CUTANEOUS MANIFESTATIONS OF CHRONIC RENAL FAILURE AND RENAL TRANSPLANTATION

DISSERTATION SUBMITTED FOR AWARD OF

M.D. DEGREE BRANCH XII-A

DERMATOLOGY, VENEREOLOGY AND LEPROLOGY

APRIL 2012

TIRUNELVELI MEDICAL COLLEGE

THE TAMIL NADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU.

CERTIFICATE

This is to certify that this dissertation entitled **"CUTANEOUS MANIFESTATIONS OF CHRONIC RENAL FAILURE AND RENAL TRANSPLANTATION"** submitted by **Dr. R. Suganya Gnanadeepam,** to the faculty of Dermatology, Venereology and Leprology, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD Degree - Branch XII-A - Dermatology, Venereology and Leprology is a bonafide research work carried out by her under our direct supervision and guidance.

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I, **Dr. R. Suganya Gnanadeepam,** declare that the dissertation titled **"CUTANEOUS MANIFESTATIONS OF CHRONIC RENAL FAILURE AND RENAL TRANSPLANTATION"** has been done and prepared solely by me. This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD Degree - Branch XII-A - Dermatology, Venereology and Leprology examination to be held in April 2012.

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ACKNOWLEDGEMENT

It gives me great pleasure to acknowledge all those who guided, encouraged and supported me in all the successful completion of my dissertation.

I wholeheartedly thank the respected Dean **Dr. M. Manoharan M.S.,** Tirunelveli Medical College for having permitted me to carry out this study at Tirunelveli Medical College.

First and foremost I wish to thank **Dr. P. Nirmaladevi, M.D.,** Prof. & HOD, Dept. of Dermatology, Venereology and Leprology, for having guided me throughout the period of this work.

I wish to thank **Dr.V.Ramasubramaniyam**, D.M., Prof. & HOD, Nephrology department for his valuable suggestions and guidance throughout the period of this study. I also thank the assistant professors in the department of Nephrology for their expert guidance.

My sincere thanks to **Dr. K.Dhanalakshmi M.D.,** Assistant Professor for having guided me throughout the period of this work.

I owe my heartiest thanks to my Assistant Professors **Dr. S.Judithjoy M.D., and Dr. P. Sivayadevi M.D.,** for their valuable suggestions, support and expert guidance throughout the work.

I owe my heartiest thanks to my Associate Professor **Dr. M. Selvakumar M.D.,** and Assistant professor **Dr. R. Karthikeyan M.D.,**

for their valuable suggestions, support and expert guidance throughout the work.

I owe my sincere thanks to all those patients who participated in the study for their co-operation which made this study possible.

CONTENTS

INTRODUCTION

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The kidney and the skin are the two large networks of the body with their abundant blood supply, far in excess of their nutritional demands, the former for the constancy of the milieu interior and the latter maintaining mainly homeostasis. No wonder therefore, that they share many diseases and reflect mutually one another's pathology which should be made use of by the clinician. Scientific and technologic improvements during the second-half of the 20th century have provided renal replacement therapy as a life sustaining option for many individuals who otherwise might have died. In each and every year of the last decade, the number of individuals with ESRD (end stage renal disease) has grown approximately from 20 to 30,000 per year.

Cutaneous examination of patients with ESRD has shown that 50 – 100% of patients have at least one dermatologic condition. In addition to ESRD, uraemia and conditions associated with renal replacement therapy are fraught with numerous and often, relatively unique cutaneous manifestations.

AIMS OF THE STUDY

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1. To study the various cutaneous manifestations and their incidence in patients with chronic renal failure.
2. To study the agewise and sexwise incidence of the individual cutaneous manifestation.
3. To study the incidence of cutaneous manifestations in renal transplant recipients.
4. To study the incidence of cutaneous manifestations of associated systemic disorder that may contribute to chronic renal failure.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Definition:

Chronic renal failure is defined as the irreversible, substantial and usually longstanding loss of renal function causing ill health usually referred to as uraemia.

End stage renal disease represents a clinical state in which there is an progressive and irreversible kidney dysfunction of a degree sufficient to render the patient permanently dependent upon renal replacement therapy (dialysis or renal transplantation) in order to avoid life threatening uremia.

Uraemia is the clinical and laboratory syndrome reflecting dysfunction of all organ systems as a result of untreated or under treated acute or chronic renal failure.[1]

Prevalence and incidence :

The true prevalence of chronic renal failure is unknown because many patients are asymptomatic or its presence has not been recognized. The prevalence of end-stage renal disease will vary from country to country and will depend upon the incidence of particular disease and the availability and capacity of dialysis and transplant programs.

There are real differences in the incidence of end-stage renal disease according to age, gender and race. In western countries, the incidence is lowest

in children and highest in the elderly between 30 and 60 years and is slightly higher in males than females.[2] The higher prevalence in developing countries may be due to higher incidence of infections leading on to, as well as genetic and environmental predisposition and socio-economic factors and access to medical care.

Etiology:

Chronic renal failure may be caused by any condition, which destroys the normal structure and function of the kidney. There are many causes of chronic renal failure, for most renal diseases can eventually lead to a significant reduction in function.[3]

Review of the 2007 report revealed diabetes mellitus is now responsible for close to 50% of new cases of ESRD. Hypertension and cystic or hereditary kidney diseases were the next most common causes.

Etiology of chronic renal failure :[3]

A) Congenital and inherited diseases

1. Polycystic kidney
2. Alport's syndrome
3. Congenital hypoplasia

B) Vascular diseases

1. Arteriosclerosis (Hypertension)
2. Vasculitis (Polyarteritis nodosa, Systemic lupus erythematosus, Scleroderma)

C) Glomerular diseases

1. Proliferative Glomerulonephritis
2. Crescentic Glomerulonephritis
3. Membranous Glomerulonephritis
4. Mesangiocapillary Glomerulonephritis
5. Glomerulosclerosis
6. Diabetic Glomerulosclerosis
7. Secondary Glomerulonephritis (Polyarteritis nodosa, Systemic lupus erythematosus, Systemic sclerosis, Wegener's granulomatosis, Amyloidosis)

D) Interstitial diseases

1. Chronic pyelonephritis
2. Vesicoureteric reflux
3. Tuberculosis
4. Analgesic nephropathy
5. Nephrocalcinosis
6. Schistosomiasis
7. Unknown origin

E) Obstructive uropathy

1. Calculus
2. Retroperitoneal fibrosis
3. Prostatic hypertrophy
4. Pelvic tumors

F) Rare causes < 1% of the cases

1. Alport's syndrome
2. Hemolytic Uraemic Syndrome
3. Metabolic disorders

Pathophysiology of Chronic Renal Failure:[4,6]

The exact pathogenesis of the clinical syndrome of uraemia is unknown. The pathophysiology of uraemic syndrome is attributable to accumulation of products of protein metabolism and loss of other renal functions such as fluid and electrolyte homeostasis and synthesis of certain hormones (1,25 – dihydroxy cholecalciferol).[5] The various uremic toxins[7] are byproducts of protein and aminoacid metabolism such as urea, guanido compounds, methyl guanidines, urates, hippurates, end-products of aromatic amino acid metabolism and other nitrogenous substances, inhibitors of ligand protein binding, glucurono conjugates and inhibitors of somatomedin and insulin action. The pathophysiology has been explained based on two hypothesis. They are as follows:

1. **Intact nephron hypothesis :** That is most nephrons are non-functioning, while the remaining few function normally.
2. **Trade off hypothesis** : It is the concept that adaptations arising in chronic renal failure may control one abnormality, but only in such a way as to produce other changes characteristic of uraemic syndrome. The best

example of 'trade off' is increase of parathormone secretion essential for increased fractional excretion of phosphate.

When kidney function is entirely normal, GFR (glomerular filtration rate) can be augmented by 20 – 30% in response to the stimulus of a protein challenge. As GFR declines to levels as low as 30% of normal, patients may remain asymptomatic with only biochemical evidence of the decline in GFR. As GFR falls to below 30% of normal, an increasing number and severity of uremic clinical manifestations and biochemical abnormalities supervene. When GFR falls below 5 – 10% of normal, continued survival without renal replacement therapy become impossible.[7]

Clinical presentation and assessment:

In the early stages of the disease, the patient may be asymptomatic and the existence of renal insufficiency may be revealed incidentally subsequently because of the widespread effects of progressive renal failure, symptoms and signs are referable to almost every system. None of these symptoms alone is indicative of underlying renal disease, but the occurrence of more than one would suggest the possibility of renal failure.

Indications of chronicity of renal failure :[2]

1. **Symptoms** : fatigue, breathlessness, anorexia, nausea, vomiting, hiccoughs, pruritus, dry skin, bone pain, nocturia, muscle cramps, drowsiness, seizures, amenorrhoea, decreased libido.

2. **Signs :** Pallor, pigmentation, increased respiratory rate, hypertension, increased jugular venous pulsation, pedal edema, pulsus paradoxus (pericardial tamponade), excoriations due to pruritus, brown nails, xerosis, paresthesia, absent reflexes.

3. **Investigations** : Complete hemogram shows normochromic normocytic anemia, increased blood urea and serum creatinine, serum electrolytes showing hyperkalemia, hyperphosphatemia, hypocalcemia, hyponatremia and low serum bicarbonate, serum proteins showing hypoalbuminemia, urinalysis shows proteinuria, total 24 hrs urine collection for estimating urinary proteins and creatinine clearance, urine sediment findings showing RBCs, RBC cast, WBC cast, blood sugar, hepatitis B & C viral detection, Blood VDRL, Anti nuclear antibodies, double stranded DNA, c-ANCA, p-ANCA, serum complements and imaging studies such as plain X-ray abdomen to detect radio-opaque stones or nephrocalcinosis, renal ultrasonogram showing small kidneys usually, CT-Scan, MRI, radio-nuclide scan, intravenous pyelogram, voiding cysto-urethrogram and renal biopsy.

Systemic effects of uraemia:[6]

The effects of uremia are diverse and almost every system is affected. They include cardiovascular, pulmonary, hematologic, neuromuscular, gastrointestinal abnormalities, endocrine and metabolic disturbances and the most clinching dermatologic abnormalities.

Dermatologic abnormalities :

Reports indicate that 50 – 100% of patients with end-stage renal disease have atleast one cutaneous disorder.[7] The abnormalities affecting the skin may be manifested as :

I. Specific cutaneous manifestations of chronic renal failure.

II. Skin manifestations due to renal transplantation.

III. Skin manifestations due to treatment (drugs & dialysis) of renal failure (not included in this study).

I. Specific cutaneous manifestations of CRF:

Primary dermatological manifestations associated with uremia are :

A. Skin changes :

1**. *Pruritus :***

Uraemia is the most common metabolic cause of pruritus and pruritus is the most common and troublesome cutaneous manifestation of uraemia.

Incidence :

Significant pruritus affects 15 – 49% [1] of patients with chronic renal failure. Pruritus more commonly begins approximately 6 months after initiation of dialysis and typically increases with the length of time on dialysis. It has no consistent association with age, sex, race or precipitating disease. Pruritus may be episodic or constant, localized or generalized and mild or severe. The axillae, scalp, nose and ears are the most frequent areas of pruritus. When localized, the forearms and upper back are predominantly affected.[2] Pruritus

often worsens at bedtime. Pruritus is not a feature of acute renal failure. For about 25% of the patients with pruritus, it occurs only during or soon after dialysis, and it is more severe at these times for an additional 42% of the patients.[8]

Etiopathogenesis :

Several researchers have concluded that end stage renal disease pruritus is multifactorial.[9,10] Some proposed causes of uraemic pruritus include the following :

- Xerosis – In a study by Kato (2000),[11] the skin water content was quantified by using a hygrometer to determine the amount of high frequency conductance in the skin surface. Final analysis concluded that dialysis patients have less water content in their stratum corneum of their skin, but there was no association with pruritus severity
- Decreased transepidermal elimination of pruritogenic factors
- Hyperparathyroidism – results in hypercalcemia and skin calcifications which in turn stimulates skin mast cells with consequent release of histamine.[12]
- Hyperphosphatemia
- Hypervitaminosis A[13] – elicit xerotic and pruritic skin in uremic individuals not receiving dialysis. Certain patients have been shown to exhibit increased levels of retinol.[14]

- Increased dermal mast cell proliferation and elevated histamine levels[15] – mast cells proliferate in renal failure and are known to function as a storage and release site for histamine. Mast cell histamine release plays an important role in the pathogenesis of various allergic conditions. The mast cell proliferation theory was refuted when ultra violet light therapy was shown to decrease the number of mast cells without a corresponding decrease in pruritus.
- Increased serotonin levels[16]
- Uraemic sensory neuropathy[17] – Johannson, Hlliges and stahle – Backdahl (1989),[18] identified and implicated a fine neuron specific immunoreactive nerve fibre laden with enolase, an acidic enzyme found in neurons, neuroendocrine cells and tumours derived from them. This discovery was considered the probable cause for end stage renal disease pruritus since the immuno-histochemical stains that demonstrated these fibres were not evident in non-pruritic end stage renal disease patients.
- Middle molecule theory : suggests the retention of unidentified pruritogenic substances that accumulate in the dialysis patient since they are poorly dialyzable as a result of their molecular size of 300 – 12,000 dalton. Beta2 microglobulin, advanced glycosylation end products and parathyroid hormones are the middle molecules that have been evaluated, but their role is uncertain.

Clinical presentation

i. Normal or xerotic skin

ii. Excoriations from scratching

iii. Prurigo nodularis

iv. Lichen simplex chronicus

Treatment of pruritus :

i) Exclude other clinical causes such as scabies and other non-end stage renal disease causes of pruritus and treat it.

ii) Regular daily application of emollients reduce xerosis, that contribute to pruritus.

iii) Augmentation of dialysis efficacy[15,19]

iv) Normalization of serum calcium and phosphate levels

v) Parathyroidectomy

vi) UVB therapy[20] – may reduce the epidermal vitamin A content [14], suppress histamine releasing factors in sera of uremic patients and induce formation of photoproducts with antipruritic effects.

PUVA causes reduction in dermal histamine.[21] These form the mainstay of therapy.[14] Reduction of skin phosphorous to normal values, possibly through an effect of vitamin D.[22]

vii) In dialysis, lowering the Mg concentration of the dialysate.[23]

viii) Cholestyramine (5 g bd)[24] – it binds uric acid

ix) Oral activated charcoal[26] (6g daily x 8 weeks). By chelation in the gut of a circulating toxin.[25]

x) Heparin infusion[27] is useful in reducing uraemic solutes in blood.

xi) IV lidocaine 100 mg – was effective in relieving uremic pruritus for upto 24 hrs in some patients.[28] Topical anesthetics such as pramoxine have been tried.

xii) Nicergoline 30 mg orally Qid + 5 mg IV at dialysis for 2 weeks (dopamine agonist)[29]

xiii) Ketotifen 1 – 2 mg bd (mast cell stabilizer)[30]

xiv) Transcutaneous electrical needle stimulation, a modified acupuncture technique[31] – lateral inhibition impulses halt itch.

xv) Topical capsaicin 0.025%, an irritant cream that depletes substance P in peripheral sensory neurons,[32] thereby suppressing itch sensation.

xvi) Cimetidine[33]

xvii) Erythropoietin – reduction of plasma histamine concentration.[34]

xviii) Opiate receptor antagonists – naloxone and naltrexone[35] are helpful, as endogenous opioids are implicated in the causation of pruritus.

xix) Mexiletine[35]

xx) Oral evening primerose oil[36] and topical tacrolimus[37] (0.1% for 2-6 weeks).

2. Xerosis / Ichthyosis:

Cutaneous dryness is the most frequent cutaneous abnormality in uremic patients. Significant xerosis occurs for unknown reasons in 50 – 75% [39] of the dialysis population. When xerosis is associated with desquamation it can cause an ichthyosis like appearance. The extensor surfaces of legs and arms are most severely affected with large dark scales whereas over the abdomen, the scales are whitish to translucent and somewhat smaller and finer. The scalp is frequently involved with pityriasic desquamation. The flexor surfaces, the axillae and the ante-cubital and the popliteal fossae are relatively spared. Some patients may develop acquired ichthyosis. Patients with dry skin may also show signs of abnormal keratinization or excessive production of keratin such as follicular keratosis, onychodystrophy and plantar hyperkeratosis occur even without concomitant xerosis. Xerosis generally appears before initiation of dialysis therapy and seems to be little influenced by dialysis.[38]

Etiopathogenesis of Xerosis :

The pathogenesis is poorly understood .Factors implicated are :

i. Impairment of exocrine sweat gland secretion with decreased sweating.[39,40]

ii. Decrease in water content in the epidermis

iii. Hypervitaminosis A – plasma and skin content of Vitamin A and its carrier, retinol binding protein are increased in uremic patients[38]

iv. Increased plasma levels of parathormone with secondary hyperparathyroidism.

v. Disorder in vitamin D metabolism

vi. Uremia induced alteration in corneocyte maturation.

Pathology :

A reduction in the size of eccrine glands[40] as well as atrophy of sebaceous glands.[39]

Electron microscopy:

Increased number of corneal cell layers with desmosomal junctions present up to the skin surface. Increased number of keratinosomes showing several degrees of alterations.[38]

Treatment :

There is no specific treatment for uremic xerosis and ichthyosiform dermatoses. Emollients may give symptomatic relief.

3. Pigmentary alterations :

A multitude of uremia related changes are responsible for the pigmentary alterations.

i. Pallor – it was common before the widespread use of erythropoietin. It is attributed to the significant anemia (reduced erythropoiesis and increased hemolysis)

ii. Sallow yellow discolouration is attributed to retained urochromes and carotene in the epidermis and subcutaneous tissue.

iii. Diffuse hyperpigmentation in sun exposed areas results from an increased deposition of melanin in the basal layer of the epidermis and superficial dermis. Due to an increase in poorly dialyzable β melanocyte stimulating hormone,[41,42] there is increased melanogenesis with resultant deposition of melanin.

iv. An increased prevalence of hyperpigmented macules on the palms and soles has been reported in a large series of uremic patients.[43]

4. Uraemic frost :

First described by Hirschprung in 1865 uremic frost[38] is rarely seen today because of early dialytic intervention.

