Report

Cutaneous disorders in uremic patients on hemodialysis: an Egyptian case-controlled study

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Summary

Background We studied the prevalence of mucocutaneous disorders in uremic adults and children on hemodialysis (HD) vs. controls, in Egypt.

Methods A total of 206 Egyptians with uremia (163 adults and 43 children) undergoing HD, and 199 healthy controls (161 adults and 38 children), were examined for mucocutaneous abnormalities.

Results Specific cutaneous diseases associated with renal insufficiency were found in five adults, including acquired perforating dermatosis and pseudo-porphyria. Non-specific abnormalities included xerosis (54%), pallor (42.2%), nail changes (34.9%), hair changes (34%), pruritus (32%), hyper-pigmentation (22.2%), coated tongue (14.1%), ecchymosis (1.5%), and gingival hypertrophy (1.5%). Disorders found significantly more often in uremics than controls included pallor, nail changes, hair changes, pruritus, hyper-pigmentation and coated tongue in adults ($P < 0.05$), and nail changes, hair changes, and hyper-pigmentation in children ($P < 0.05$). The prevalence of each mucocutaneous abnormality was similar in uremic adults and children except for pallor [more common in adults ($P = 0.001$)], and hyper-pigmentation [more common in children ($P = 0.003$)]. A greater number of hepatitis C virus-positive than -negative adult uremics had hyper-pigmentation ($P < 0.05$), and more diabetic uremics had pruritus than did non-diabetics ($P < 0.05$).

Conclusion Mucocutaneous disorders occur in adults and children with uremia, some of which are specific associations with the underlying renal disease. Occurrence of some of the non-specific abnormalities, such as xerosis, ecchymosis, and gingival hypertrophy, may be coincidental or associated with factors other than renal insufficiency.

Introduction

The skin is an important diagnostic window to diseases involving internal organs, including the kidneys.[1] In uremia or chronic renal failure (CRF), most affected patients undergo hemodialysis (HD) for up to 4 h, two or three times per week.[2]

Nearly all patients with uremia have at least one dermatological disorder that may range from benign to life-threatening. These disorders may be as a result of the underlying pathologic process that induced the renal disease or related to the severity and duration of renal failure.[3] We studied the prevalence of mucocutaneous disorders in uremic adults and children undergoing HD, vs. controls, in Egypt.

Subjects and methods

A total of 206 Egyptian uremics (163 adults and 43 children) undergoing HD at Ain Shams University and Ahmed Maher Hospitals in Cairo, and 199 age- and gender-matched controls (161 adults and 38 children), were included in the study, performed during the period May 2008 to January 2009. Patients were selected according to their pre-dialysis laboratory results (serum creatinine >4 mg/dl, blood urea >100 mg/dl, serum potassium >6.5 meq/l, serum bicarbonate <15 meq/l, and glomerular filtration rate <15 ml/min) and clinical history, including onset, course, and duration of their renal disease, history of underlying/associated diseases, previous and current medications, and duration of HD. Patients were divided into two groups based on their age: adults and children (≤18 years old). The controls were randomly selected individuals who attended the Dermatology Outpatient Clinic and healthy hospital staff members of Ain Shams University Hospitals.

Patients and controls were examined thoroughly for the presence of mucocutaneous disorders, with emphasis on manifestations of uremia, underlying disease, and disease complications.

Data were analyzed statistically using SPSS statistical package version 15 (SPSS Inc., Chicago, IL, USA). Chi-square

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test was used for comparison between two variables. Probability (*P*) value was considered statistically not significant if >0.05, significant if ≤0.05, and highly significant if ≤0.001.

Results

A total of 206 uremic patients (110 males and 96 females; 163 adults and 43 children) on HD for a mean duration of 5.8 years (adults) and 3.4 years (children), were included in this study. In total 19 patients were diabetic and 187 patients were non-diabetic. A total of 95 patients were hepatitis C virus (HCV)-positive and 111 patients were HCV-negative. Among adult uremics, diabetes mellitus was the most common cause of CRF, affecting 19 patients (11.6%), followed by hypertension in 16 patients (9.8%), repeated renal stones [15 patients (9%)], chronic pyelonephritis [five patients (3%)], systemic lupus erythematosus (SLE) [four patients (2.4%)], gout [three patients (1.8%)], and congenital polycystic kidney [three patients (1.8%)]; the cause was unknown in 98 patients (60.2%). Congenital polycystic kidney was the cause of renal failure in four children (9%) and SLE in two (4.6%); the cause of renal insufficiency was unknown in 37 children (86.4%).

