A prospective study of cutaneous abnormalities in patients with chronic kidney disease

E. A. Thomas, B. Pawar[1], A. Thomas

Departments of Dermatology, and [1]Nephrology, Christian Medical College and Hospital, Ludhiana, Punjab, India

ABSTRACT

There are diverse ways in which the skin is affected by chronic kidney disease (CKD). Various specific and nonspecific skin abnormalities are observed in patients with CKD. The aim of the study was to document the prevalence of skin diseases that commonly occur in patients with CKD on medical treatment and dialysis. A total of 99 patients with CKD were examined for evidence of skin diseases. Ninety-six had at least one cutaneous abnormality attributable to CKD. The most prevalent finding was xerosis (66.7%), followed by pallor (45.45%), pruritus (43.4%), and cutaneous pigmentation (32.3%). Other cutaneous manifestations included dermatitis (27.27%); Kyrle's disease (17.17%); fungal (8.08%), bacterial (11.1%), and viral (5.05%) infections; purpura (10.1%); gynecomastia (4.04%); and yellow skin (5.05%). The common nail changes were half and half nails (36.36%) and onycholysis (13.13%). CKD is associated with various cutaneous abnormalities caused either by the disease or by treatment, the most common being xerosis and pruritus. The dermatologic complications can significantly impair the quality of life in certain individuals; therefore, earlier diagnosis and treatment is important to improve their quality of life.

Key words: Chronic kidney disease, dialysis, uremic pruritus

Introduction

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.[1] In a study by Pico *et al.*,[2] all patients with CKD had one or more skin manifestations, while Bencini *et al.*[3] noticed skin changes in 79% of the patients. This study was conducted to determine the prevalence of cutaneous abnormalities in stable and dialysis-dependent CKD patients.

Address for correspondence:
Dr. Emy Abi Thomas, Department of Dermatology, Christian Medical College and Hospital, Ludhiana, Punjab - 141 008, India.
E-mail: emyabi@gmail.com

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Materials and Methods

Patients with CKD, on medical treatment or dialysis were included in this prospective, observational study. The history of duration of CKD and dialysis as well as the onset of skin disease with regard to diagnosis of CKD were taken. A complete clinical and dermatological examination was carried out. The creatinine clearance of these patients was calculated using the Crockroft–Gault formula.[4]

Staging of CKD was done according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines.[5]

In all patients, a complete blood count; renal function tests such as blood urea, serum creatinine and electrolytes, serum calcium, inorganic phosphorus, and alkaline phosphatase; urine analysis and renal ultrasound were performed. Specific investigations such as skin biopsies, culture and sensitivity for bacterial infections, Gram's stain, potassium hydroxide mount, and fungal culture were done wherever clinically indicated.

The severity of xerosis was assessed using a modified version of grading used by Morton:[6] Grade- 0 (smooth skin),

grade- 1 (rough skin), and grade- 2 (rough skin with scaling).

Patients with CKD stage V were further classified as either stable CKD, hemodialysis-dependent CKD (HD-CKD), and on continuous ambulatory peritoneal dialysis (CAPD). Renal transplant recipients were excluded from this prospective observational study.

Results

Of the 99 patients, 78 were males. By staging the severity of CKD according to the K/DOQI clinical practice guidelines,[5] 1 patient was found to be in stage II, 8 in stage III, 10 in stage IV, and 80 in stage V. Stage V patients were further divided into stable (6), HD-CKD (70), and CAPD (4). There were no patients with stage I CKD. Most of the patients were in the age group of 40-60 years, with a mean age of 50.5 years. The youngest patient was 11 years old and the eldest, 86 years old. The etiology of CKD in this study showed that diabetic nephropathy was the cause of CKD in 42 patients followed by chronic interstitial nephritis (18), chronic glomerulonephritis (14), hypertension (5), autosomal dominant polycystic kidney disease (6), obstruction (6), amyloidosis (2), and undetermined etiology in 6 patients.

A total of 10 patients (9 male and 1 female) were Hepatitis C Virus (HCV) antibody-positive and 2 (2 male) were Hepatitis B Surface Antigen (HBsAg) positive. Anemia was a common problem when these patients were first seen, 7 had hemoglobin levels of less than 5 g/dl, 54 patients had hemoglobin levels in the range of 5-8 g/dl and 38 had greater than 8 g/dl. In this study, 96 patients had at least one cutaneous abnormality; 42 had multiple skin lesions, whereas 3 patients did not have any symptoms and signs of skin disease. Skin abnormalities in relation to staging of CKD are shown in Table 1.