It is a classic manifestation of CRF consisting of white amorphous deposits on the skin of the face, commonly on beard area, neck and trunk. It dissolves readily when challenged by a drop of water.

Pathogenesis :

When the blood urea nitrogen 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.[42]

5. Perforating disorders:

Perforating disorders are seen in 4 – 10% of patients with CRF . They may present as four primary perforating disorders:

i. Kyrle's disease

ii. Perforating folliculitis

iii. Reactive perforating collagenosis

iv. Elastosis perforans serpiginosa or as

v. Perforating disorder secondary to uremic follicular hyperkeratosis.

Pathogenesis : Etiology unclear. Proposed to be

- Local trauma (scratching)
- Dermal microdeposition of substances such as uric acid and calcium pyrophosphate or hydroxy apatite followed by an inflammatory response

and connective tissue degradation, which allows transepidermal elimination of degraded dermal deposits.[44,45]

- Dysregulation of Vitamin A or Vitamin D metabolism
- Abnormality of collagen or elastic fibres.
- Diabetic microangiopathy.

i. Kyrle's disease :

It has been widely reported to occur in CRF. Josef Kyrle first reported it in 1916 and called it hyperkeratosis follicularis et parafollicularis in cutem penetrans.[46] It has a tendency to affect blacks and it has overwhelming coincidence with diabetes mellitus and CRF.

Clinical criteria[46] described by kyrle are :

- Chronic generalized papular eruption of size 2 – 8 mm in diameter with hyperkeratotic cone – shaped plugs present over extensor aspect of extremities.
- Asymptomatic , follicular or extra follicular lesions.
- Hyperkeratotic verrucous plaques.
- Do not involve mucous membrane, palmar or plantar surfaces.

Histopathological criteria :[47]

- Keratotic plug fills an epithelial invagination
- Focal parakeratosis

- Basophilic cellular debris not staining with elastic tissue stains present within the plug.
- Abnormal keratinization of all the epidermal cells including the basal cells is present in atleast one region deep to the plug

There are numerous reports in literature of various studies in which skin lesions satisfying the above criteria having occurred in renal failure.[46,48,49,50]

Thus Kyrle's disease appears to have a definite association with chronic renal failure.

Treatment:[51]

- Topical keratolytics
- Topical and intralesional glucocorticoids
- Topical Tretinoin
- Topical 5 – FU
- UVB[44,52]
- PUVA[44,52]
- Cryotherapy
- Systemic isotretinoin
- Control of serum phosphorous level
- Rarely cured after renal transplantation[53]

ii. Perforating folliculitis:

It was in 1968 that Mehregan and Cosky[54] first reported perforating folliculitis in 25 patients.

Clinically, perforating folliculitis has the following features:

- Elevated erythematous follicular papules with central plugs of keratinous material over the hairy areas of arms, forearms, thighs and legs.
- Usually asymptomatic, may be mildly pruritic.

Histopathological features:[55]

- Widely dilated hair follicles plugged by a thick mass of orthokeratotic and parakeratotic material.
- A curled up hair usually cut across is present.
- Follicular epithelium is disrupted with areas of perforation usually above the level of sebaceous gland, caused by the hair.
- At sites of perforation, dermis shows a focal inflammatory infiltrate containing degenerated collagen and degenerated elastic fibres, which have lost their orceinophilic properties and stain brightly eosinophilic. However there are no increases in elastic fibres.

Lesions with both clinical and histopathological criteria have been reported to occur in renal failure.[56,57,58]

iii Reactive perforating collagenosis :[55]

The acquired form of this inherited disorder clinically characterized by umbilicated discrete papules usually over sites of trauma and histologically by

cup shaped areas of depression with parakeratotic keratin, basophilic collagen and perforation through which collagen is extruded has been reported to occur in chronic renal failure.[59] The nosological relationship between reactive perforating collagenosis and the acquired perforating dermatosis of renal failure still remain uncertain.[60]

Pathogenesis :

Transepidermal elimination of histochemically altered collagen.[55]

iv. Elastosis perforans serpiginosa :[61]

Anecdotal reports of this condition with renal failure are found.

v. Uraemic follicular hyperkeratosis :[62]

It, described by Garcio and Bravo et al, combines features of Kyrle's disease and perforating folliculitis[55] occurs quite commonly in patients with renal failure and patients on dialysis.

Clinical features :

Follicular papules with central keratinous plug, which may coalesce to form verrucous plaque present over extensor surfaces of lower extremities.

Histopathology :

Resemble perforating folliculitis with the perforation in the infundibular region in small lesions and at the base in larger lesions. Since the distinction between these dermatoses is not clear-cut and there is considerable overlap especially in patients with renal failure, it has been proposed to group them under a common title of acquired perforating disorder.[63,64]

Treatment :

Topical keratolytics, topical glucocorticoids, topical retinoic acid, topical 5-Fluorouracil, UVB, control of serum phosphorus level .

vi. Metastatic calcification :

It is a frequent complication of chronic renal failure and occurs when the calcium phosphate product exceeds the critical value. Abnormally elevated levels of parathormone may trigger deposition of calcium pyrophosphate in the dermis, subcutaneous fat or arterial walls. Vascular calcification is very common in patients with long term chronic renal failure and is seldom symptomatic. Rarely, calcium deposited gives rise to important clinical categories of calcinosis cutis and calciphylaxis.

i. Calcinosis cutis :

It is a term used to describe a group of disorders in which calcium deposits are found in the skin.[65] Virchow initially described it in 1855. Calcinosis cutis is seen in the setting of chronic renal failure occurring with hyperparathyroidism.

Pathogenesis :

Multiple factors in calcium metabolism are affected. Hyperphosphatemia due to decreased renal clearance occur relatively early. Hypocalcemia occurs as a direct result of their hyperphosphatemia and is worsened by renal failure induced vitamin D deficiency. As a compensatory measure, excess parathyroid hormone is produced. This augmentation of parathyroid hormone results in an

increase in calcium and phosphate mobilization and an elevated solubility product and subsequently the formation and precipitation of calcium salts.

Clinical features :

Hard papules, nodules or plaques, which typically occur around large joints, may produce a chalky discharge. This occurs in sub-acute fashion, without livedo, or ischemic pain.

Histopathology:

Granules and deposits of calcium are seen in the dermis with or without a surrounding foreign body giant cell reaction. Massive calcium deposits may be located in the subcutaneous tissue. In areas of necrosis, calcium deposition is frequently found within the walls of small and medium sized blood vessels. Calcium deposition may be confirmed by Von kossa and Alizarin red stains .

Treatment :

Medical :

a) Dietary measures : Restriction of dietary phosphates and calcium, consumption of ketogenic diet including free fatty acids, which causes accumulation of keto acids, metabolic products of fatty acids that result in decreased pH and thus preventing crystallization.

b) Magnesium or aluminium antacids may be effective phosphate binders in patients with hyperphosphatemia. However, use in patients with renal insufficiency may result in magnesium or aluminium toxicity.

c) Probenecid causes increased renal phosphate clearance and colchicines (1-1.2 mg/day) act by reducing inflammation associated with pruritus.

d) Intralesional corticosteroid – antiinflammatory and antifibroblastic activity.

e) Sodium etidronate and diphosphonates reduce bone turnover and inhibit the growth of ectopic hydroxyapatite crystals. On prolonged treatment paradoxical hyperphosphatemia may result.

f) Warfarin

g) Calcium channel blockers – diltiazem (120 mg/day) causes reduction in mineral content of calcified tissues.

Surgery *:* Excision

Indications:

i. Pain

ii. Recurrent infections

iii. Ulcerations

iv. Functional impairment

Complications :

Pain, paraesthesia, ulceration, infection, cosmetic disfigurement, mechanical compromise, restricted mobility, vascular occlusion resulting in gangrene.

Prognosis : Excellent

ii. Calciphylaxis :

Synonym : Calcific uremic arteriolopathy

It is a highly morbid syndrome characterized by rapidly progressive calcification of small and medium sized blood vessels. Bryant and White first reported it in association with uremia in 1898. It is a rare, serious complication of chronic renal failure.[66] The mechanism of experimental calciphylaxis in nephrectomised rats was described by Hans selye, physiologist in 1962.[67] He was the first to coin the term calciphylaxis to characterize this enigma.

Pathogenesis :

Factors implicated are :

- Chronic renal failure
- Hypercalcemia
- Hyperphosphatemia
- Elevated calcium - phosphate products[68]
- Secondary hyperparathyroidism[69]

Selye demonstrated that a series of events might be necessary for the formation of calciphylaxis using a rat model. He defined calciphylaxis as a condition of hypersensitivity induced by a set of sensitizing agents in which calcinosis occurred only in those subsequently subjected to a group of challenges and only after a critical lag time. Experimental sensitizing events and agents included nephrectomy and exposure to parathyroid hormones and vitamin D, substances used as challenges - included egg albumin and metallic salts. Calciphylaxis was the end result.

Histopathology:

Calcification within the media of small and medium sized arterioles with intimal hyperplasia. A mixed inflammatory infiltrate frequently occurs. Subcutaneous calcium deposits with panniculitis and fat necrosis may sometimes be found. Vascular microthrombi are frequently evident.

Clinical features :

It may present as a violaceous pattern of livedo reticularis found primarily on the trunk and extremities which results in extensive cutaneous necrosis.

Treatment:[70]

Medical:

- Aggravating factors should be addressed and triggering factors should be eliminated
- Dietary alteration (reduction of phosphorous rich foods), non calcium containing phosphate binders (Sevelamer or Lanthanum carbonate), reduction of dialysate calcium concentration
- Prevention of superimposed infections with wound care and debridement of gangrenous tissue, antibiotics and hyperbaric oxygen
- Pain management

Surgical :

Total or subtotal parathyroidectomy[71,72] with auto transplantation

Complications :

Ranges from moderate interference of activity to death

- Non healing ulcers and cutaneous gangrene
- Amputation
- Sepsis
- Gastrointestinal hemorrhage, infarction and organ failure (heart, brain)

Prognosis : Grave[70]

Mortality rate : 60 – 80% [71] particularly when the trunk is involved

Cause of death:

- Sepsis
- Organ failure

Exceptional cases of metastatic soft calcifications presenting as large tongue masses[73] or perforating papules[74] have been reported.

7. Purpura:

Purpura, petechiae, ecchymoses are due to mild thrombocytopenia or more marked platelet dysfunction and increased vascular fragility[42] or associated poor quality collagen. It is partly reversed by dialysis.

8. Gynecomastia:[75] can occur as a complication of hemodialysis

9. Vascular disorders :

i. *Microangiopathy* – severe microangiopathy has been revealed in skin biopsies from 75% of patients with chronic renal failure [76], due to reduction of vascular endothelial growth factor.

Histopathology:

- Endothelial cell activation and / or necrosis
- Basement membrane zone thickening
- Reduplication of the basal lamina involving both venules and arterioles (tend to regress after successful renal transplantation).

ii. Skin necrosis – Proximal skin necrosis and / or peripheral gangrene may occasionally occur in uremic patients.

Proximal skin necrosis can involve the trunk, shoulders, buttocks or thighs. Lesions usually spread rapidly covering large areas and have a bad prognosis.

Distal skin necrosis of the fingers and toes can lead to digital gangrene but the disease is usually self-limiting

9. Poor wound healing is due to decreased collagen turnover caused by chronic acidosis

10. Restless leg syndrome is characterized by burning, painful paresthesia of the dorsal or plantar surface of the feet and it is due to peripheral neuropathy[82]. Treatment is with Dopamine agonists, Gabapentin and Opioids.

B. Oral mucosal changes :

Jaspers has reviewed oral changes, which occurs in uremia.[77] The lesions described are :[78]

- Stomatitis is due to chemical burn caused by ammonia released by bacteria due to the increased content in the salivary secretion. The other causes are candidial infection and impaired immunity.[78]
- Ulcerative stomatitis can occur anywhere in the mouth.
- Hemorrhagic lesions
- Hyperkeratosis occurs in long standing renal failure due to the effect of toxic chemicals in the oral mucosa.[77]

C. HAIR ABNORMALITIES: [38]

They are

- Loss of hair on forearms and legs
- Diffuse alopecia of scalp[79]
- Fine dry and brittle hair
- Trichocalasia and trichorrhexis nodosa
- Hair discolouration

Microscopic examination of hair in uremia shows hair in telogen phase. With scanning electron microscope, uraemic hair shows irregular diameter, flattening and twisting of its shaft and mild cuticular abnormalities.

D. Nail Changes:

It occurs in patients with uremia as well as in those undergoing dialysis. Nail changes include:[80]

i. Half and half nail

ii. Brown nail bed arc

iii. Mee's lines

iv. Muercke's lines

v. Terry's lines

i. Half and half nail:

Synonym : Lindsay's nails.[81]

Bean first described half and half nails in 1953. Although not pathognomonic of renal failure, they occur in 33% [81] of patients with azotemia and 40% of those 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 colour from reddish to brown. Although the condition has been observed in toenails, it is more commonly seen in fingernails.

Causes :[80]

- deposition of melanin in the nail plate due to stimulation of matrix melanocytes or pink due to normal nail bed.
- Increase of capillaries and thickening of their walls.
- Proximal half of the nail appears white because of edema of the nail bed.

Pigment is more visible distally than proximal because of looser attachment of the distal nail plate to the nail bed. The nail changes do not correlate with serum calcium, phosphorus or bicarbonate.[83] It is the **most useful onychopathologic indicator of renal failure.**

ii. Brown nail bed arc :[84]

Described by Stewart and Raffle as a brown arch affecting the distal part of the finger nail bed, just proximal to the point of separation of the nail from its bed.

Cause is due to lipochromes, which are fat soluble pigments occurring in natural fat.(eg: lutein, carotene)

iii. Mee's line:

Single or multiple transverse white bands, which moves with nail growth. It is due to disturbance of nailgrowth at nail matrix.

iv. Muercke's lines:

Double white transverse horizontal lines that represent an abnormality in the vascular bed of the nail. These lines do not move with nailgrowth.

v. Terry's nails:

These nail changes are fairly specific to chronic renal failure, but may be encountered in patients with chronic liver disease and in healthy individuals. It has been applied to nails in which only the distal 20% is normal, which occurs due to decreased vascular supply to nailbed. Here the proximal 80% of nail is normal and distal end is brownish black.

vi. Onychodystrophy :

Nail plate is thick, dull and opaque with a yellowish, whitish or grey color. Rarely, a severe onychodystrophy with spontaneous resolution may occur.[85]

II. Skin manifestations due to renal transplantation :

The best therapeutic option for many patients with ESRD is renal allograft transplantation. Successful transplantation results in regression of many of the metabolic and cutaneous changes of uremia.

Studies have shown that 50 – 100% of renal transplant recipients have a transplant related cutaneous complaint. Dermatological disorders associated with renal transplantation are a function of the immunosuppressive medications prescribed [86] as well as the immunosuppressed conditions produced. CD 4 lymphocytopenia occurs due to polyclonal antilymphocyte globulins and suppression of cell mediated immunity. Both humoral and cell mediated immunity are decreased due to immunosuppressive drugs. Factors such as time after transplantation, geographic location, climate and skin type greatly modify the clinical disorders associated with renal transplantation.

Dermatologic disorders associated with renal transplantation include the following:

I. Medication related disorders :

- Cushingoid changes
- Gingival hyperplasia
- Photosensitivity
- Striae
- Disorders of the pilosebaceous unit
    - Acne

- Folliculitis
- Hypertrichosis
- Keratosis pilaris
- Sebaceous gland hyperplasia
- Epidermal cysts

The specific cutaneous manifestations caused by individual medications given after renal transplant include:

- Calcineurin inhibitors : alopecia, pruritus, acne, gingival hyperplasia, hypertrichosis caused by cyclosporine
- Tacrolimus : alopecia, pruritus, ecchymoses, diaphoresis
- Corticosteroids : Skin atrophy, telangiectasias, purpura, acne, striae.
- Sirolimus : acne, oral thrush, oral ulcers, eyelid edema
- Mycophenolate mofetil : peripheral edema, acne, thrush
- Azathioprine : aphthous stomatitis, alopecia, hypersensitivity reaction.

II. Immunosuppression – related disorders:

- **Viral infections**
  - Herpes simplex virus
  - Varicella – zoster virus
  - Epstein – Barr virus
- **Bacterial Infections**
  - Staphylococcus aureus
  - Bartonella henselae

- Mycobacteria
- Mycobacterium tuberculosis and atypical mycobacteria

❖ **Fungal infections**

- Superficial mycoses – Dermatophytes, pityrosporum species and candidiasis
- Deep fungal infections – Aspergillus, Cryptococcus, Nocardia and Rhizopus species
- Parasitic infestation – Scabies

❖ **Premalignant and malignant conditions**

- Actinic keratoses
- Squamous cell carcinoma
- Basal cell carcinoma
- Keratoacanthoma
- Melanoma
- Kaposi's sarcoma
- Miscellaneous malignancies- Lymphoma, Merkel cell carcinoma (MCC) and dermatofibrosarcoma protuberans.

Miscellaneous disorders:

Transfusion associated graft versus host disease

Porokeratosis

Medication related dermatologic disorders:

Many cutaneous changes seen in renal transplant recipients are related directly to medications used to suppress rejection of renal allograft. A full blown cushingoid appearance develops in 55 – 90%[86] of patients and is associated with the high doses of corticosteroids used early after transplantation. Cutaneous findings include moon facies, development of a cervical fat pad (buffalo hump), striae distensiae, cutaneous atrophy and telangiectasias. Changes may resolve or improve when the corticosteroids dose is reduced, although they may continue, since steroids are used long term. Gingival hyperplasia, which occurs in approximately one third of patients receiving cyclosporin A, tends to occur early and improve over time.[103]

Other cutaneous changes involve poorly understood alterations in the pilosebaceous unit and may result from either cyclosporine A or corticosteroids.[86]

Acne develops in 15% of patients and primarily affects the chest and back. Most severe in the first year, acne later improves with reduction of the corticosteroid dose. Sebaceous gland hyperplasia and epidermal cysts are found with increased frequency and have been associated with the use of both cyclosporin A and corticosteroids. Hypertrichosis develops in 60% of patients and may be associated with the development of keratosis pilaris.