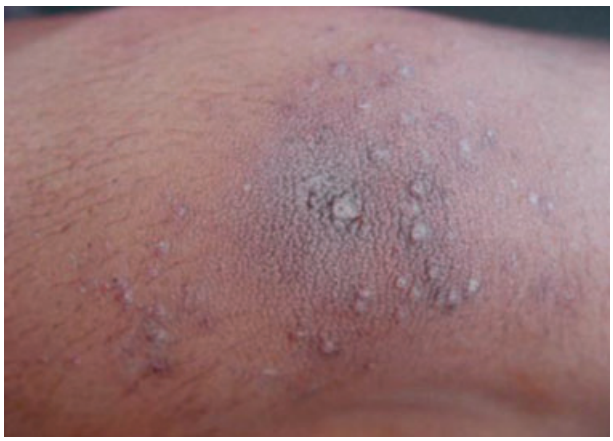

Figure 1 Acquired perforating dermatosis involving the elbow

The control group consisted of 199 (161 adults and 38 children) age- and gender- matched, non-uremic apparently healthy persons.

A total of 128 adult uremics (78.5%) had mucocutaneous disorders; five patients (3%) had specific manifestations of CRF, including acquired perforating dermatosis (APD) (Fig. 1) in four patients (2.5%) and pseudoporphyria (Fig. 2) in one patient (0.6%). In total, 102 patients (62.5%) had non-specific abnormalities and 21 (13%) had other manifestations. No member of the adult control group had specific skin manifestations of uremia (Table 1).

Non-specific mucocutaneous manifestations of uremia were reported in 102 (62.5%) adult uremics: xerosis in 89 (54.6%), pallor in 79 (48.5%), pruritus in 58 (35.6%), nail changes in 57 (34.9%) [including absent lunula in 55 (33.7%), nail striations in 44 (26%), and half-and-half nails in 40 (24%)], hair changes in 55 (33.7%) [including hair loss in 40 (24.5%) and dry brittle hair in 20 (12.3%)], hyper-pigmentaion in 29 (17.8%), coated tongue in 26 (16%), ecchymosis in three (1.8%), and gingival hypertrophy in three patients (1.8%). In the control group, the prevalence of xerosis was 47.8%, pallor 10.6%, pruritus 21.7%, nail changes 3.1%, hair changes 12.4%, hyper-pigmentation 1.9%, coated tongue 2.5%, ecchymosis 0.6%, and for gingival hypertrophy 0.6%. Only pallor, pruritus, nail changes, hair changes, hyper-pigmentation, and coated tongue were more common among uremics than controls, with a statistically significant difference ($P < 0.05$) (Table 1).

Prevalence of each abnormality in HCV-positive vs. -negative adult uremics was as follows: xerosis in 48 patients (55.2%) vs. 41 (53.9%), pruritus in 29 (33.3%) vs. 29 (38.2%), nail changes in 30 (34.5%) vs. 27

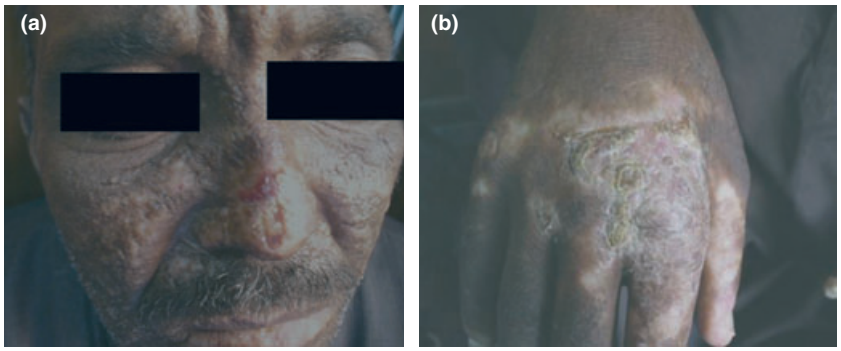

Figure 2 Pseudoporphyria involving the face (a) and hand (b)