One patient on hemodialysis developed bullous dermatosis of hemodialysis. Other skin lesions seen in patients with CKD were diabetic bullae (1), diabetic dermopathy (1), psoriasis (2), vitiligo (1), acanthosis nigricans (2), Darier's disease (1), neurofibromatosis (1), and Schamberg's disease (1).

Nail changes in CKD are shown in Table 2. Among the nail changes observed, Lindsay's nails (half and half nails) were the most common and were seen in 36 patients (36.36%). Other nail changes included onycholysis (13.13%), onychomycosis (7.07%), and Mee's lines (8.08%). Beau's lines (5.05%), koilonychia (5.05%), subungual hyperkeratosis (6.06%), Muehrcke's line (3.03%), brown nail bed arc (4.04%), and Splinter hemorrhage (1.01%).

Table 1: Cutaneous manifestations in different stages of chronic kidney disease

Skin manifestations	III	IV	V stable	V CAPD	V HD	Total	Percentage
Xerosis							
Mild (grade-I)	3	6	3	3	36	51	66.7
Severe (grade II)	2	2	1	1	9	15	43.4
Pruritus							
Mild	3	4	1	1	17	26	45.45
Severe	2	2	0	1	12	17	32.3
Pallor	-	2	4	1	38	45	5.05
Pigmentation	-	1	1	1	29	32	10.1
Yellow skin	-	-	1	-	4	5	17.7
Purpura	-	1	2	-	7	10	4.04
Kyrle's disease	1	-	1	3	12	17	11.1
Gynecomastia	-	-	-	-	4	4	5.05
Infections							
Bacterial	2	2	-	2	5	11	8.08
Viral	-	-	-	1	4	5	1.01
Fungal	3	2	-	1	2	8	1.01
Parasitic	-	-	-	-	1	1	27.27
Mycobacterium							
Lupus vulgaris	-	-	-	-	1	1	
Dermatitis	4	4	6	-	13	27	

CAPD = Continuous ambulatory peritoneal dialysis, HD = Hemodialysis

Table 2: Nail changes in different stages of chronic kidney disease

Nail changes	III	IV	V stable	V CAPD	V HD	Total	Percentage
Half and half nail	5	3	2	1	25	36	36.36
Onycholysis	2	-	-	2	9	13	13.13
Onychomycosis	2	2	-	1	2	7	7.07
Pitting	1	1	-	1	4	7	7.07
Mee's line	1	-	-	1	6	8	8.08
Beau's line	-	2	-	-	3	5	5.05
Koilonychia	-	-	-	-	5	5	5.05
Subungual hyperkeratosis	-	-	1	-	5	6	6.06
Clubbing	2	-	-	-	2	4	4.04
Muehrcke's line	-	-	-	-	3	3	3.03
Brown nail bed arc	-	-	-	-	4	4	4.04
Splinter hemorrhage	-	-	1	-	-	1	1.01

CAPD = Continuous ambulatory peritoneal dialysis, HD = Hemodialysis

Oral mucosa changes seen in this study were macroglossia with teeth markings (tongue sign of uremia) in 9 (9.09%) of the patients; of this 22.22% were in stage IV and 77.79% in stage V. Other mucosal changes were angular cheilitis (5.05%), ulcerative stomatitis (2.02%), and xerostomia (5.05%).

Discussion

Xerosis was the most common cutaneous abnormality (66.7%), which is comparable with other studies.[7-10] This abnormality was observed mainly in patients who were on

maintenance hemodialysis (45.45%); this being similar to Anderson *et al*.,[11] who reported a high frequency of xerosis (50-70%) in dialysis patients [Figure 1]. None of the patients had xerosis from childhood, but one patient had hypothyroidism prior to the diagnosis of CKD. Features of atopy, associated with dry skin and keratosis pilaris-like lesions were seen in eight patients. A reduction in the size and functional abnormality of eccrine sweat glands, suggesting compromised eccrine secretion leading to epithelial dehydration[12] may contribute to the development of xerosis.