Infections :

The iatrogenically induced decrease in cell-mediated immunity predisposes the renal transplant recipients to infection by a variety of organisms. Patients are at heightened risk of developing oppurtunistic infections during the first 6 months after transplantation because of the use of higher doses of immunosuppressive agents.[92]

Bacterial infections :

Patients may develop infections from a variety of acid-fast bacilli, specifically typical or atypical mycobacteria.[86,87] Organisms of the Mycobacterium fortuitum / Mycobacterium chelonae complex are more common causes of AFB cutaneous infections, although others, such as Mycobacterium kansasii and Mycobacterium marinum,[88,90] also have been reported. Therapeutic options for these infections include antimicrobials, surgical debridement and / or reduction in immunosuppression.

Fungal infections :

Fungal organisms are the most common cause of infection in the renal transplant recipients,[89] occurring in 7 – 75%.

Pityriasis versicolor has been shown to be the most common fungal infection[86,91] and occurs in 18 – 48 % of transplant recipients, which is a higher rate than found in the general population. Colonization of the upper back with pityrosporum yeasts has been shown to occur 2 – 3 times more often in the transplant recipients, than the general population.

Pityrosporum organisms predispose patients to increased incidence of folliculitis. Dermatophytes although common after renal transplantation, is no more common than in the general population.[88]

Viral infections :

Severe viral infections usually occur during the first year after transplantation[87] and predominantly result from herpes viruses. Infection from HPV (human papilloma virus) tend to develop later. Surveys suggest that the prevalence of HPV is 15-50% after the first year and increases to 77-95% by 5 years after transplantation.[92]

Common and plane warts, which predominate, occur most frequently in sun-exposed areas and usually are multiple in number.[93,94] HPV 1,2,3 and 4 are found commonly, although oncogenic types 16 and 18, and types 5 and 8, associated with epidermodysplasia verruciformis are also encountered.

Treatment :

Eradication is difficult because the lesions respond poorly to therapy and recur frequently.

Treating warts early and aggressively is best in transplant recipient patients. Using routine modalities such as cryotherapy, electrocoagulation and carbon dioxide laser surgery and radiotherapy are not more effective and may result in scarring.

Treatment with oral or topical retinoids may be given. Interferon should not be used, as it may trigger allograft rejection. Imiquimod, when used limitedly, is both effective and safe.

Malignancy :

Malignancies are more common after organ transplantation and most are primary cutaneous malignancies.

Incidence :

- Non-melanoma skin cancers are 20-40 times greater in transplant recipients than in general population.

- The incidence increases as the time elapsed after transplantation increases because of the duration of immunosuppressive therapy.[95]

- The cumulative risk of cutaneous malignancy is 10 – 30% at 5 years, 10 – 44% at 10 years and 30 – 40% at 20 years. [96]

Prevalence :

- of skin cancer varies according to geographic location, amount of UV exposure and predominant skin type.

Most malignancies occur on sun-exposed areas and usually are found on the head, neck and upper extremites.

Non-melanoma skin cancer (NMSC):

- Squamous cell carcinoma (SCC) is the most common cutaneous malignancy and occurs 50 – 250 times [96] more common than in

general population and Basal cell carcinoma (BCC) occurs 6 – 10 times [96] more frequently in the renal transplant recipient patients.

- NMSC occur at a younger age in RTRs (renal transplant recipients) and are characterized by a more rapid and aggressive course, a higher recurrence rate and a greater metastatic potential.
- Actinic keratosis show a more severe cytologic atypia, occur at a younger age and rapidly progresses to SCC.

Predisposing factors : to the development of NMSC includes :

- exposure to UV rays
- skin phototype I and II
- immunosuppression
- HPV infection

Management (of NMSC) include :

- Sun avoidance
- Use of broad spectrum sunscreens
- Early detection of malignant and precancerous lesions
- Aggressive therapy
- Complete surgical excision with margin control is necessary.
- Adjuvant radiotherapy or chemotherapy may have a role in association with surgery in certain patients.
- Imiquimod is safe and effective for superficial BCC and actinic keratoses when used on small surface areas.

- Chemoprevention using systemic retinoids are used for multiple malignancies. Partial and complete remissions have been reported with retinoid use, but long-term therapy is necessary because the beneficial effect is lost 2 – 3 months after stopping treatment.

Kaposi's sarcoma :

- Incidence : 400 – 500 times higher than in general population
- Accounts for approximately 3-5% of transplant – related malignancies in RTRs
- Incidence varies according to geographic regions and is higher in Jewish, Mediterranean, Arabic ancestry and in blacks
- Highest incidence is in the first year after transplantation (usually 2 – 24 months after transplantation)[95]
- The development of Kaposi's sarcoma in RTRs is associated with human herpes virus 8. Mucocutaneous lesions occur in 60% of patients.

Treatment:

- Cessation of immunosuppressive medications
- Radiotherapy
- Chemotherapy
- Excision
- Cryotherapy

Melanoma:

- Incidence : Occurs 2 – 9 times more common than in general population.
- Risk of melanoma in RTRs, may include transmission by the donor. Studies are conflicting regarding the prognosis of melanoma in transplant patients, including the risk of recurrence of melanoma following transplantation.

Other malignancies :

Malignant fibrous histiocytomas, atypical fibroxanthomas, merkel cell carcinoma and dermatofibrosarcoma protuberans have been reported, although the incidence of the malignancies are unknown.

Although lymphomas are the second most common malignancy in transplant recipients, cutaneous lymphomas are relatively rare. Cutaneous B-cell lymphomas are more common than T-cell lymphomas.

Miscellaneous disorders:

- Transfusion associated Graft versus host disease have occurred in patients who have received nonirradiated packed red blood cells. This condition usually has a poor prognosis.
- Porokeratosis, a disorder of epidermal keratinization, has been reported as an unusual manifestation of immunosuppression in solid organ transplant recipients. Several of the clinical variants have been reported, including

disseminated superficial porokeratosis, single lesions of porokeratosis of Mibelli and rare cases of disseminated porokeratosis of Mibelli.

II. Skin Manifestations due to Treatment of CRF (Dialysis and drugs):

1. Pruritus
2. Xerosis
3. Pigmentary change – diffuse brown hyperpigmentation, diffuse bluish grey discoloration of the skin and nails, acquired hair and skin fairness.
4. Chronic hemodialysis related porphyria / pseudoporphyria / drug induced bullous dermatoses.
5. Arterio – venous shunt dermatitis
6. Vascular malformations
7. Contact dermatitis – both irritant and allergic, may occur to dialysis tubing, nickel (needles) and topical medications
8. Nail changes – Half and half nails
   - Splinter haemorrhages
   - Onycholysis
9. Hair Changes - Alopecia
   - Discoloration of hair
   - Fine brittle hair
   - Hair shaft abnormalities
10. Infections
11. Pre-malignant conditions - Multiple actinic keratosis
    - Porokeratosis

12. Malignancy : Basal cell carcinoma
13. Nephrogenic fibrosing dermopathy
14. Cutaneous calcinosis in hemodialysis.

Histopathological changes of uremia in skin:

They include:[97]

Epidermal:

- moderately thickened stratum corneum
- reduction of prickle cell layers with cells having pyknotic nuclei
- vacuolated cytoplasm of the epidermal cells
- flattening of DEJ

Dermal :

- dilatation of the capillaries and lymphatics in mild azotemia
- dermal atrophy and loss of dermal blood vessels and appendages in advanced renal failure.

Management of renal failure :

Management of chronic renal failure falls into 3 distinct parts:

- Investigations to detect the underlying renal disease and to determine any reversible factors which are exacerbating the uremic state.
- Measures designed to limit adverse effects of loss of renal function and when possible to prevent further renal damage
- In patients with progressive destruction of renal tissue, supportive measures in the form of either dialysis or transplant are required.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was done for 2 years from October 2009 to October 2011 at Nephrology OPD, ward and medicine ward, Tirunelveli Medical College Hospital, Tirunelveli. Approval was obtained from the institutional ethical committee prior to the conduct of this study.

During this period, 100 patients who had the presence of skin manifestations were selected and studied. 80 patients were known cases of chronic renal failure, diagnosed at Nephrology department or medical department and 20 patients were renal transplant recipients who were referral cases.

Patient selection:

Inclusion criteria :

1. Age : All ages
2. Sex : Both males and females
3. Patients with chronic renal failure
4. Renal transplant patients

Exclusion criteria :

1. Patients with HIV infection
2. Patients with previous malignancies
3. Drug related cutaneous manifestations
4. Patients on dialysis

- The name, age, sex, address, outpatient, inpatient number were noted. All patients were examined under good light. Detailed patients' history and dermatological examination including cutaneous, scalp, mucosal, palms, soles and nail lesions were done. Photographs were taken using Canon digital camera for all patients, after informed consent.
- All patients were thoroughly investigated with routine hematologic and biochemical investigations.
- A thorough history was taken and general examination was done. The skin, hair, nails, mucosa were examined thoroughly for specific lesions of chronic renal failure, renal transplant related skin lesions and associated skin lesions.
- Selected cases were investigated as follows and treated accordingly.
    a) Scraping of skin for direct microscopic examination with 10% KOH for evidence of superficial mycosis in affected patients.
    b) Tzanck smear when indicated in viral infections.
    c) Pus culture and sensitivity
    d) Skin biopsy for HPE in selected cases.

OBSERVATION AND RESULTS

OBSERVATIONS AND RESULTS

The number of patients studied with chronic renal failure and renal transplant were 100. Of these, 80 patients presented with CRF and 20 were renal transplant recipients.

Statistical analysis:

The study subsets of CRF and RTR were described and distributed in respect of their age between the gender by means of averages namely mean. The student's unpaired 't' test was used to interpret the difference of age between gender. The specific cutaneous manifestations of CRF and RTR, incidence of associated skin lesions and systemic diseases contributing to etiology of CRF between the genders were analysed and interpreted by 'Z' test of proportions. The stastistical software PASW [Predictive and Analysis Soft Ware] statistics - 18 (the so called SPSS) was used for the above statistical procedures. The P values less than 0.05 was considered significant under two trial conditions ($P < 0.05$) and P value more than 0.05 was considered as non-significant.

Age incidence :

The age of the patients ranged from 16 – 70 years with a mean of 46 years. The mean age of CRF cases was 47.9 ± 14.5 [n = 80] and the mean age of RTR cases was 34.5 ± 11.0 [n = 20] years. The commonest age incidence among males and females in CRF patients is between 40 – 60 years and in RTR, it is 20 – 40 years.

Sex incidence :

Out of 100 patients, 62 were males and 38 were females. Out of 80 CRF patients, 47(58.7%) were males and 33(41.2%) were females. Out of 20 RTR, 15(75%) were males and 5(25%) were females.

TABLE I

Age and genderwise distribution of mean ages of study subsets and matching between genders :

Category	Male			Female			Difference between mean	't' test	d.f	Significance
	n	Mean	SD	n	mean	SD				
CRF[Total-80]	47	49.2	14.5	33	46.0	14.6	3.2	0.973	78	P>0.05
RT [Total-20]	15	37.1	9.3	5	27.0	13.3	10.1	1.886	18	P>0.05

I.Incidence of specific cutaneous manifestations of chronic renal failure:

A. Skin

1. Pruritus :

Out of 80 patients, 32(68.1%) males and 15(45.5%) females suffered from pruritus. The total incidence in both sexes was 58.8 %. 20 of these patients had excoriations due to pruritus, 2 of them developed prurigo nodularis and another 5 developed lichen simplex chronicus.

TABLE II

Incidence of pruritus :

Gender	n	Incidence of pruritus	
		Frequency	Percentage
Male	47	32	68.1%
Female	33	15	45.5%
Total	80	47	58.8%

2. Xerosis / ichthyosis :

Dryness of skin was noted in 28 (35%) patients, ichthyosis was noted in 18 (22.5%) patients and acquired plantar hyperkeratosis in 5 (6.2%) patients.

TABLE III

Incidence of xerosis/ichthyosis :

Clinical Features	Male = 47		Female = 33		Total = 80	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Xerosis	16	34.0%	12	36.4%	28	35.0%
Ichthyosis	10	21.3%	8	24.2%	18	22.5%
Plantar hyperkeratosis	4	8.5%	1	3.0%	5	6.2%
Total	30	63.8%	21	63.6%	51	63.7%

3. Pigmentary alterations :

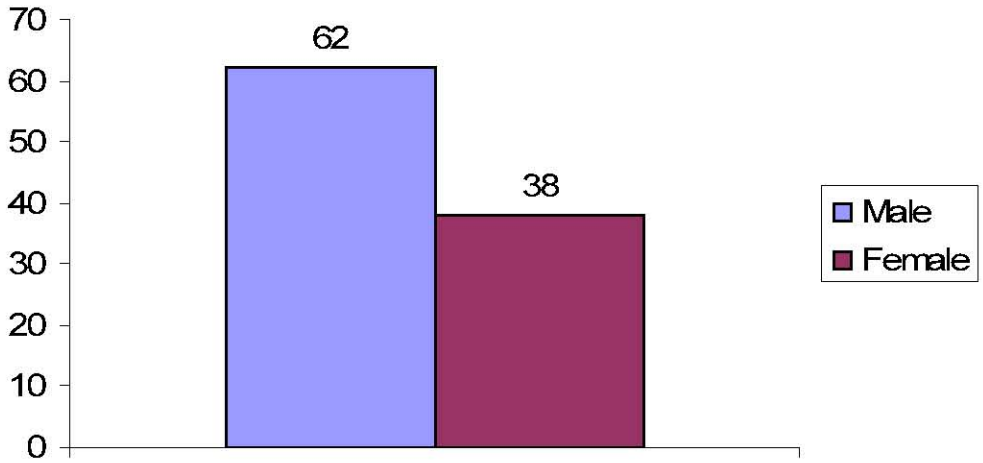
Among pigmentary alterations 7 has yellow discoloration, 10 had diffuse hyperpigmentation, 5 had hypermelanotic macules of palms and soles and 22 were pale. The total number of patients with pigmentary alterations was 44 (55%).

TABLE IV

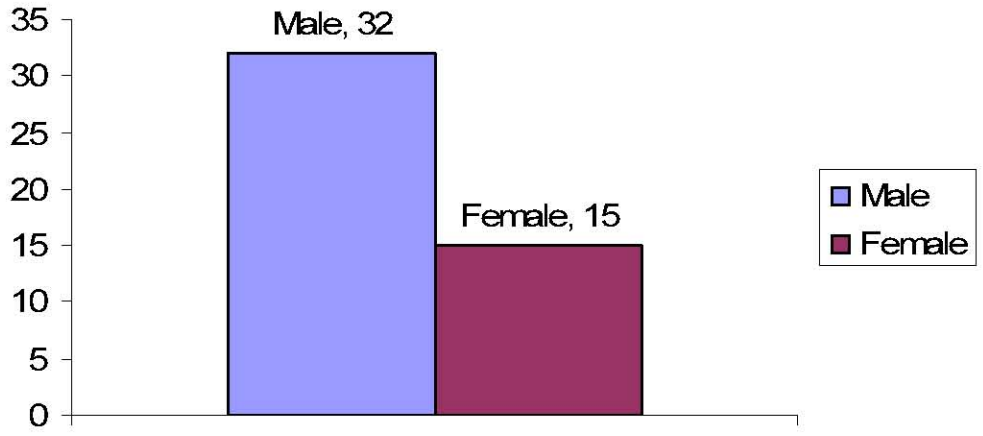
Incidence of pigmentary alterations :

Clinical Features	Male = 47		Female = 33		Total = 80	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Yellow discoloration	4	8.5%	3	9.1%	7	8.7%
Diffuse hyperpigmentation	8	17.0%	2	6.1%	10	12.5%
Hypermelanotic macules of palms and soles	3	6.4%	2	6.1%	5	6.2%
Pallor	12	25.5%	10	30.3%	22	27.5%
Total	27	57.4%	17	51.5%	44	55.0%

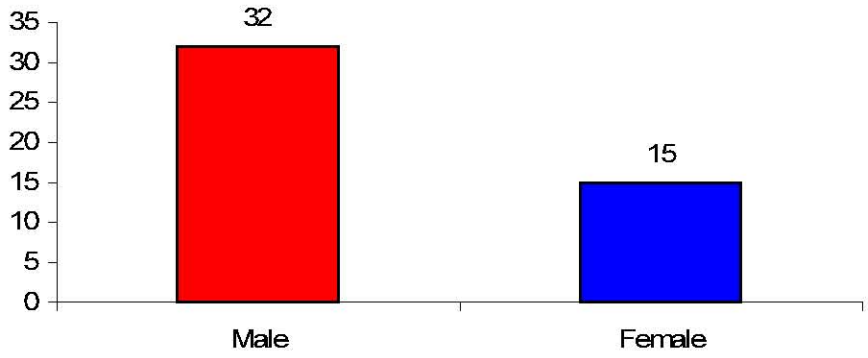
No. of patients with CRF & Renal transplantation



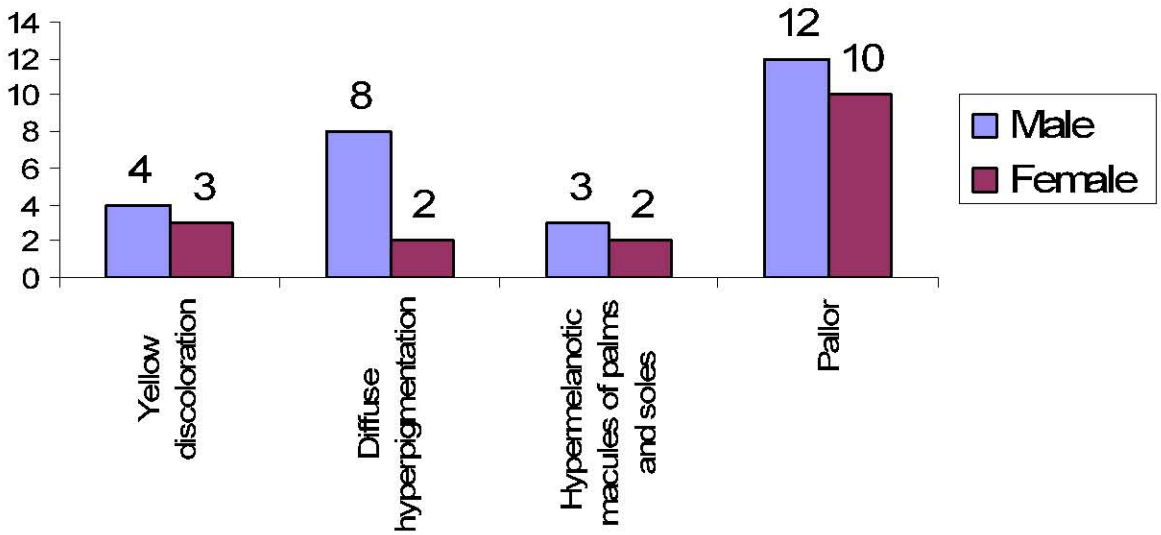
Incidence of pruritus



Incidence of Xerosis / Ichthyosis



Incidence of pigmentary alterations



4. Uremic frost : Not noted

5. Perforating dermatoses :

Clinical morphology of perforating dermatoses is seen in 10 patients. With the help of histopathological findings, Kyrle's disease was seen in 2 patients, perforating folliculitis in 1 patient. Others showed features of nodular prurigo and prurigo simplex.