Table 1 Prevalence of specific and non-specific cutaneous manifestations of uremia

Cutaneous manifestation	Adult uremics no. (%)	Controls no. (%)	χ^2	*P*
Specific				
APD	4 (2.5)	0 (0)	4.00	0.063
Bullous Dermatosis	1 (0.6)	0 (0)	0.991	0.503
NFD	0 (0)	0 (0)	–	–
CUA	0 (0)	0 (0)	–	–
Nonspecific				
Xerosis	89 (54.6)	77 (47.8)	1.488	0.134
Pallor	79 (48.5)	17 (10.6)	55.82	0.001**
Pruritus	58 (35.6)	35 (21.7)	7.585	0.004*
Nail changes	56 (34.4)	5 (3.1)	31.114	0.001**
Hair changes	55 (33.7)	20 (12.4)	44.013	0.001**
Hyper-pigmentation	29 (17.8)	3 (1.9)	23.086	0.001**
Coated tongue	26 (16)	4 (2.5)	17.482	0.001**
Ecchymosis	3 (1.8)	1 (0.6)	0.988	0.316
Gingival enlargement	3 (1.8)	1 (0.6)	0.988	0.316

*$P \leq 0.05$ (Significant); **$P \leq 0.001$ (Highly significant).
APD, acquired perforating dermatosis; NFD, nephrogenic fibrosing dermopathy; CUA, calcific uremic arteriopathy.

Table 2 Cutaneous disorders among HCV-positive vs. HCV-negative adult uremics

Cutaneous manifestation	HCV +ve uremics no (%)	HCV −ve uremics no (%)	χ^2	*P*
Xerosis	48 (55.2)	41 (53.9)	1.55	>0.05
Pruritus	29 (33.3)	29 (38.2)	1.57	>0.05
Nail changes	30 (34.5)	27 (35.5)	0.117	>0.05
Hyper-pigmentation	18 (20.7)	8 (10.5)	3.93	<0.05*
Ecchymosis	3 (3.4)	0 (0)	0.53	>0.05

*$P < 0.05$ (Significant).

Table 3 Cutaneous manifestations among diabetic vs. non-diabetic adult uremics

Cutaneous manifestation	Diabetic uremics no (%)	Nondiabetic uremics no (%)	χ^2	*P*
Xerosis	12 (63)	77 (53.5)	1.61	>0.05
Pruritus	10 (52.6)	48 (33.3)	3.84	<0.05*
APD	1 (5.2)	3 (2)	0.064	>0.05

*$P < 0.05$ (Significant).
APD, acquired perforating dermatosis.

Table 4 Prevalence of specific and non-specific cutaneous manifestations of uremia in uremic children vs. controls

Cutaneous manifestation	Uremic children no. (%)	Controls no. (%)	χ^2	*P*
Specific				
APD	0 (0)	1 (2.6)	1.146	0.469
Bullous Dermatosis	0 (0)	0 (0)	–	–
NFD	0 (0)	0 (0)	–	–
CUA	0 (0)	0 (0)	–	–
Nonspecific				
Xerosis	23 (53.5)	20 (52.6)	0.006	0.558
Pallor	8 (18.6)	8 (21.1)	0.076	0.500
Pruritus	8 (18.6)	7 (18.4)	0.000	0.606
Nail changes	15 (34.9)	0 (0)	12.449	0.001**
Hair changes	15 (34.9)	7 (18.4)	13.157	0.001**
Hyper-pigmentation	17 (39.5)	1 (2.6)	15.895	0.001**
Coated tongue	3 (7)	0 (0)	2.753	0.145
Ecchymosis	0 (0)	0 (0)	–	–
Gingival enlargement	0 (0)	0 (0)	–	–

**$P < 0.001$ (Highly significant).
APD, acquired perforating dermatosis; NFD, nephrogenic fibrosing dermopathy; CUA, calcific uremic arteriopathy.