Pruritus is one of the most characteristic and annoying symptoms of CKD. In this study, 43.4% of patients complained of pruritus, a finding similar to that in a study by Udayakumar *et al*., where they found the prevalence of pruritus to be 53%.[9] In our study, 29.3% of CKD patients on maintenance hemodialysis had pruritus, which is consistent with the report by Pico *et al*.,[2] who found the prevalence of pruritus among hemodialysis patients to be 19-90%. Among the 29 patients on hemodialysis with pruritus, 13 patients did not improve with dialysis, 4 had some improvement, and the remaining 12 patients reported further aggravation of pruritus after starting hemodialysis. There are a significant number of proposed etiologies for pruritus in CKD including: Integumentary changes related to xerosis, urochrome deposition, uremic toxemia, calcium and phosphate dysregulation, mast cell proliferation with a concomitant increase in histamine levels, dialysis component allergic reactions, and hypovitaminosis D.[13] Tapia has suggested that pruritus in CKD may be due to a slowly accumulative metabolic process or hormonal derangement.[14] Parathyroid hormone and divalent ions (eg, calcium phosphate and magnesium ions) have also been implicated in the pathogenesis of uremic pruritus, as itching frequently accompanies severe secondary hyperparathyroidism and an elevated calcium phosphate product. The lack of consistent correlation between levels of parathyroid hormone, calcium, phosphorous, and uremic pruritus severity indicates that other factors are more important in the pathogenesis of uremic pruritus.[15,16] Abnormal cutaneous innervations with reduction in total number of skin nerve terminals has been described in dialysis patients, associated with dysfunction of the transmission of itch sensations.[17] Pallor of the skin was observed in 45 (45.45%) patients, and this was more commonly seen in patients on maintenance hemodialysis (38.38%). Diffuse hyperpigmentation on sun-exposed areas were seen in 32.3% patients, and this was mainly encountered in patients on maintenance hemodialysis. This is consistent with the report of Deepshikha *et al*. that hyperpigmentation predominantly on sun exposed areas in the Indian population could be due to tropical climate and excessive sun exposure in these patients.[10] Nunley *et al*.[18] reported that pigmentary alterations occurred in 25-70% of dialysis patients and increases over the duration of renal disease. The pigmentation on sun-exposed areas has been attributed to an increase in melanin in the basal layer of the epidermis due to an increase in poorly dialyzable beta-melanocyte–stimulating hormone.[19] 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*.,[2] but we encountered yellowish discoloration in only 5 (5.05%) patients, probably because of the dark complexion of Indians, which masks this finding. The yellowish skin color has been attributed to retained lipid soluble pigments such as lipochromes and carotenoids, which are deposited in the dermis and subcutaneous tissue.[20]

Acquired perforating disorders (APD) such as perforating folliculitis, Kyrle's disease, and reactive perforating collagenosis have been described in CKD. We encountered Kyrle's disease in 17 (17.17%) patients, among whom, 12 patients (12.12%) were on maintenance hemodialysis [Figure 2]. APD has been reported to occur in 4.5-10%[21] of patients receiving maintenance hemodialysis. The abundance of polymorphonuclear neutrophil remnants in the early stages of these disorders has led to the speculation that cellular dissolution of neutrophils with proteolytic enzyme release, including collagenase and elastase elaboration, may initiate the pathologic process.[22]

Purpura was seen in 10 (10.1%) patients, among whom, 7 were on maintenance hemodialysis. This is consistent with the report of Remuzzi *et al*.,[23] that defects in primary hemostasis-like increased vascular fragility, abnormal platelet function, and use of heparin during dialysis are the main causes of abnormal bleeding in these patients.

Gynecomastia was observed in 4 patients (4.04%). It occurs during the early stages of regular dialysis treatment and is explained on the basis of 'refeeding' after starting the treatment.[24] As a consequence of CKD and protein energy malnutrition, pituitary gonadotropic and testicular function remain suppressed; moreover, following treatment and increase in daily protein intake, a 'second puberty' ensues, which may lead to transient gynecomastia.

Twenty-six (26.26%) patients in this study had cutaneous infections; 11 (11.1%) were bacterial, 5 (5.05%) viral, 8 (8.08%) fungal, 1 (1.01%) parasitic, and 1 (1.01%) cutaneous tuberculosis. Patients with chronic renal failure (CRF) have impaired cellular immunity due to a decreased T lymphocyte cell count;[2] this could explain the high prevalence of infection in these patients. Darier's