TABLE V

Incidence of perforating dermatoses :

Clinical Features	Male = 47		Female = 33		Total = 80	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Kyrle's disease	2	4.2%	0	0.0%	2	2.5%
Perforating folliculitis	1	2.1%	0	0.0%	1	1.2%
Others	3	6.4%	4	12.1%	7	8.7%
Total	6	12.8%	4	12.1%	10	12.5%

6. Metastatic calcification : Not noted

7. Purpura : over legs were noted in 7 patients, of which the cause was mainly due to underlying thrombocytopenia.

TABLE VI

Incidence of purpura :

Gender	N	Incidence of purpura	
		Frequency	Percentage
Male	47	3	6.4%
Female	33	4	12.1%
Total	80	7	8.7%

8. Gynecomastia : Not noted

9. Vascular disorders : Digital gangrene present over toes was noted in one patient.

10. Poor wound healing : following trauma was seen in 3 patients.

11. Restless leg syndrome : Three patients had burning pain over the soles of the feet, of which 1 patient had associated diabetes mellitus.

B. Mucosal changes :

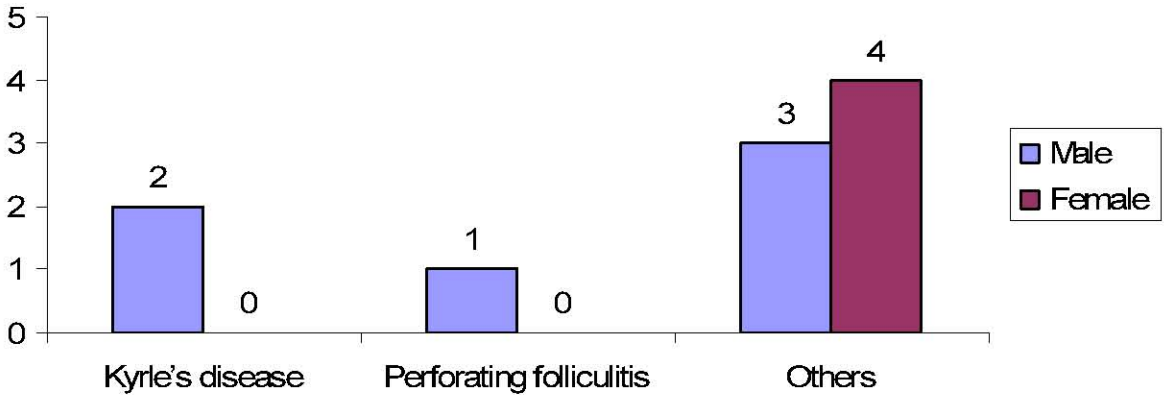
Stomatitis was noted in 14 patients, 3 had oral ulcers and 1 had leukokeratosis of oral mucosa. The total number of patients with mucosal changes was 18, and the incidence was 22.5 %

TABLE VII

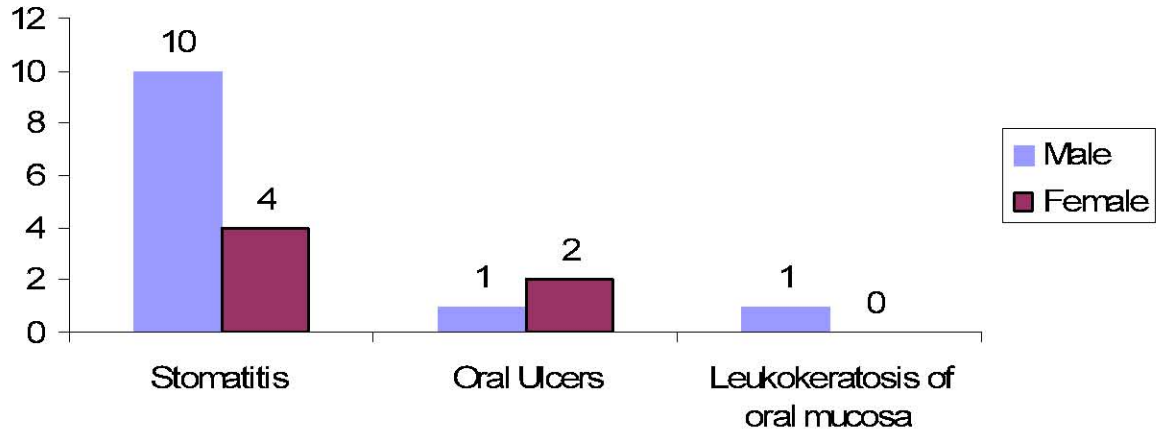
Incidence of mucosal changes:

Clinical Features	Male = 47		Female = 33		Total = 80	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Stomatitis	10	21.3%	4	12.1%	14	17.5%
Oral ulcers	1	2.1%	2	6.1%	3	3.7%
Leukokeratosis of oral mucosa	1	2.1%	0	0.0%	1	1.2%
Total	12	25.5%	6	18.2%	18	22.5%

Incidence of Perforating disorders



Incidence of Mucosal Changes



C. Hair abnormalities :

Diffuse alopecia is seen in 6 patients and 10 had brittle hair. The total number of patients with hair abnormalities was 16. The incidence was found to be 20 %

Table VIII

Incidence of hair abnormalities:

Clinical Features	Male = 47		Female = 33		Total = 80	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Diffuse alopecia	2	4.2%	4	12.1%	6	7.5%
Brittle hair	4	8.5%	6	18.2%	10	12.5%
Total	6	12.8%	10	30.3%	16	20.0%

D. Nail changes :

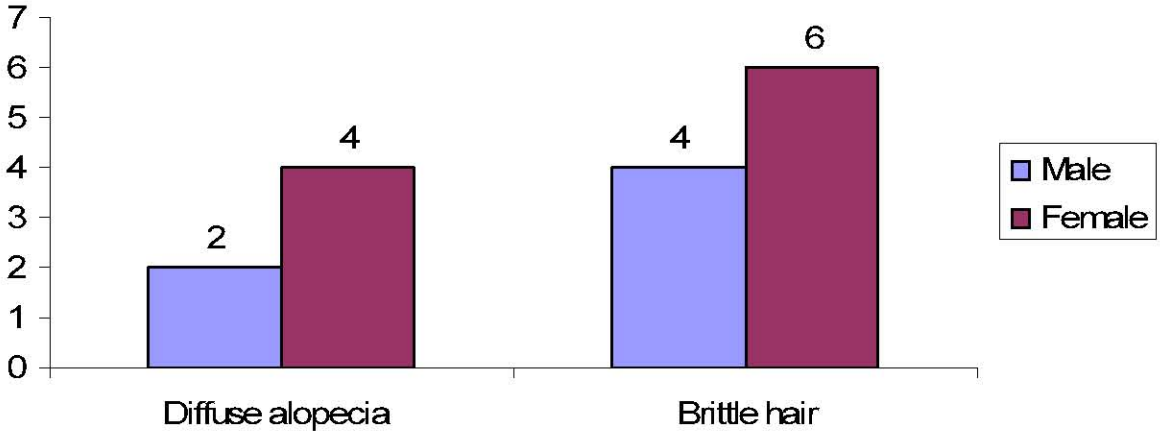
21 (26.2%) had 'half and half' nails, 7 (8.7%) had brown nail bed arc. 7 had shiny nails, 6 had onychodystrophy (nail scraping was done and examined under 10% KOH and found to be negative) and 1 had melanonychia. Other features like Mee's lines, Muercke's lines and blue nails were not noted. The total number of patients with nail changes is 46 (57.5%)

TABLE IX

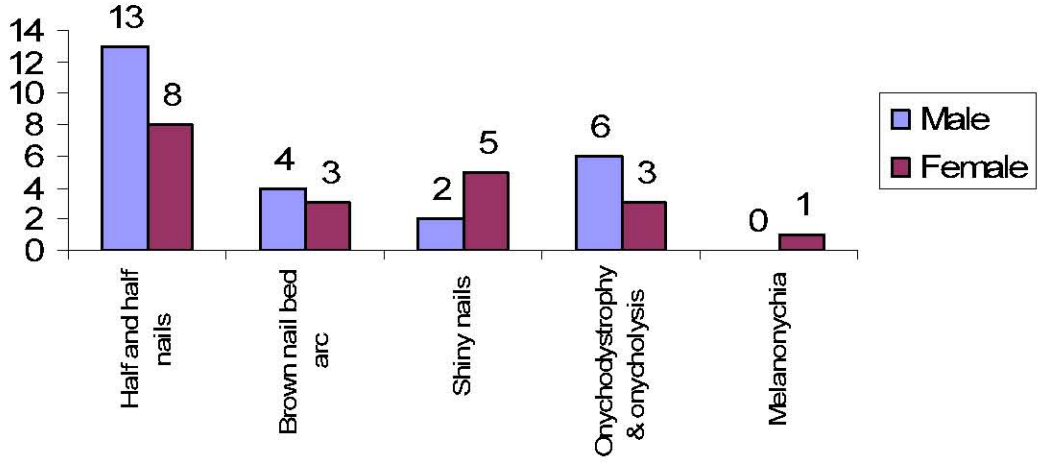
Incidence of nail changes:

Clinical Features	Male = 47		Female = 33		Total = 80	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Half and half nails	13	27.6%	8	24.2%	21	26.2%
Brown nail bed arc	4	8.5%	3	9.1%	7	8.7%
Shiny nails	2	4.2%	5	15.1%	7	8.7%
Onychodystrophy and onycholysis	6	12.7%	3	9.1%	9	11.2%
Melanonychia	0	0.0%	1	3.0%	1	1.2%
Total	25	53.2%	20	60.6%	45	56.2%

Incidence of Hair Abnormalities



Incidence of Nail Changes



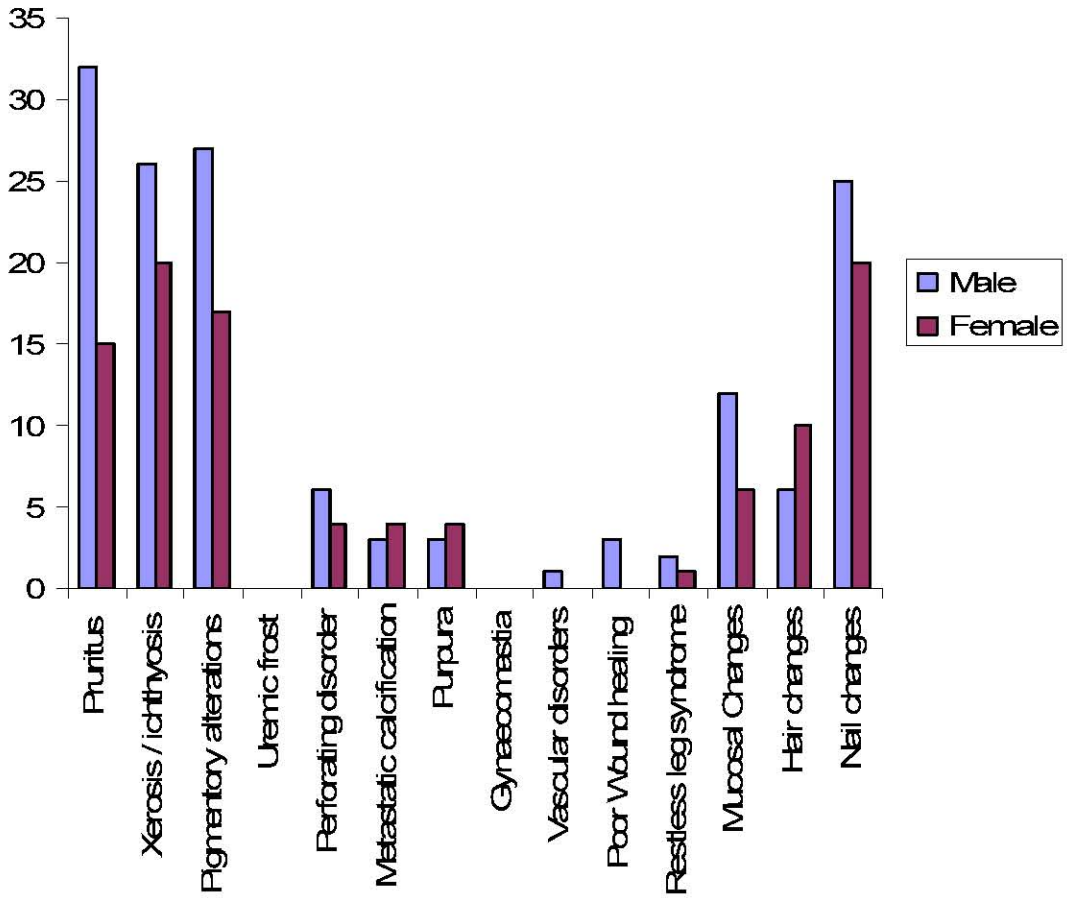
SPECIFIC CUTANEOUS MANIFESTATIONS OF CRF

TABLE X

Incidence of specific cutaneous manifestations of CRF:

Clinical features	Male = 47		Female = 33		Significance	Total = 80	
	Freq.	%	Freq.	%		Freq	%
Pruritus	32	68.1%	15	45.5%	P<0.05	47	58.8%
Xerosis / ichthyosis	26	55.3%	20	60.6%	P>0.05	46	57.5%
Pigmentary alterations	27	57.4%	17	51.5%	P>0.05	44	55.0%
Uremic frost	-	-	-	-	-	-	-
Perforating disorder	6	12.8%	4	12.1%	P>0.05	10	12.5%
Metastatic calcification	-	-	-	-	-	-	-
Purpura	3	6.4%	4	12.1%	P>0.05	7	8.7%
Gynecomastia	-	-	-	-	-	-	-
Vascular disorders	1	2.1%	0	0.0%	-	1	1.2%
Poor wound healing	3	6.4%	0	0.0%	-	3	3.7%
Restless leg syndrome	2	4.3%	1	3.3%	P>0.05	3	3.7%
Mucosal changes	12	25.5%	6	18.2%	P>0.05	18	22.5%
Hair abnormalities	6	12.8%	10	30.3%	P>0.05	16	20.0%
Nail abnormalities	25	53.2%	20	60.6%	P>0.05	45	56.2%

Specific Cutaneous Manifestations of CRF



II. Incidence of skin manifestations specific to renal transplantation :

Bacterial infections :

Furunculosis was seen in 3 patients and infected leg ulcers in 1 patient. Pus culture revealed staphylococcus aureus in 2 patients.

Viral infections :

Herpes simplex labialis was seen in 1 patient and 1 patient had herpes zoster. Tzanck smear revealed multinucleated giant epithelial cells. Verruca vulgaris was noted in 4 patients. Incidence of viral infections is found to be 35%.

Fungal infections :

Pityriasis versicolor was noted in 5 patients. 2 patients had Tinea corporis. Scraping for direct microscopic visualization of fungal elements with 10% KOH was done and was found to be positive in both cases. Oral candidiasis was seen in 1 patient. Incidence of fungal infections is 40%.

Parasitic infestations :

Scabies was seen in 1 patient.

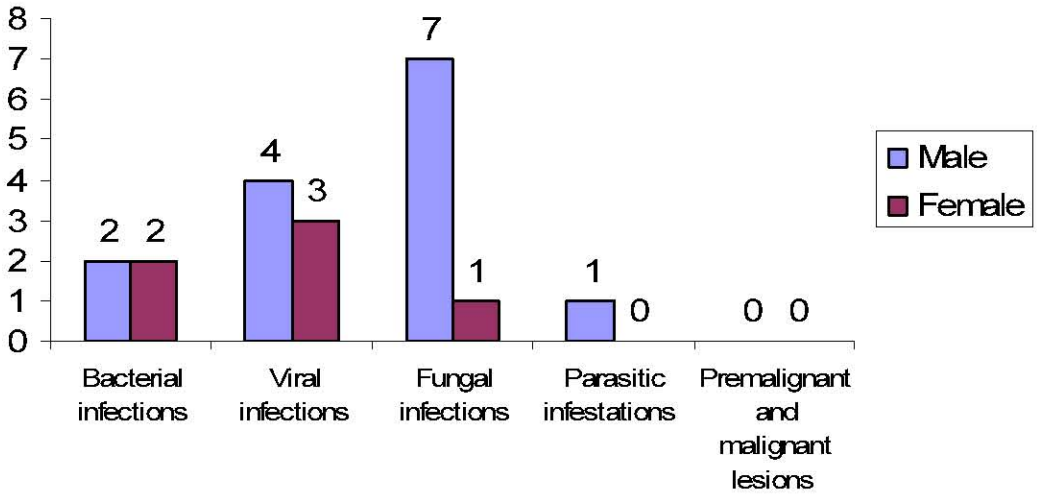
Premalignant and malignant lesions were not noted in any patient.