(35.5%), hyper-pigmentation in 18 (20.7%) vs. eight (10.5%), and ecchymosis in three (3.4%) vs. 0%, with statistically significant difference only for hyper-pigmentation (Table 2). Comparing diabetics with non-diabetics, we found xerosis in 12 (63%) vs. 77 (53.5%), pruritus in 10 (52.6%) vs. 48 (33.3%), and APD in one (5.2%) vs. three (2%), with statistically significant difference only for pruritus (Table 3).

Other cutaneous disorders among uremic adults included contact dermatitis in eight (5%), onychomycosis in five (3.1%), vitiligo in three (1.8%), primary cutaneous amyloidosis in three (1.8%), tuberous sclerosis (TS) in two (1.25%), and SLE in one patient (0.6%). These manifestations were also found in controls with the following close frequencies respectively: three (1.9%), four (2.5%), four (2.5%), three (1.25%), 0 (0%) and 0 (0%).

Manifestations associated with complications of uremia and/or HD were one HCV-positive patient with actinic lichen planus, two patients had recurrent cellulitis, and three had recurrent macerated toe webs.

Among uremic children, 41 (95.5%) had mucocutaneous disorders; none had specific cutaneous manifestations of uremia, 36 (83.9%) had non-specific abnormalities (Table 4), and five (1.2%) had other problems. The most common non-specific cutaneous disorder among uremic children was xerosis [in 23 patients (53%], followed by hyper-pigmentaion in 17 (39.5%), nail changes in 15 (34.9%), hair loss in 15 (34.9%), pruritus in eight (18.6%), pallor in eight (18.6%), and coated tongue in

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Table 5 Cutaneous disorders in adults and children with uremia

Cutaneous manifestation	Adult uremics no. (%)	Uremic children no (%)	χ^2	*P*
Specific				
APD	4 (2.5)	0 (0)	1.076	0.389
Bullous dermatosis	1 (0.6)	0 (0)	0.265	0.791
NFD	0 (0)	0 (0)	–	–
CUA	0 (0)	0 (0)	–	–
Nonspecific				
Xerosis	89 (54.6)	23 (53.5)	0.017	0.515
Pallor	79 (48.5)	8 (18.6)	12.44	0.001**
Pruritus	58 (35.6)	8 (18.6)	4.504	0.023
Nail changes	56 (34.4)	15 (34.9)	0.204	0.393
Hair changes	55 (33.7)	15 (34.9)	0.21	0.382
Hyper-pigmentation	29 (17.8)	17 (39.5)	2.265	0.099
Coated tongue	26 (16)	3 (7)	9.28	0.003*
Ecchymosis	3 (1.8)	0 (0)	1.603	0.246
Gingival enlargement	3 (1.8)	0 (0)	1.603	0.246

*$P < 0.05$ (Significant); **$P < 0.001$ (highly significant).
APD, acquired perforating dermatosis; NFD, nephrogenic fibrosing dermopathy; CUA, calcific uremic arteriopathy.

three patients (7%). In the control group, there was xerosis in 52.6% of children, hyper-pigmentation in 2.6%, pruritus in 18.4%, hair loss in 18.4%, and pallor in 21.1%. A highly significant difference ($P < 0.001$) was found between the patient group of children and controls only in the prevalence of nail changes, hair changes, and hyper-pigmentation (Table 4).

Other cutaneous diseases in uremic children included pityriasis alba in five patients (11.6%) and drug induced erythroderma in one.

Pallor was more common among adults than children with uremia ($P < 0.001$), while hyper-pigmentation was more common among children ($P < 0.05$) (Table 5).

Discussion

CRF is one of the most common debilitating diseases occurring around the world. In Egypt, the incidence of CRF has been estimated to be 74 per million.[4] During the past few decades, obstructive/reflux nephropathy attributed to urinary schistosomiasis has constituted the major cause of CRF in young patients in Egypt. However, because of effective schistosomiasis control programs, this etiology is gradually giving way[5] to interstitial nephropathy, probably related to environmental pollution[6] and drugs.[4] The most common specific etiology for end stage renal disease in older patients is diabetes mellitus type II.[7]

In our study, 65 adult patients had CRF (39.8%), most often because of diabetes mellitus, followed by hypertension, repeated renal stones, chronic pyelonephritis, SLE, gout, and congenital polycystic kidneys. Congenital polycystic kidneys and SLE were reported in six children (13.9%), but the cause of renal disease was unknown in rest of the children.