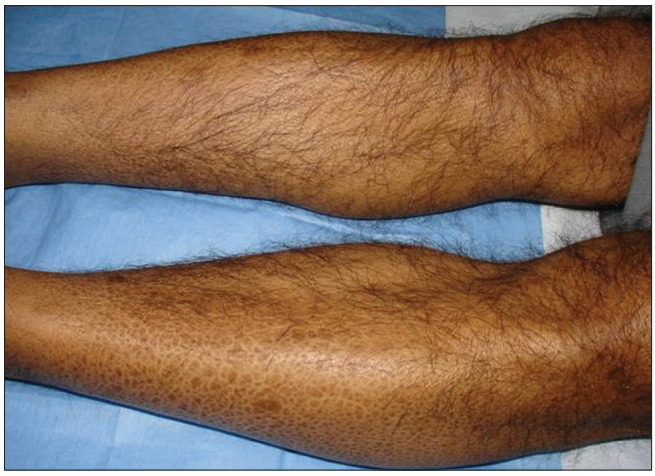

Figure 1: Xerosis secondary to renal failure

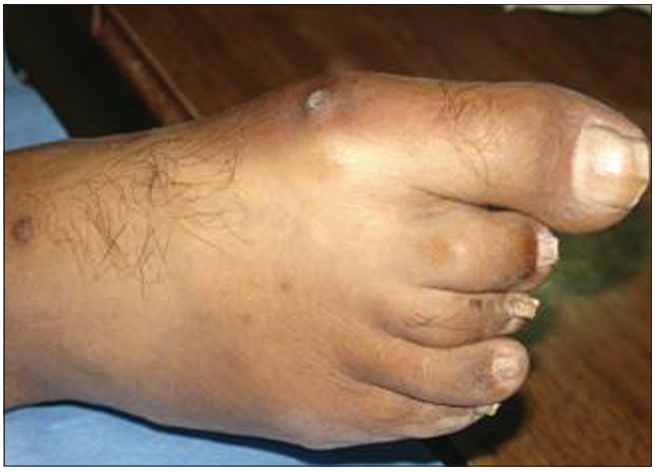

Figure 2: Kyrle's disease

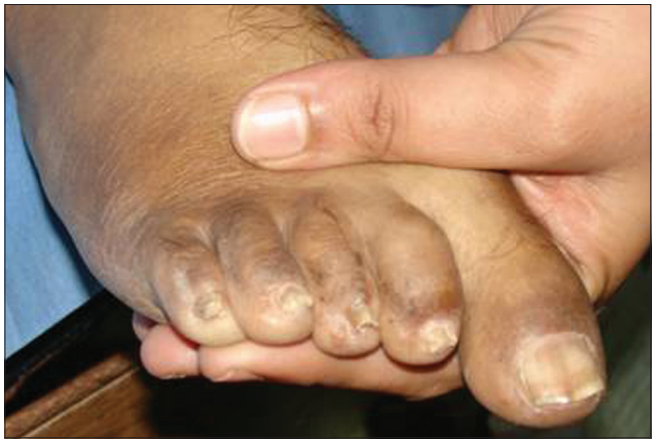

Figure 3: Lindsay's nail with Pincer nail deformity

disease and Schamberg's disease were seen in one patient each of CRF on hemodialysis. Darier's disease is an autosomal dominant disorder of keratinization characterized by persistent eruption of hyperkeratotic papules involving mainly the seborrhoeic areas of face and trunk. Schamberg's disease (progressive pigmented purpuric dermatosis) is an uncommon eruption characterized by petechiae and patches of brownish pigmentation (hemosiderin deposits), particularly on the lower extremities, which may remain for months or years and present only a cosmetic problem.

One patient on maintenance hemodialysis developed bullous lesion on the dorsa of hands, unassociated with trauma. This patient also had hyperpigmentation of the exposed areas, and no associated milia formation. Uroporphyrin and coproporphyrin concentrations in the plasma, urine, and stool specimens were within normal limits.

Lindsay's nails (half and half nails) were the most common nail abnormality seen in this study (36.36%) and more commonly seen in hemodialysis patients [Figure 3]. Previous studies have found a prevalence of 16-50.6%.[2,8,9] Although half and half nails are not always seen in renal failure, they occur in as many as 40% of the patients on dialysis.[18] Pico *et al*.[2] reported that the nail changes increased in prevalence with respect to time of dialysis and was significantly more pronounced in patients receiving hemodialysis. The pathogenesis of half and half nails has been attributed to increased levels of melanocyte stimulating hormone (MSH).[25]

Sparse body hair and diffuse alopecia with dry lusterless hair have been reported in patients with CKD.[7] In our study, 16 patients had sparse body hair and 7 had dry lusterless hair, which could be due to decreased secretion of sebum.

Mucosal changes in the oral cavity have been reported in up to 90% patients with CKD.[26] Macroglossia with teeth marking (tongue sign of uremia) was first described by Mathew in 92% of patients with CKD,[27] which was seen in 9.09% of our patients. Xerostomia was seen in 5.05% of the patients, which could be attributed to mouth breathing and dehydration.

Dermatologic conditions such as uremic frost, erythema papulatum uremicum, uremic roseola, and uremic erysipeloid now seldom occur in patients with CKD. Certain specific disorders associated with CKD such as calciphylaxis and fibrosing dermopathy of uremia were not seen in our study, and this could be attributed to shorter duration of dialysis in our patients.

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 conjunction with 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. Prompt recognition and treatment of infection in patients with CKD, especially on maintenance dialysis is useful for improving the quality of life.

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