TABLE XI

Incidence of specific cutaneous manifestations of RTR:

Cutaneous Manifestations	Clinical Features	Male = 15		Female = 5		Significance	Total = 20	
		Freq.	%	Freq.	%		Freq	%
Bacterial infections	Furunculosis	2	13.3%	1	20.0%	P>0.05	3	15.0%
	Infected leg ulcers	0	0.0%	1	20.0%	-	1	5.0%
	Total	2	13.3%	2	40.0%	P>0.05	4	20.0%
Viral infections	Herpes simplex labialis	0	0.0%	1	20.0%	-	1	5.0%
	Herpes zoster	1	6.7%	0	0.0%	-	1	5.0%
	Verruca vulgaris	3	20.0%	1	20.0%	-	4	20.0%
	Plane wart	0	0.0%	1	20.0%	-	1	5.0%
	Total	4	26.7%	3	60.0%	P>0.05	7	35.0%
Fungal infections	Pityriasis versicolor	4	26.7%	1	20.0%	-	5	25.0%
	Dermatophytosis	2	13.3%	0	0.0%	-	2	10.0%
	Oral candidiasis	1	6.7%	0	0.0%	-	1	5.0%
	Total	7	46.7%	1	20.0%	P>0.05	8	40.0%
Parasitic infestations	Scabies	1	6.7%	0	0.0%	-	1	5.0%
Pre-malignant and malignant lesions	-	-	-	-	-	-	-	-

Cutaneous Manifestations Specific to Renal Transplantation



III. Incidence of associated skin lesions :

These were classified as :

1. Systemic diseases contributing to the etiology of CRF :

Skin changes of diabetes mellitus like acanthosis nigricans, perforating folliculitis, peripheral neuropathy were noted in 12 patients. Skin changes of SLE like malar rash, erythematous scaly plaques, discoid rash and diffuse alopecia of scalp were noted in 2 patients. Cutaneous findings of scleroderma like hide-bound skin, sclerodactyly, salt and pepper pigmentation, and digital pitted scars were seen 1 patient. One patient had vasculitic ulcer on lower legs, and 1 presented with pupura due to idiopathic thrombocytopenia.

TABLE XII A

Incidence of associated systemic diseases, contributing to etiology of CRF :

Diseases	Male = 47		Female = 33		Significance	Total = 80	
	Freq.	%	Freq.	%		Freq.	%
Diabetes mellitus	6	12.8%	5	15.2%	P>0.05	11	13.7%
SLE	0	0.0%	2	6.1%	-	2	2.5%
Scleroderma	0	0.0%	1	3.0%	-	1	1.2%
Vasculitis	0	0.0%	1	3.0%	-	1	1.2%
ITP	1	2.1%	0	0.0%	-	1	1.2%
Total	7	14.9%	9	27.3%	P>0.05	16	20%

2. Nonspecific cutaneous conditions associated with CRF:

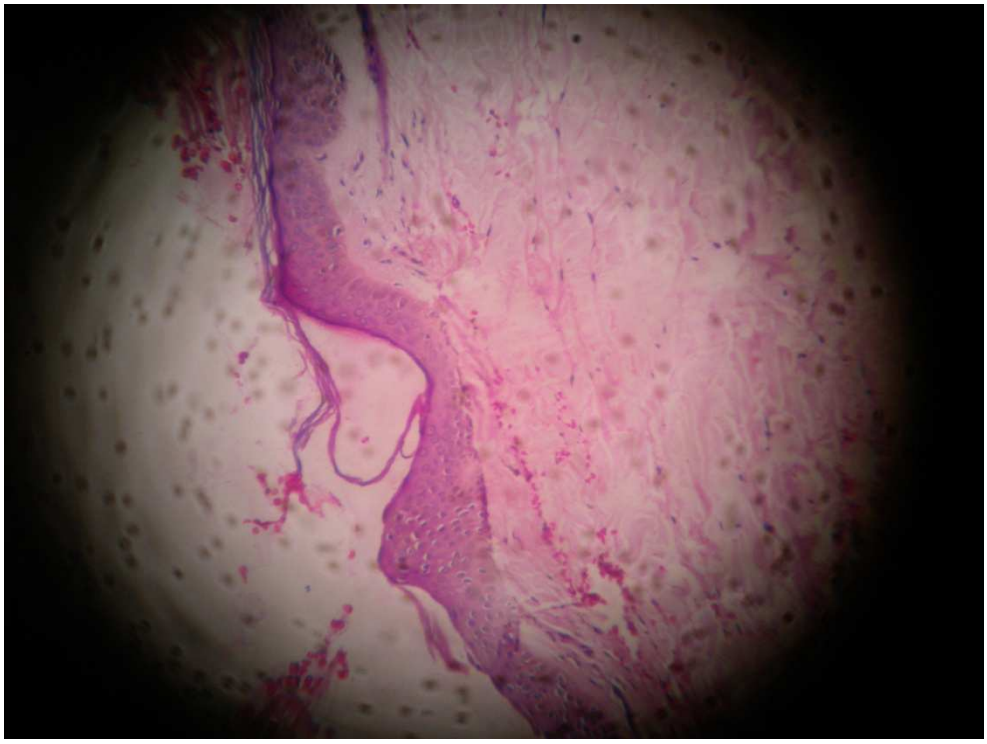
Non specific skin diseases associated with these patients were lichen planus, psoriasis, erythroderma, eczema with sensitization, stasis eczema, vitiligo, phrynoderma, urticaria, seborrheic keratosis, DPN and erythema nodosum.

TABLE XII B

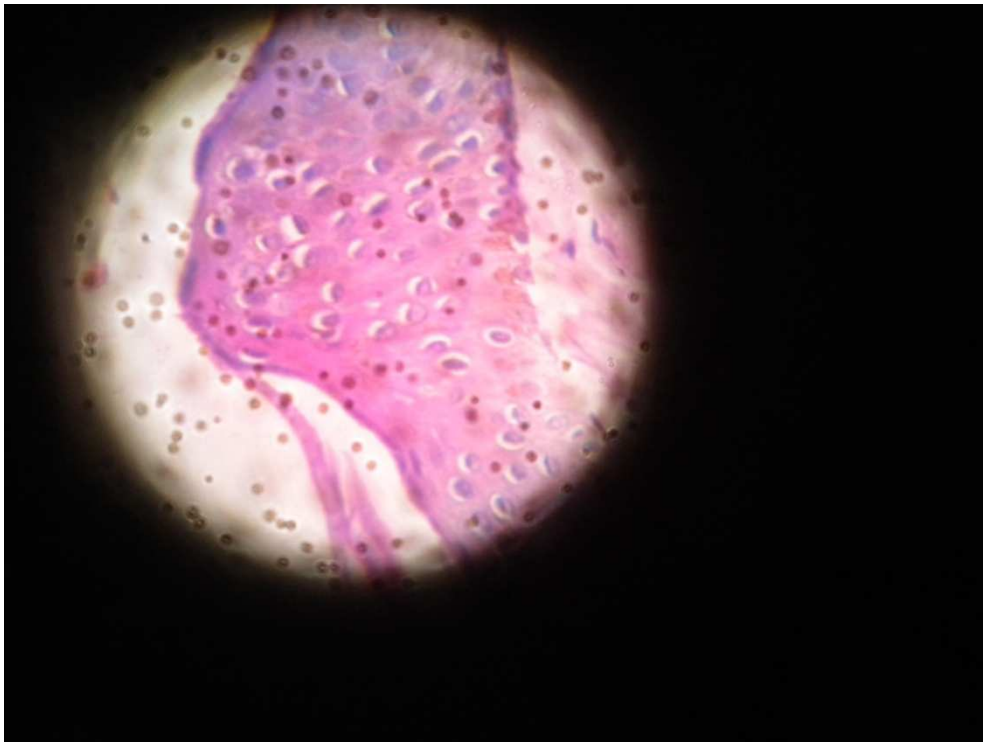
Incidence of associated skin lesions : (CRF and RTR)

Diseases	Male = 62		Female = 38		Significance	Total = 100	
	Freq.	%	Freq.	%		Freq.	%
Lichen planus	3	4.8%	1	2.6%	P>0.05	4	4.0%
Psoriasis	2	3.2%	0	0.0%	-	2	2.0%
Erythroderma	1	1.6%	0	0.0%	-	1	1.0%
Eczema with sensitization	1	1.6%	0	0.0%	-	1	1.0%
Stasis eczema	4	6.4%	3	7.9%	P>0.05	7	7.0%
Vitiligo	6	9.7%	4	10.5%	P>0.05	10	10.0%
Phrynoderma	2	3.2%	1	2.6%	P>0.05	3	3.0%
Urticaria	2	3.2%	3	7.9%	P>0.05	5	5.0%
Seborrheic keratosis/ DPN	6	9.7%	4	10.5%	P>0.05	10	1.0%
Erythema nodosum	1	1.6%	0	0.0%	-	1	1.0%
Total	28	45.2%	16	42.1%	P>0.05	44	44.0%