CRF is known to be responsible for a variety of specific and non-specific mucocutaneous disorders.[8,9] Previous studies have found one or more cutaneous abnormalities among 79–100% of uremics.[9–12] In our study, the prevalence of cutaneous manifestations was 78.5% in adult uremics, and 95% in the children. We found specific manifestations in 3% of adults and none of the children. Specific cutaneous manifestations of uremia include APD, bullous dermatosis, nephrogenic fibrosing dermopathy (NFD), and calcific uremic arteriopathy (CUA). APD is a term used to describe the hyperkeratotic follicular papules associated with diabetes mellitus, CRF, liver diseases and internal malignancies,[13] in addition to the rare idiopathic APD.[14] In contrast to our population, APD was reported in eight (11%), and 21 (21%) of uremic patients in previous studies.[9,15]

Pseudoporphyria is a vesiculobullous disease similar to porphyria cutanea tarda, but without biochemical abnormalities in porphyrin metabolism, except when associated with CRF (plasma levels of porphyrin may be minimally elevated).[16] Pseudoporphyria results from increased oxidative stress, because of reduced levels of glutathione, and decreased subcutaneous oxygenation during HD that may facilitate frictional blistering.[17] Pseudoporphyria was found in one adult male patient (0.6%) in our study, whereas other investigators reported pseudoporphyria in 13% of 66 uremic adults.[18] Other specific cutaneous manifestations of uremia, such as NFD and CUA, were not found in our study group, possibly because these are rare disorders.[19,20]

We detected non-specific cutaneous manifestations of uremia in 65% of our adult patients and 85% of the children. Xerosis was reported to be the most common cutaneous abnormality in uremics (46–90%),[9,21–23] and 54% of our patients had xerosis (54.6% of adults and 53.3% of children). However, we also found xerosis in 47.8% of adult controls and 52.6% of control children, perhaps because the controls were examined during winter, when xerosis is common.

Pallor of the skin as a result of anemia has been reported as a hallmark of CRF and was found in 42.2% of our uremic patients (48.5% of adults and 18.6% children), vs. 12.6% of controls (10.6% of adults and 21% of children). Udayakumar *et al.* reported pallor in 60% of uremic patients.[9] The difference in prevalence of pallor in our adult patients vs. controls was highly statistically significant, but not for uremic children. The greater prevalence of pallor in adult vs. uremic children was highly

significant. The lower prevalence of pallor among uremic children could be explained by their regular receipt of erythropoietin, which is supplied free by the Egyptian Ministry of Health and Population (MOHP); the high prevalence of pallor among control children might be explained by the high prevalence of anemia in Egypt (46.6% of adolescents).[24]

Nail changes may reflect different systemic diseases. Absent lunula is an expected finding in elderly, anemic and/or malnourished patients.[25] We found absent lunula in 33.7% of our adult uremic patients and 37.2% of the children, nail striations in 26% of adults and 39% of children, and half-and-half nails in 24.5% of adults and 27.9% of uremic children. Saray *et al.* reported these manifestations in 32, 9, and 7.7% of uremic patients respectively.[26] Another study reported half-and-half nails in 21% of patients on HD.[9]

Sparse body hair and diffuse alopecia with dry, lusterless hair have been reported among uremic patients.[21] In our study, hair changes were found in 33.7% of adult uremics and 34.9% of the children, including hair loss and dry brittle hair. Similarly, Udayakumar *et al.* reported that 30/100 uremic patients had sparse body hair, 11 had diffuse alopecia and 16 had dry, lusterless hair.[9] It has been proposed that dry, lusterless hair is because of decreased secretion of sebum.[27] Singh *et al.* reported a 30% prevalence of dry hair in CRF patients not undergoing dialysis.[28] Comparing patients and controls, the difference was found to be significantly higher in uremics. The role of anemia in induction of hair loss among uremics should not be neglected.

