kyrle's disease, and reactive perforating collagenosis have been described in CKD. APD has been reported to occur in 4.5-10%^[25] of patients receiving maintenance hemodialysis. Proteolytic enzyme release, including collagenase and elastase elaboration, may initiate the pathologic process.^[26] Although the exact pathophysiological mechanism for APD in ESRD is unknown, it is thought to be the result of dermal connective tissue dysplasia and decay.^[1]

Kyrle's disease is a chronic, genetically determined, hyperkeratotic disorder occurring in the middle forties and show a marked predisposition for the calf, the tibial region, and the posterior part of the thigh.^[27] Keratotic, partly parakeratotic plugs containing basophilic debris lying in an invagination of the epidermis are seen on histopathology.^[28]

The lesions of APD may resolve spontaneously. When treatment is desired, topical retinoids, topical and intradermal steroids, and UVB light have been tried with variable results.^[29]

Nephrogenic systemic fibrosis (NSF) also known as nephrogenic fibrosing dermopathy, is a rare, systemic fibrotic disorder found uniquely in renal failure. Nearly all known cases of NSF occur in patients with exposure to gadolinium contrast- enhanced MRI or MRA within 2-3 months of symptom onset. It is characterized by visible fibrosis of the skin with thickened, hyperpigmented and/or shiny changes. Fibrotic skin across joints leads to flexion contractures and immobility. Sclerotic changes are noted most frequently in the feet, ankles, shins, thighs, fingers, hands, and lower arms. Histopathological confirmation can be made by observing spindle-shaped cells in the background of dermal fibrosis, with deposition of collagen and mucin. Dual immunolabelling with CD34 and procollagen is diagnostic.

Unfortunately, there is also no effective treatment for NSF.^[29,30]

Infections Patients with chronic renal failure (CRF) have impaired cellular immunity due to a decreased T lymphocyte cell count; ^[4] this could explain the high prevalence of infections in these patients.

Oral mucosa changes seen are macroglossia with teeth markings (tongue sign of uremia), usually in severe disease. Other mucosal changes are angular cheilitis, ulcerative stomatitis, xerostomia, gingivitis, and uremic breath.^[13]

Nail examination reveals pallor in most of the cases. Among the nail changes observed in various studies, Lindsay's nails (half-and-half nails) were the most common. Other nail changes included onycholysis, onychomycosis, and Mee's lines, Beau's lines, koilonychia, subungual hyperkeratosis, Muehrcke's lines, brown nail bed arc, and splinter hemorrhage. ^[4] Although not pathognomonic for renal failure, half-and-half nails occur in as many as 40% of patients on dialysis and disappear several months after successful renal transplantation. Half-and-half nails are characterized by a dark distal band that occupies 20-60% of the nail bed and by a white proximal band. The distal dark band may range in color from reddish to brown and commonly involves fingernails.^[5] The discoloration does not change with nail growth, indicating the problem begins in the nail bed. The discoloration also does not fade with pressure.^[29]

V. CKD and Hemodialysis

Hemodialysis has prolonged the life expectancy of CKD patients, and has brought about an increase in the number of manifestations, by giving time for these changes to manifest. It also has improved symptoms such as pruritus.^[32]

Dermatologic conditions such as uremic frost, erythema papulatum uremicum, uremic roseola, and uremic erysipeloid are now rare. ^[31] Certain specific disorders associated with CKD such as calciphylaxis and fibrosing dermatopathy of uremia were not seen in our study, and this could be attributed to shorter duration of dialysis in our patients. Changes like uremic frost is rarely seen in the present day because of early dialytic intervention. When the blood urea nitrogen (BUN) level is adequately high (usually > 250-300 mg/dL), the concentration of urea in sweat is increased greatly. Evaporation results in the deposition of urea crystals on the skin.

Porphyria cutanea tarda was not observed in this study. Plasma porphyrins are poorly dialyzed and are mildly to moderately elevated in most patients on dialysis. A bullous disease that is clinically similar to but metabolically distinct from porphyria cutanea tarda (PCT) has been described in the dialysis population. True PCT also has been reported to occur in patients on dialysis.^[5]

VI. CONCLUSION

Recent advances in the treatment have improved the quality of life and life expectancy of these patients, resulting in changes in the frequency and types of disorders observed in CKD. Some prophylactic measures can prevent some of the cutaneous manifestations, such as emollients for xerosis and pruritus, sun screens, avoidance of sun exposure and adequate clothing for pigmentary changes, and cutaneous malignancies. Ultraviolet (UV) B phototherapy probably is the most effective therapeutic choice and may have prolonged benefit in pruritus.^[5,31] Oral mucosal pigmentation maybe a significant marker of underlying disease and may precede the diagnosis of renal disease, as seen in this study. Decrease in troublesome symptoms such as pruritus has been seen as an effect of initiating hemodialysis. Specific and rare skin lesions of CKD must always be kept in mind, to aid the prompt diagnosis and possibly detect underlying renal disease early. Prompt recognition and treatment of infection in patients with CKD, especially on maintenance dialysis is useful for improving the quality of life.

TABLES –

Table 1 : Age and sex distribution of patients in the study

Age group (in years)	Number of cases	
	Males (48/75) 64%	Females (27/75) 36%
< 20 years	1	3
21-30	3	2
31-40	4	4
41-50	5	9
51-60	16	7
61-70	13	1
>70	6	1

Table 2 :Etiology of chronic kidney disease seen in our study.

Cause of CKD	Number of cases
Hypertension	34
Diabetic nephropathy	18
Drug induced CKD	4
Obstructive causes (stones, etc)	4
Sepsis	4
Post streptococcal glomerulonephritis	3
Nephrotic syndrome	2
IgA nephropathy	2
Snake bite	1
PNET	1
Chronic glomerulonephritis	1
Rhabdomyosarcoma	1

Table 3 : Nail changes observed

Nail changes	Number of cases (seen in 60/75 cases)
Pallor	50 (67%)
Lindsay's nails (half and half nails)	25 (33.3%)
Onycholysis	11 (14.6%)
Onychomycosis	8 (10.6%)
Mee's lines	12 (16%)
Beau's lines	3 (4%)
Koilonychia	9 (12%)
Subungual hyperkeratosis	7 (9.3%)
Brown nail bed arc	3 (4%)
Splinter hemorrhage	4 (5.3%)
hyperpigmented nails	35 (46.6%)

Table 4: Comparison of cutaneous manifestations seen in patients with CKD with and without hemodialysis. Significant decrease in pruritus noted in patients on hemodialysis. Significant pallor and mucosal hyperpigmentation seen in dialysis patients.

SKIN CHANGES		ON DIALYSIS (58/75) 77.3%	NO DIALYSIS (17/75) 22.7%
Xerosis	+	44	12
	-	12	5
Pruritus	+	24	12
	-	34	5
Hyperpigmentation	+	30	12
	-	28	5
Mucosal pigmentation	+	25	6
	-	33	11
Pallor	+	54	4
	-	7	10

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