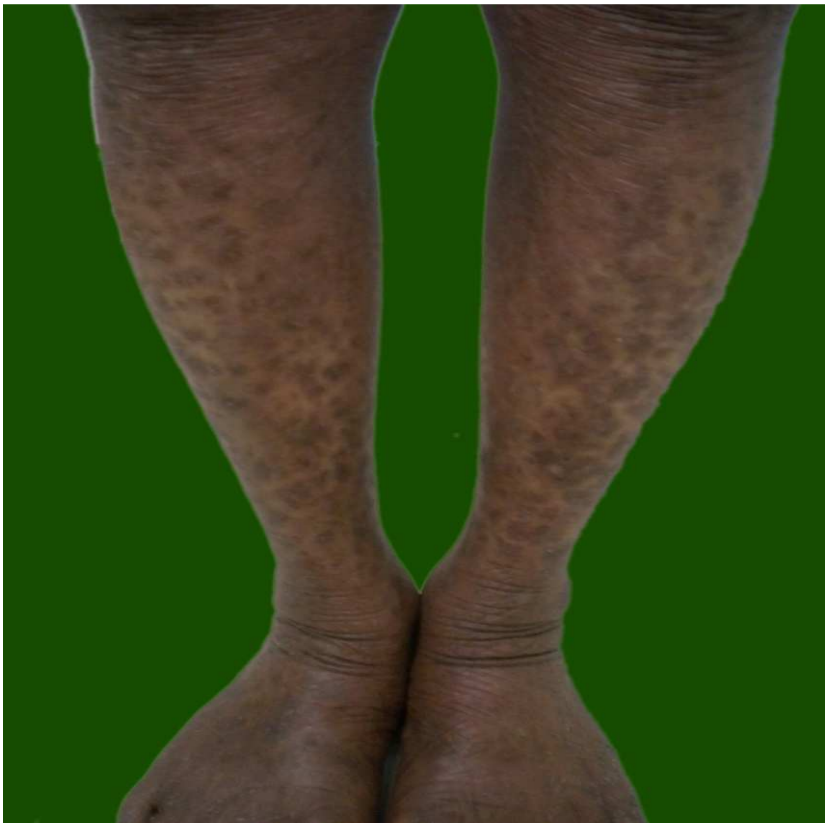
HPE of Uraemic skin



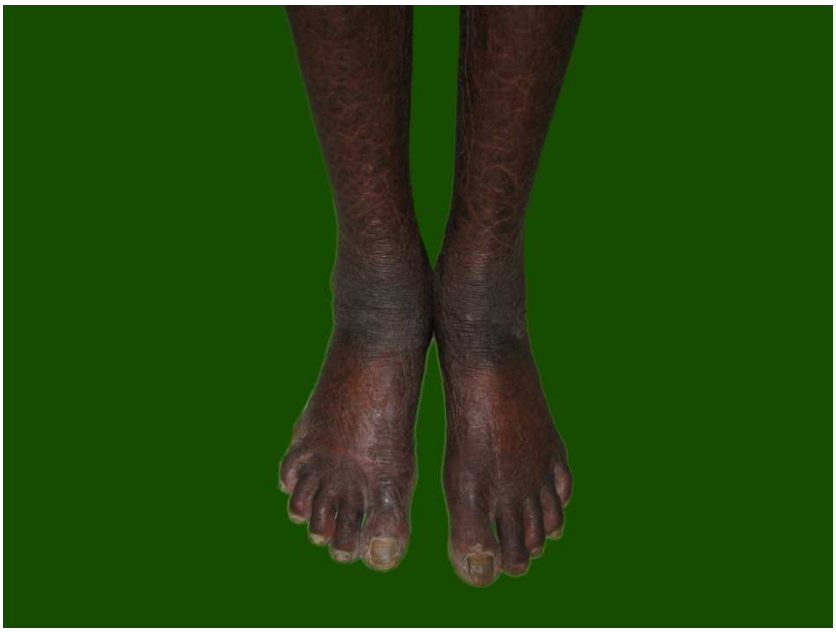
HPE of Uraemic skin



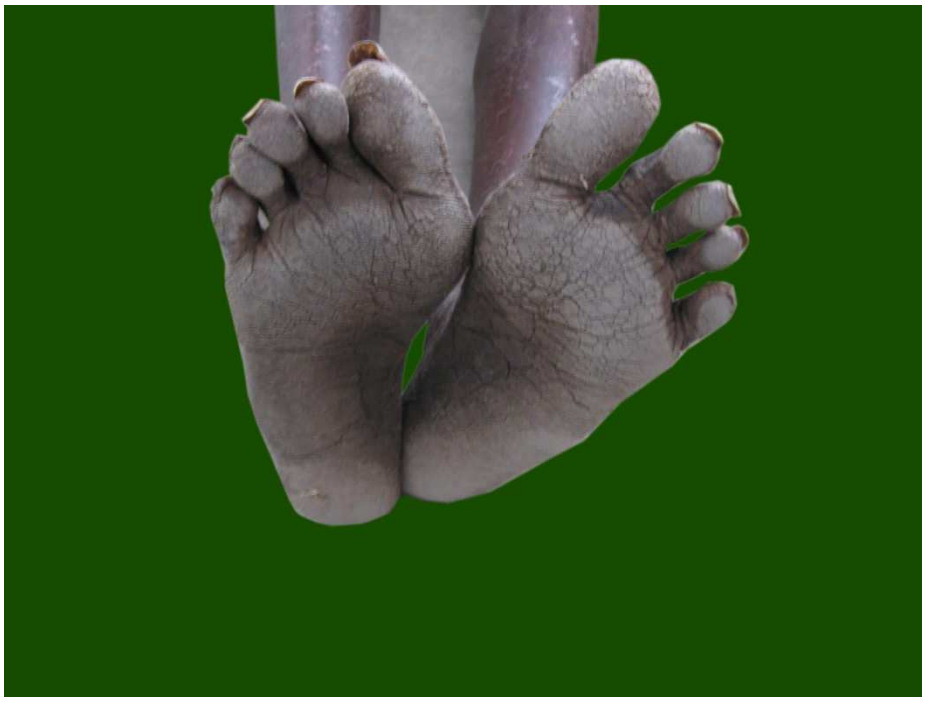
Ichthyosis



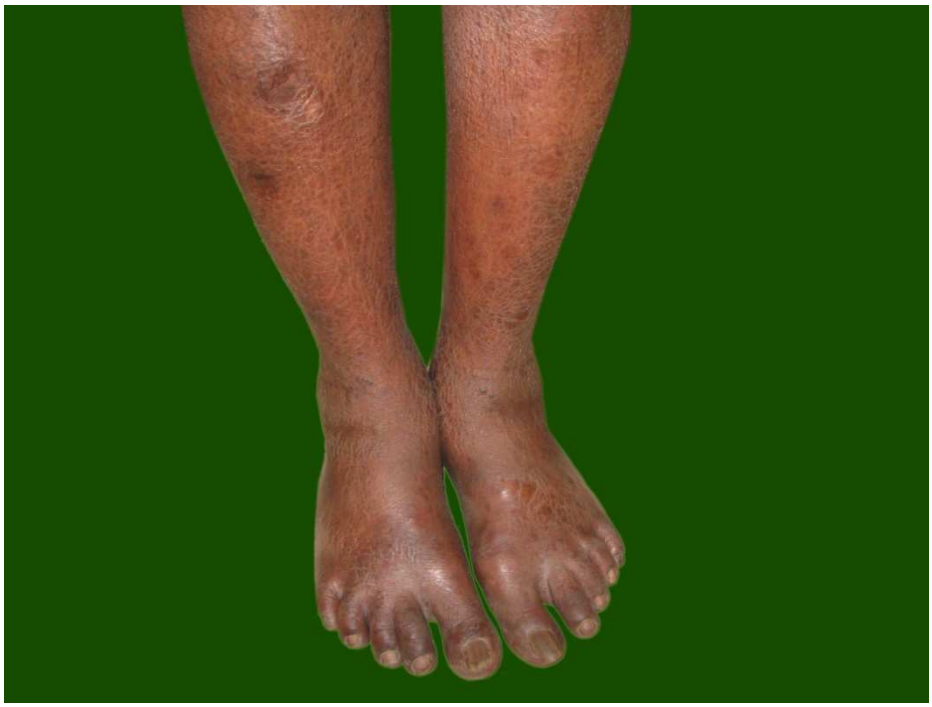
Ichthyosis



Plantar hyperkeratosis

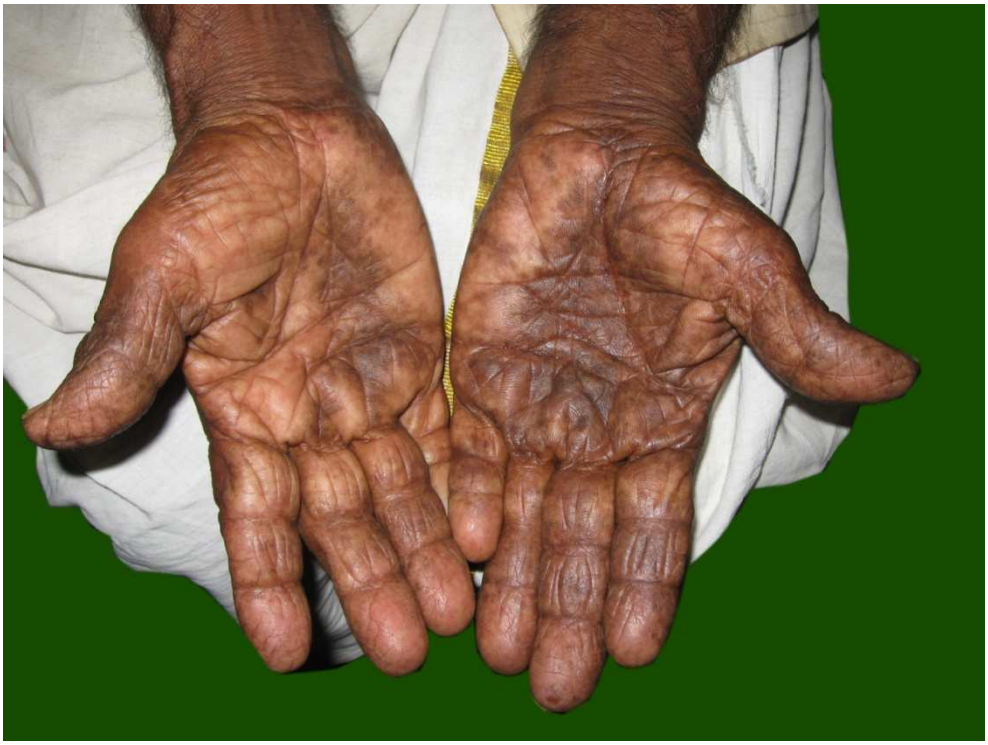


Xerosis

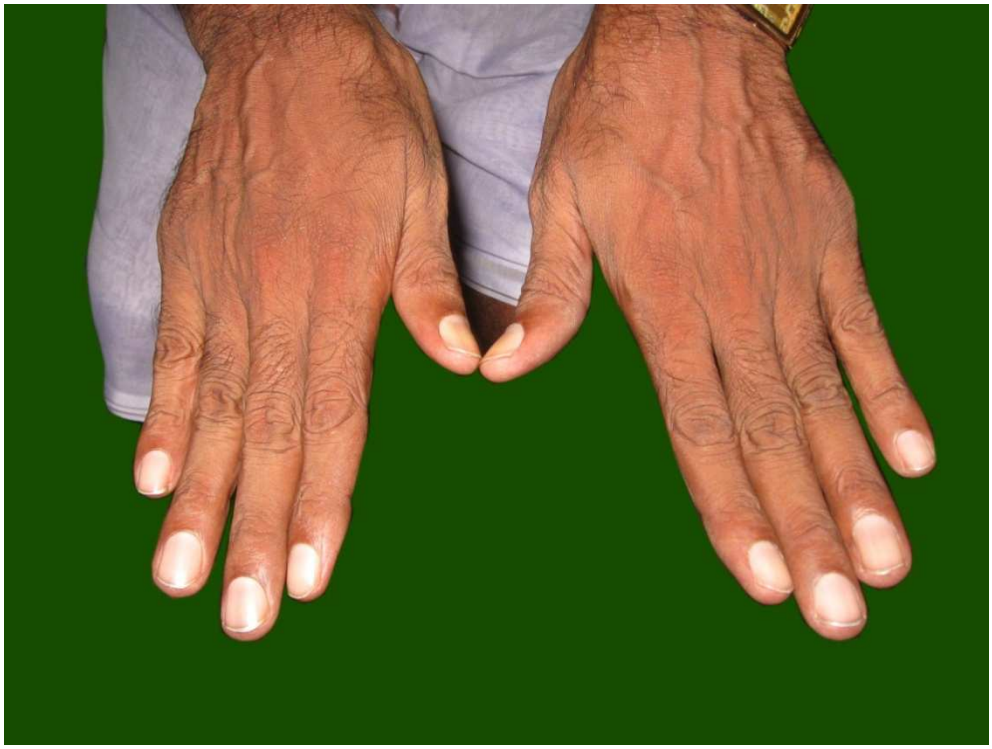


Pigmentation over face

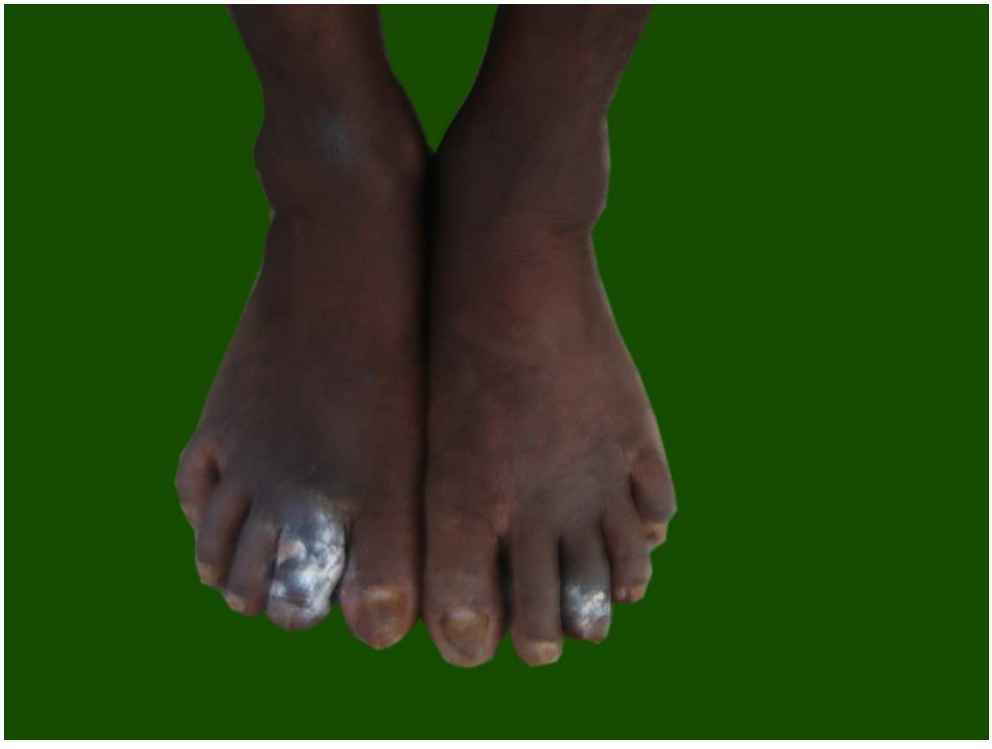
Hypermelanotic macules of palms



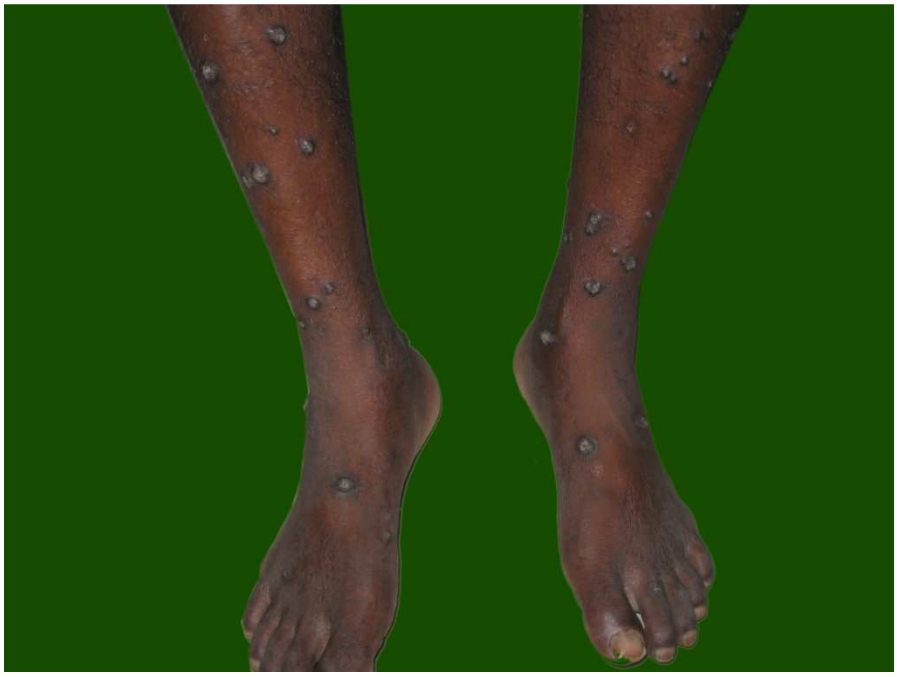
Pallor of nails



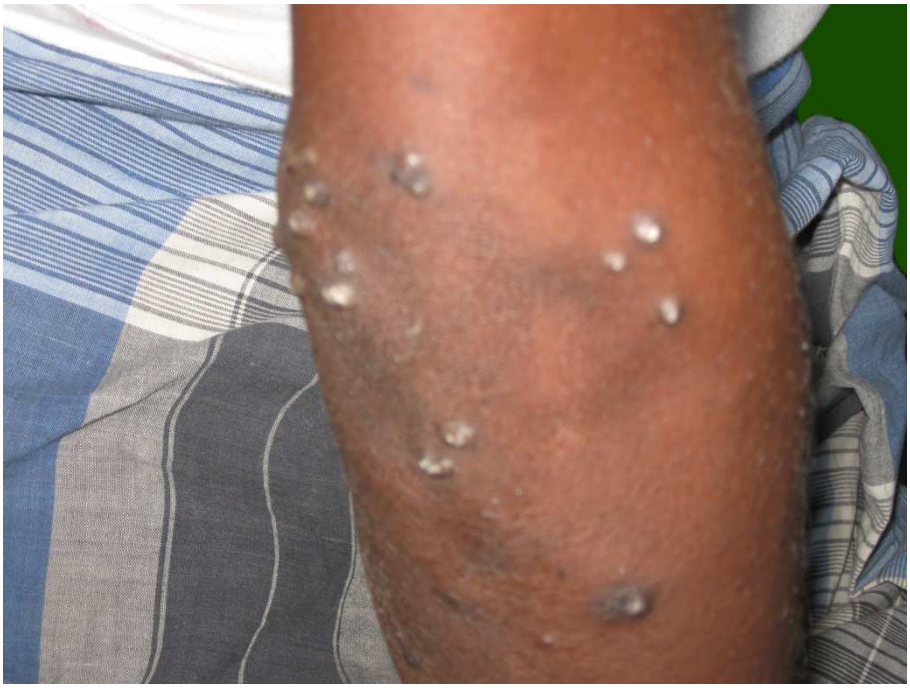
Digital Gangrene



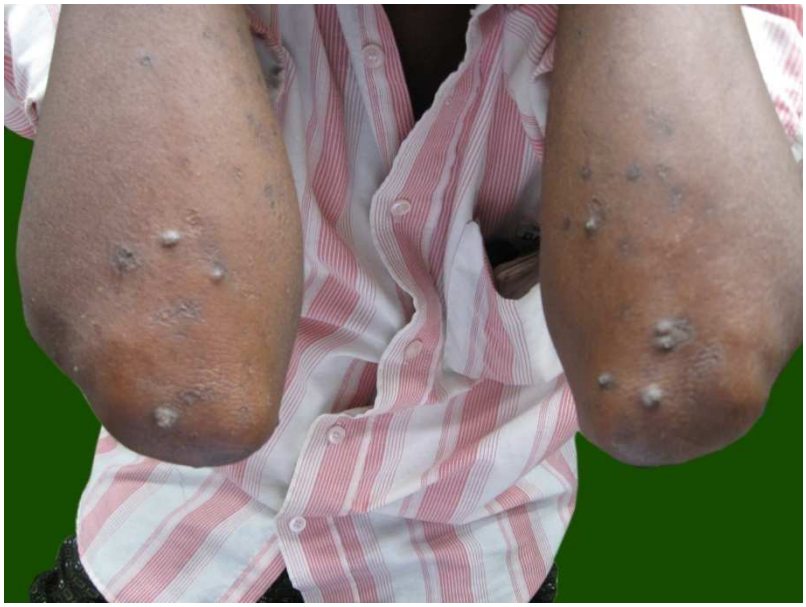
Kyrle’s disease



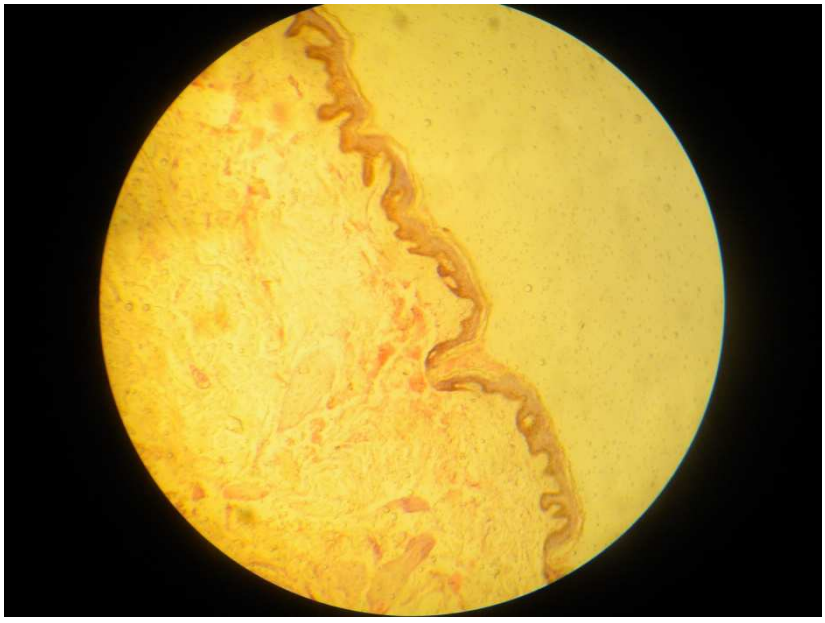
Kyrle’s disease



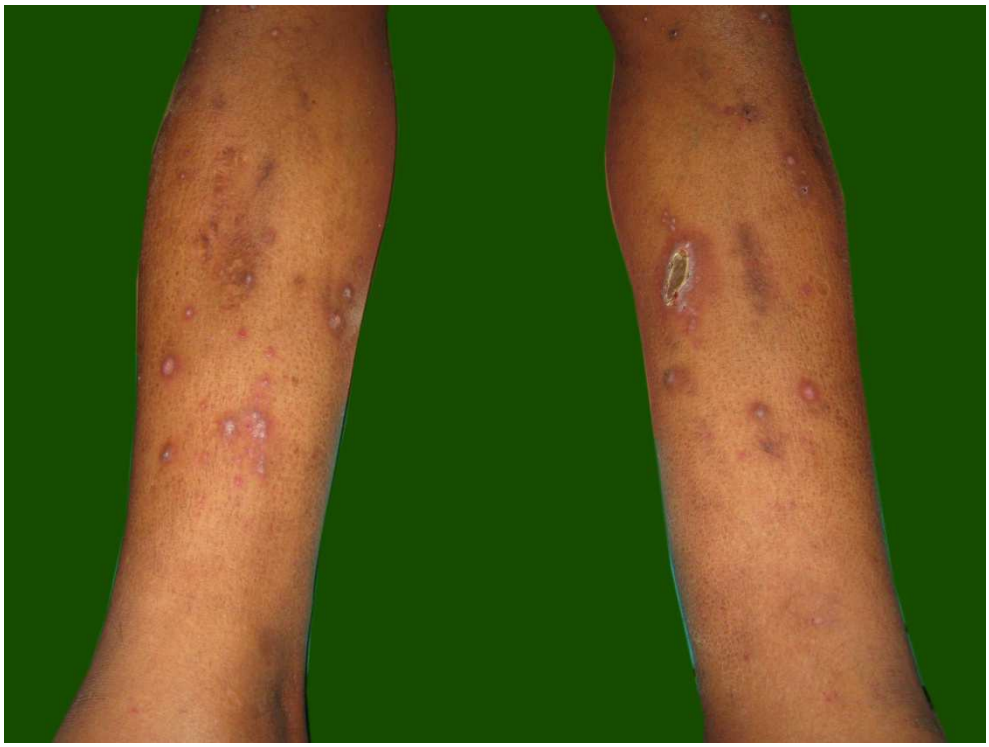
Kyrle’s disease



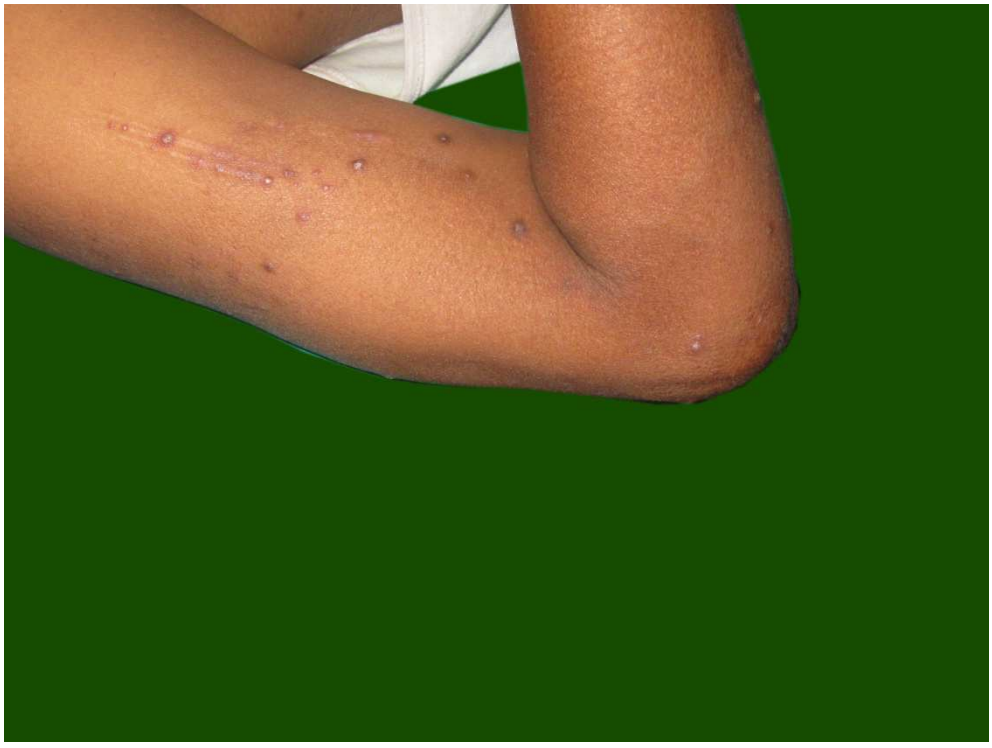
HPE of Kyrle’s disease



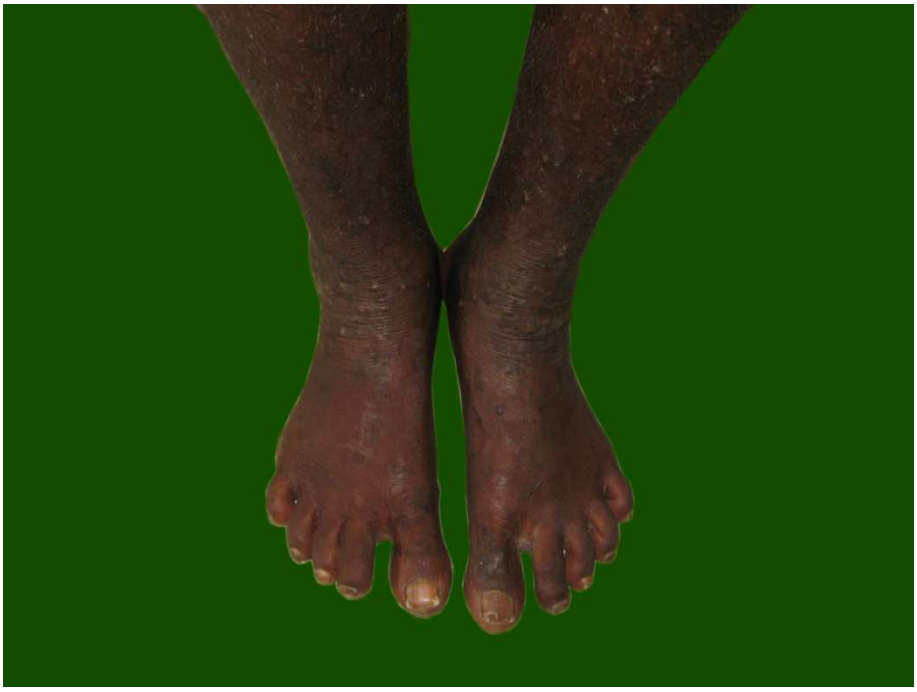
Perforating folliculitis



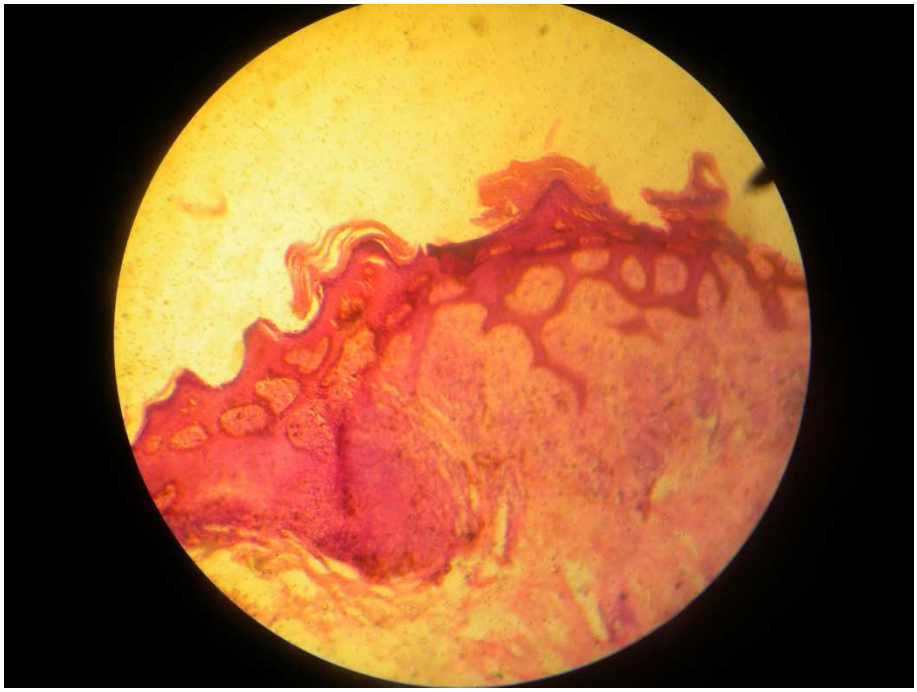
Perforating folliculitis



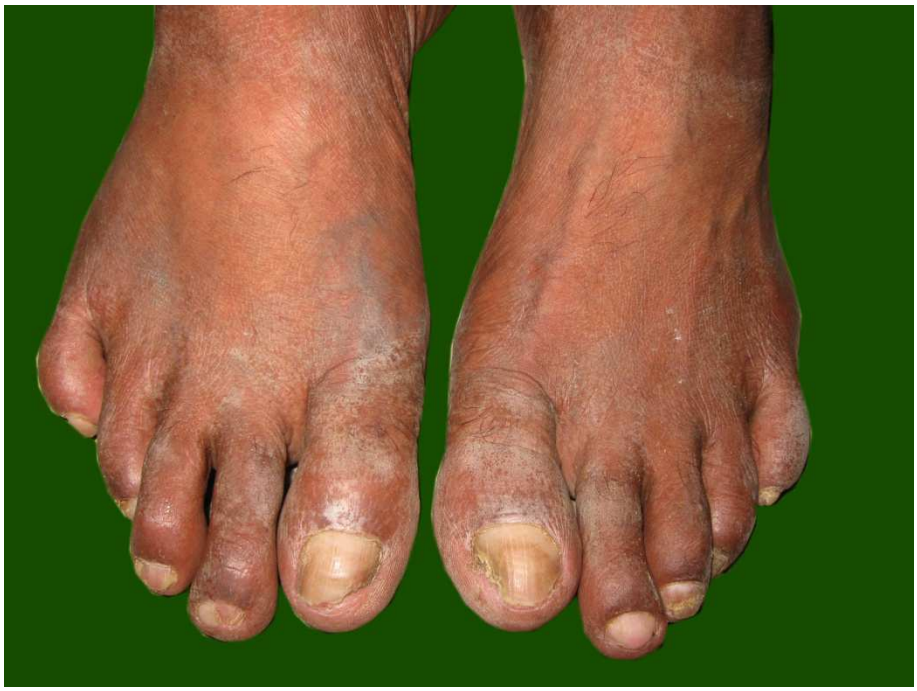
Prurigo nodularis



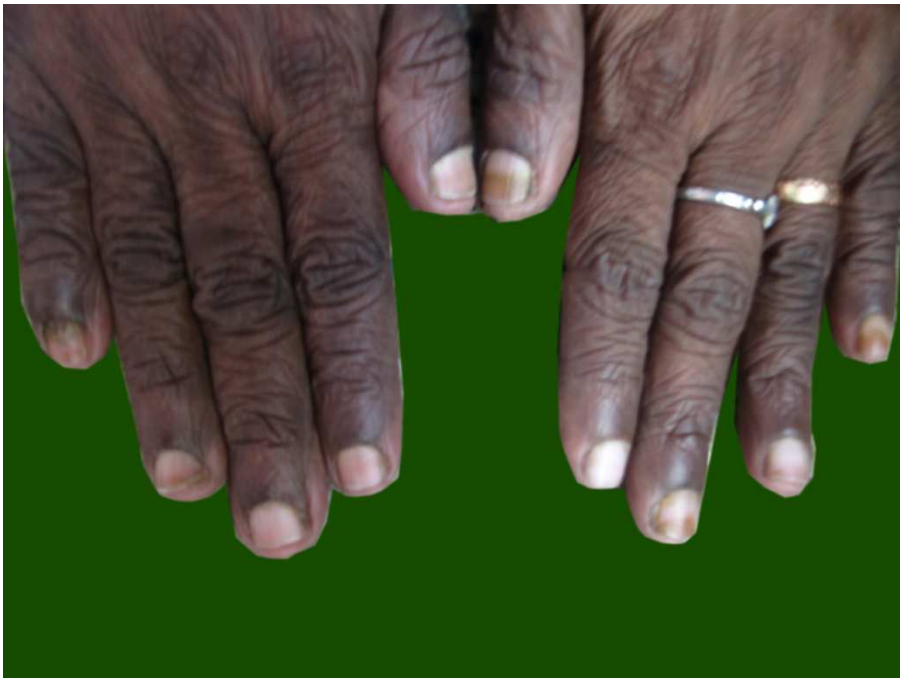
HPE of Prurigo nodularis



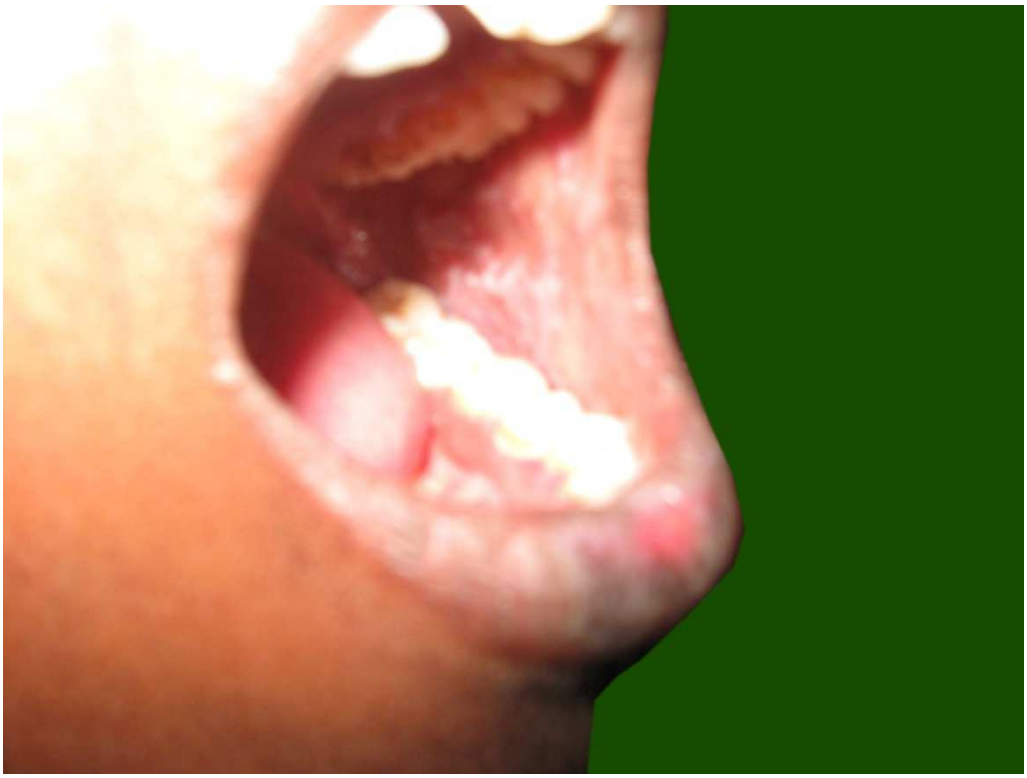
Half and Half nails



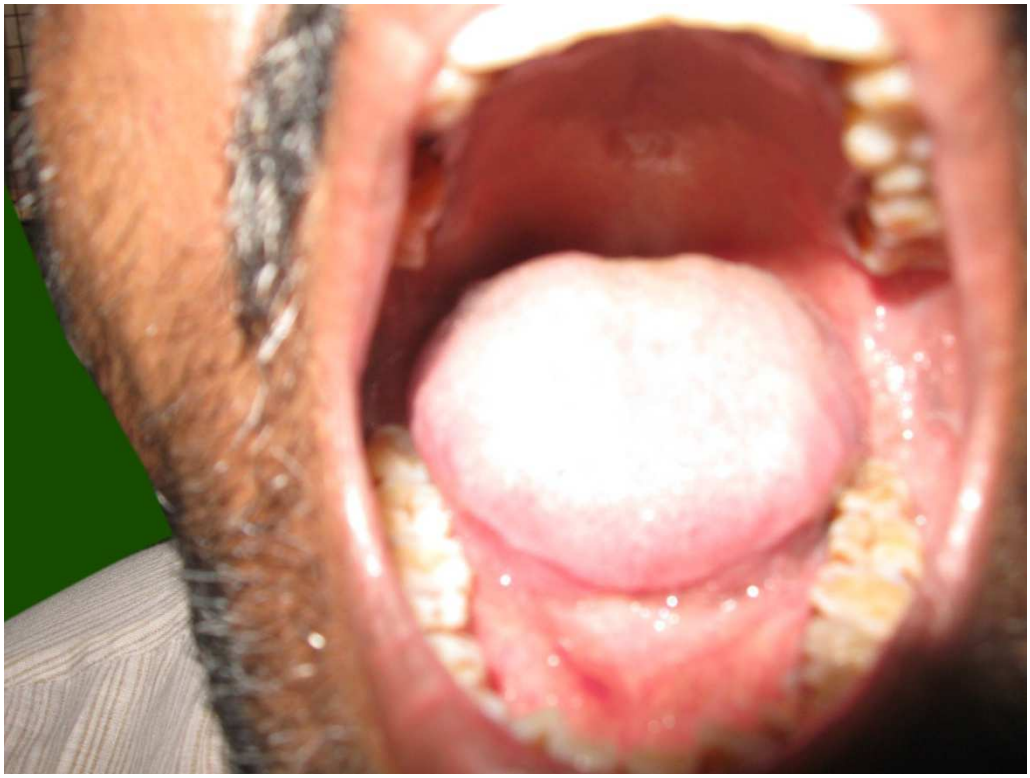
Half and Half nails



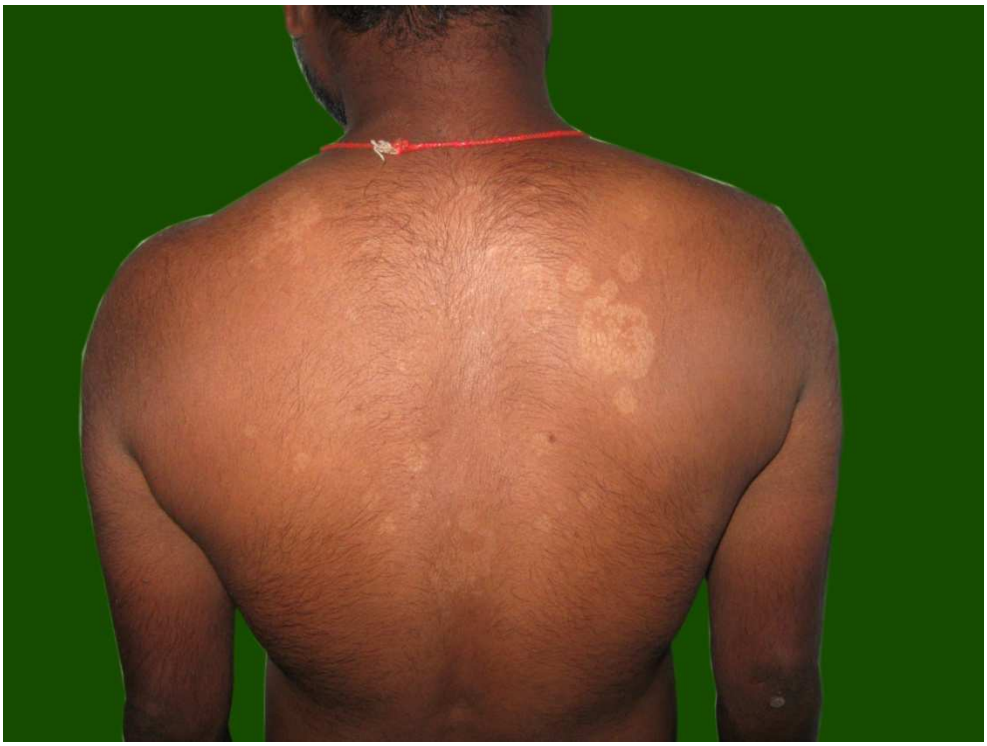
Leukokeratosis of oral mucosa



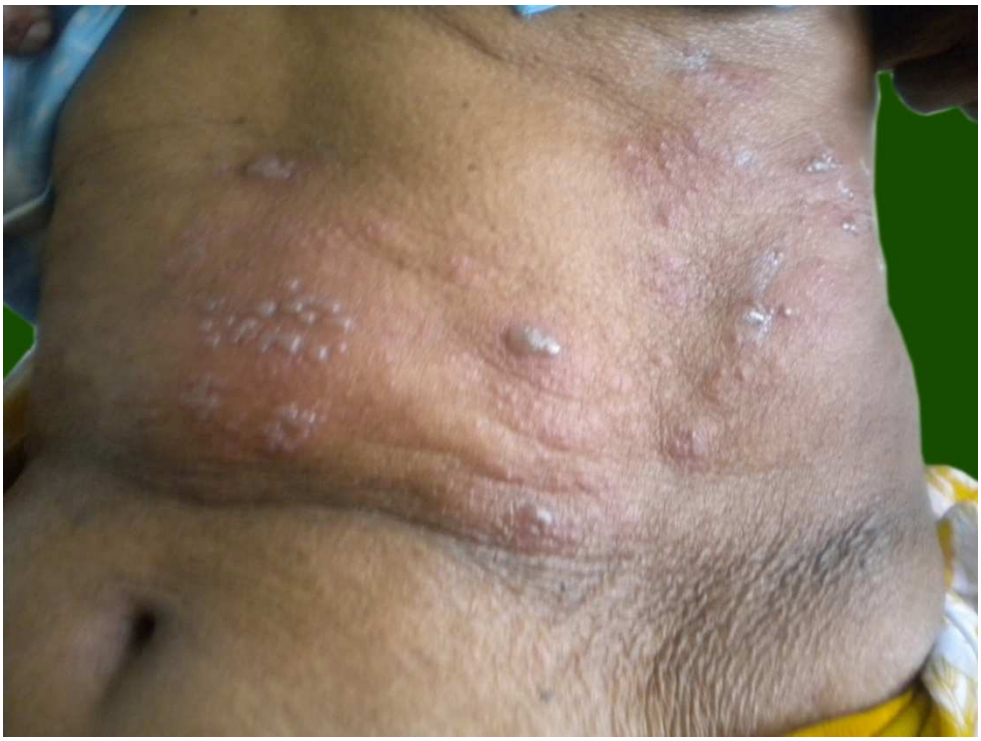
Oral ulcer



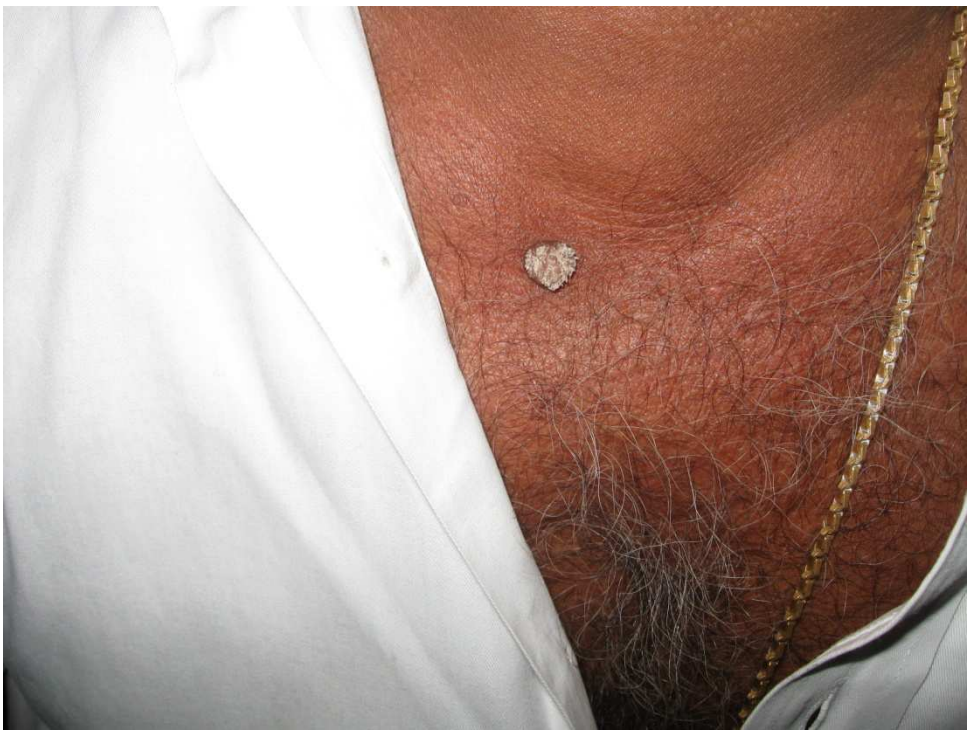
Pityriasis versicolor



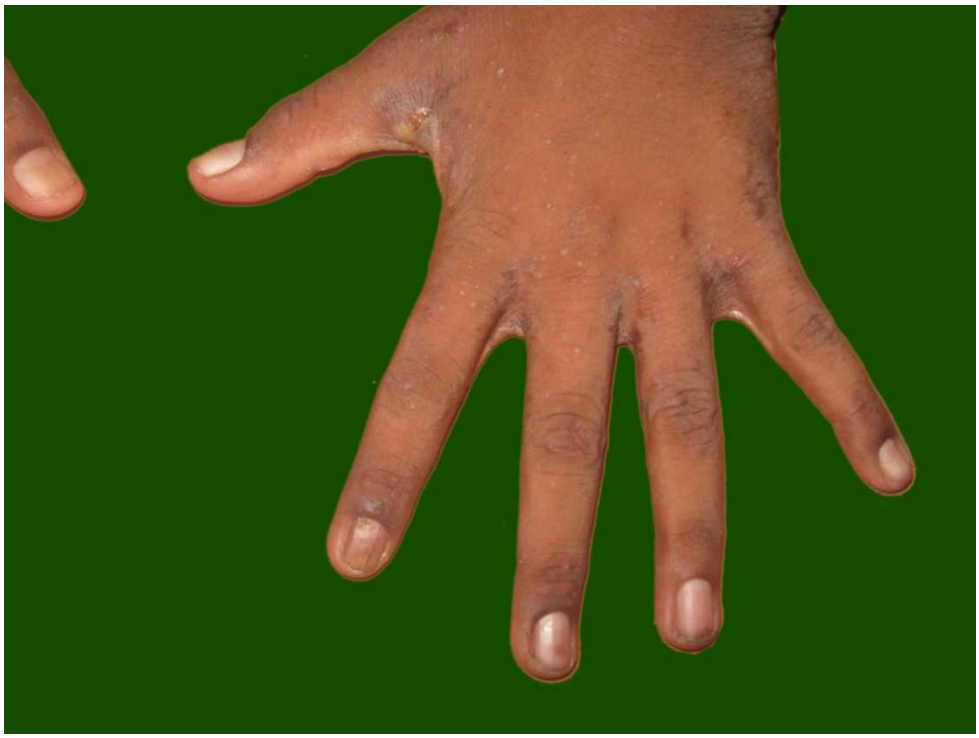
Herpes zoster



Verruca vulgaris



Scabies



DISCUSSION

DISCUSSION

In this study including 80 patients with CRF, the mean age was around 48, which is in par with the literature of 30 – 60 years.[2] There was a male preponderance in this study which goes in par with the literature.[2] The commonest age incidence among males and females in CRF patients is between 40 – 60 years and in RTR, it is 20 – 40 years.

I. Specific cutaneous manifestations of CRF :

A. Skin changes :

1. Uremic pruritus was seen in 58.8 % and is between the reported ranges of 50– 90%[35,87] in one study and 40–70%[98] in another study. It is the commonest cutaneous manifestation noted in my study.
2. Xerosis was seen in 28 patients involving both trunk and extremities. Ichthyosis was seen in 18 patients, mostly involving lower extremities. Most patients with xerosis also had associated pruritus. The incidence of xerosis/ichthyosis was found to be 57.5 %, which is in par with the literature of 50-75%.[99] This is the second commonest cutaneous change observed in my study.
3. Pigmentary alterations : Diffuse pigmentation over sun exposed areas which is reported in 60-78%[100] of uremic patients was seen only in 12.5% in this study. Pallor of the skin was seen in 27.5%, which is the commonest of pigmentary changes noted in my study. Hypermelanotic

macules of the palms and soles were seen in 5 (6.2%) patients, whereas considerable cases have been reported in the literature.[43] The total incidence of patients showing pigmentary changes was 55 %.

4. Perforating dermatoses : This was seen in 10 patients clinically. Using clinical and histopathologic correlation, Kyrle's disease was found in 2 patients, perforating folliculitis in 1 patient and features of nodular prurigo and prurigo simplex in 7 patients. The incidence of perforating disorders in this study was 3.7 %, which lies near the range of 4-10%[63], of patients in the literature.
5. Purpura was noted in 7 patients, giving an incidence of 8.7% Idiopathic thrombocytopenia was the etiology noted in 1 patient.

Interesting findings noted were digital gangrene in 1 patient, poor wound healing following trauma in 3 patients and restless leg syndrome in 3 patients.

B. Mucosal abnormalities :

Oral mucosal lesions were seen in 18 patients with incidence of 22.5 %, which is far less than that found in one study.[101] Uremic stomatitis was the commonest mucosal change seen in patients with severe end stage renal disease. Oral ulcers over the buccal and palatal mucosa were seen in 3 patients. Leukokeratosis was seen as whitish plaques in the oral mucosa, in 1 patient. Except for the haemorrhagic lesions, all the other oral mucosal changes were seen in this study.

C. Hair abnormalities :

About 7.5 % of the patients reported diffuse loss of hair and brittle dry hair was seen in 10 patients. The incidence of hair abnormalities was 12.5% .

D. Nail changes :

Half and half nails reported to occur in 15-50% [83] of uremic patients were seen in 26.2 % of patients in this study. Brown nail bed arc was seen in 8.7 % as compared to 20 – 45 % [84] in one study. Other changes noted are shiny nails (probably due to scratching), melanonychia, onycholysis and onychodystrophy. Blue nails, Mee's lines and Muercke's lines were not seen.

Specific lesions not noted in this study were bullous lesions, uremic frost and metastatic calcification.

II. Skin changes attributed to renal transplantation :