Pruritus, the most characteristic and annoying cutaneous symptom of CRF,[11,29,30] has a prevalence range of 19 to 90% [11] We found pruritus in 35.6% of uremic adults and 18.6% of uremic children; 68.2% of the combined population of them also suffered from xerosis. Comparing adult patients and controls, the difference was found to be significantly higher in uremics. In addition to xerosis, pruritus has been associated with hyperparathyroidism; increased serum levels of magnesium, calcium and phosphate, aluminum, and histamine; proliferation of nonspecific enolase-positive cutaneous sensory nerves; hypervitaminosis A; iron deficiency anemia, and erythropoietin deficiency.[21,31]

In patients with uremia, diffuse hyper-pigmentation of sun-exposed skin is attributed to increased melanin in the basal layer and superficial dermis as a result of failure of the kidneys to excrete beta-melanocyte-stimulating hormone.[32] We found hyper-pigmentation in 17.8% of adults and 39.5% of children; other authors have reported a prevalence of 20–22%.[11,21] However, a study conducted on Indian patients with uremia found hyper-pigmentation in 43%.[9] The differences in reported prevalence could be attributed to differences in the study populations. Hyperpigmentation may have been more common in our uremic children than adults because the children had more sun exposure.

Udayakumar *et al.* observed coated tongue in 11% of uremics.[9] Coated tongue was found in 16% of our adult uremics and 7% of children; the difference between the prevalence in uremics and controls was significantly higher only for the adult group. A low prevalence of gingival hypertrophy was found in our study (1.5% of adult uremics), probably because none of our patients received cyclosporine or calcium channel blockers which are the main causes of this problem.[33,34] This disorder may be familial in our population.[35]

Ecchymosis was found in 1.8% of our adult uremics and none of the uremic children. Other studies have reported ecchymosis in 9% and 20% of uremic patients respectively.[9,27] Defects in primary hemostasis such as increased vascular fragility, abnormal platelet function, and the use of heparin during HD are the main causes of ecchymosis.

Several non-specific manifestations of uremia have been reported in HCV-positive and chronic liver disease patients including hyper-pigmentation, pruritus, nail changes, and ecchymosis.[23] Hyper-pigmentation was more common among our HCV-positive than -negative adult uremics (20.7% and 10.5% respectively). To our knowledge, there have been no previous studies comparing the prevalence of cutaneous disorders in HCV-positive and -negative uremics.

Some of the non-specific manifestations of uremia have been found in diabetics, including xerosis, pruritus, and APD.[23] Pruritus was more common in our group of diabetic than non-diabetic patients (52.6% and 33.3% respectively). In the study by Udayakumar *et al.*, nearly all cutaneous manifestations were more common among their diabetic patients.[9]

On comparing manifestations in adults and children with uremia, all were of similar prevalence except pallor and hyper-pigmentation. Cutaneous manifestations of the underlying disease included two cases of TS (adult uremics). TS has been reported to be associated with renal hamartoma, which can precipitate renal failure.[36] We also noted malar rash, photosensitivity, hair loss, and striae distensae in one adult female patient with CRF because of SLE. SLE has been reported to cause CRF, related to focal, membranous, or proliferative glomerulonephritis.[23]

In summary, most of our patients had at least one cutaneous disorder. However, the prevalence of some of these manifestations (xerosis, ecchymosis, and gingival hypertrophy) was not significantly different than in the control populations of otherwise healthy adults and children. Thus, they should be considered coincidental manifestations rather than non-specific cutaneous manifestations of

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uremia. We should note that our patients were not matched in all reported manifestations. Hyper-pigmentation was significantly more common in HCV-positive than -negative uremics, and diabetic uremics had more frequent pruritus than non-diabetics, reflecting the impact of the specific population studied. The diseases associated with uremia should be considered in interpreting these data. Larger randomized studies are needed to determine the accurate prevalence of cutaneous manifestations in Egyptian uremic patients. Governmental support to insure adequate erythropoietin supply to uremics is recommended. Erythropoietin administration not only leads to improvement of the general condition, but also reduces the prevalence of pallor, pruritus, hair loss, and nail changes among uremics.

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