- Fungal infections (40%) was found to be the most common in this study, which is in par with literature.[86,91] Pityriasis versicolor (25%) and dermatophytosis (10%) were the two common superficial mycosis noted. Oral candidiasis was seen in 1 patient.
- Viral infections were the next highest in incidence, with verruca vulgaris (25%) found in significant number of patients, which is similar to one study of 20-40% [102] . Herpes simplex labials and Herpes zoster were seen in 5% of patients.

- ❖ Bacterial infections (20%) were low in incidence. Staphylococcus aureus was grown in pus culture in 2 of the cases.
- ❖ Classical scabies was seen in 1 patient.
- ❖ The increased incidence of cutaneous infections could be due to an increased susceptibility to infections as a result of impaired immunity in these patients.[87]
- ❖ There were no cases of premalignant or malignant skin lesions in this study. The duration after renal transplantation was between 2 – 7 years in these patients. Though the onset of malignancies is 10 - 30% [96] in 5 years of RTR, there were no cases reported in this study.

III. Associated skin lesions :

- ➢ Certain associated systemic diseases contributed to the etiology of renal failure. Skin lesions of systemic lupus erythematosus like malar rash, erythematous scaly plaques, atrophic depigmented plaques and diffuse alopecia were seen in 2 patients. Characteristic facies with pinched up nose, small mouth, sclerodactyly , salt and pepper pigmentation, hidebound skin with digital pitted scars of systemic sclerosis was noted in 1 patient. All of them had renal involvement and provided clue to the etiology of renal failure.

- Skin lesions of diabetes mellitus showing acanthosis nigricans was seen in 2 patients. Vasculitic ulcer was seen in 1 patient. Purpura as a clinical manifestation of ITP was noted in 1 patient.
- Other associated skin lesions were lichen planus, psoriasis, erythroderma, eczema with sensitization, stasis eczema, phrynoderma, vitiligo, urticaria, seborrheic keratosis and DPN, which were coincidental findings.

SUMMARY

SUMMARY

This clinical study of cutaneous manifestations of chronic renal failure and renal transplant recipients done during the period from October 2009 to October 2011, revealed the following :

1. Most of the specific cutaneous manifestations of chronic renal failure and renal transplantation were noted in this study. Pruritus (58.8%) and xerosis (57.5%) were the most common among the specific cutaneous manifestations of chronic renal failure, which is similar to another study[104]. Pigmentary changes (55%) and nail abnormalities (56.2%) were the next. Mucosal and hair abnormalities were noted in good percentage of cases. Nearly 4 % had perforating dermatosis. Interesting findings noted in this study were digital gangrene, poor wound healing and restless leg syndrome. The onset of cutaneous manifestations after CRF ranges between 6 months to 3 years in this study.
2. Skin changes due to renal transplantation were mostly due to infections (excluding medication related disorders), with fungal infections (40%) being the most commonly noted. The next to follow was viral infections (35%) with verruca vulgaris being the commonest manifestation. The high incidence of cutaneous infections in these patients could be due to impaired immunity resulting in increased susceptibility to infections. Premalignant and malignant lesions were not noted in this study. After

renal transplantation, there is improvement in pruritus in 9 (45%) patients and xerosis in 6 (30%) patients.

3. Skin changes specific to associated systemic diseases helped in finding various etiologies of chronic renal failure such as diabetes mellitus, systemic lupus erythematosus, scleroderma, vasculitis and ITP .
4. Other associated skin conditions were not related to etiology and were found to be just coincidental.

CONCLUSIONS

CONCLUSION

Pruritus and xerosis were the most common among the specific cutaneous manifestations of chronic renal failure, followed by nail abnormalities and pigmentary changes. Calciphylaxis and uremic frost were not noted in any patient. The incidence of hair and nail abnormalities were more among females than males in this study.

Cutaneous manifestations of renal transplantation were mostly due to infections, of which fungal infections were commonly observed followed by viral infections.

REFERENCES

REFERENCES

1. Robinson-Bostom L, DiGiovanna JJ: Cutaneous manifestations of end stage renal disease. J Am Acad Dermatol 2000; 43: 975-86.
2. El Nahas AM and Wineares CG. Chronic renal failure. Oxford text book of medicine 1996; 4: 3294 – 304.
3. Cumming Ed, Swainson, Davison. Diseases of the kidney and Genitourinary system. Davidson Principles and Practice of Medicine 1996; 2: 631 – 6.
4. May RC, Kelly RA and Mitch WE. Pathophysiology of Uremia 1991; 432: 1997 – 2018.
5. Ulrich H, Landthaler M, Hohenlentrak . Dialysis-associated skin changes. 2004 ; 55(5): 485-95.
6. Brenner BM , Lazarus JM. Chronic renal failure. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, editors. Harrison's Principle of internal medicine. 13th edition. New York: Mc Graw –Hill; 1994; 43: 1274-81.
7. Burton C, Harris KP. The role of proteinuria in the progression of chronic renal failure . Harrison's principles of Internal medicine 15th ed. 1996; 765(27): 1551 – 2.
8. Gilchrest BA, Stern RS, Steinman TI, Brown RS, Amdt KA and Anderson WW. Clinical features of pruritus among patients undergoing maintenance hemodialysis. Archives of dermatology1982; 11(12) :154-6.
9. Stahle-Backdahl M. Pruritus in hemodialysis patients. Skin pharmacology 1992; 5 (1): 14–20.
10. Chou et al . A study of pruitus after parathyroidectomy for secondary

hyperparathyroidism. Journal of American college of surgeons 2000; 190(11): 65-70.

11. Kato A et al . Pruitus and hydration state of stratum corneum in hemodialysis patients. American journal of nephrology 2000: 20: 437 – 42.

12. Dim Kovic et al . Uremic pruritus and skin mast cells. Nephron 1992; 6(10): 5-9.

13. Stahle – Backdahl M. Uremic pruritus: clinical and experimental studies. Acta derm venerol , stockholm 1989; 1: 154-6.

14. Berne B et al: Ultraviolet treatment of uremic pruritus reduces the vitamin A content of the skin. Eur J Clin Invest 1984: 14: 203-6.

15. Etter L, Myers SA. Pruritus in systemic disease: Mechanisms and Management. Dermatol Clin. 2002; 20: 459-72.

16. Kerr et al . Whole blood serotonin levels are markedly elevated in patients on dialytic therapy. Am J of nephrology 1992; 12: 14-18.

17. Greaves MW. Itching – Research has barely scratched the surface. New England Journal of medicine 1992; 326(18) : 1016 – 17.

18. Stahle – Backdahl M et al: Experimental and histocompatability studies of the role of parathyroid hormone in uremic pruritus. J Intern med 1989; 225: 411-4.

19. Kyriazis J, Glotosos J. Dialysate calcium concentration of less than or equal to 1.25 mmol/l: is it effective in suppressing uremic pruritus ? Nephron 2000; 8: 84-5.

20. Tan et al. Identifying effective treatment for uremic pruritus. J Am Acad Dermatol 1991; 25: 811 – 818.

21. Hindson C, Tailor A, Martin A et al. UVA – light relief of uremic

pruritus. Roo Lancet 1981; 1: 215 ; 2729 – 31.

22. Blackly JD et al: Uremic pruritus and skin ion content. Am J kidney Dis 1985; 5: 236-8.

23. Manenti L, Vaglio A, Costantino E, Danisi D, Oliva B, Pini S, et al. Treatment of uremic itch- An index case and a pilot evaluation. J Nephrol 2005; 18: 86-91.

24. Silverberg DS et al: Cholestyramine in uremic pruritus. Br J med 1971; 1: 752-3.

25. Pederson JA et al: Relief of idiopathic generalized pruritus in dialysis patients treated with oral charcoal. Ann Intern med 1980; 93: 444-6.

26. Murphy M and Carmichael AJ. Renal itch. Clinical and Experimental dermatology 2000; 25: 103 – 6.

27. Yatzidis H, Digenis P, Tountas C. Heparin treatment of uraemic itching. JAMA 1972; 222: 1183-4.

28. Tapia I et al. Pruritus in dialysis patients treated with parentral lidocaine. N Engl J Med 1977; 296: 261-3.

29. Bousquet J et al . Double blind placebo control study of nicerogoline in the treatment of pruritus in patients receiving hemodialysis. Journal of allergy and clinical immunology 1989; 83: 825 – 8.

30. Francos GC et al . Elevated plasma histamine in chronic uremia. Effects of ketotifen on pruritus. Int J Dermatol 1991; 30: 884-9.

31. Duo LJ. Electrical needle therapy of uremic pruritus .Nephron 1987; 47: 179-83.

32. Breneman DL, Scott Cardone J, Blumsack RF et al . Topical capsaicin for treatment of hemodialysis – related pruritus. J Am Acad Dermatol 1992; 26: 91-4.

33. Aubia J, Aguilera J Liorach et al. Dialysis pruritus; effect of cimetidine. Journal of dialysis 1980; 4 : 141-5.

34. De Marchi S, Cocchin E et al . Relief of pruritus and decrease in plasma histamine concentration during erythropoietin therapy in patients with uremia. New Engl J Med 1992; 326 (3): 969 – 74.

35. Sweeney S, Cropley TG. Cutaneous changes in renal disorders. In: Freedberg IM, Eisen AZ, Wolffk, Austa KF, Goldsmith LH, Katz SI, editors. Fitzpatrick's Dermatology in general medicine, 6th edition. McGraw-Hill: New York: 2003; 12: 1622-4.

36. Yoshimoto – Furuie et al: Effects of oral supplementation with evening primrose oil for six weeks on plasma essential fatty acids and uremic skin symptoms in hemodialysis patients. Nephron 1999; 81: 151-3.

37. Pauli Magnus C et al : Short term efficacy of tacrolimus ointment in severe uremic pruritus : Perit Dial Int 2000; 20: 802-3.

38. Scoggins RB, Harlan WR Jr. Cutaneous manifestations of hyperlipidemia and uremia. Postgrad Med. 1967; 4: 537-43.

39. Cawley EP, Hoch – Ligeti C and Bond GM. The eccrine sweat glands of patients in Uremia. Arch Dermatol 1961; 84: 51 – 6.

40. Park TH et al . Dry skin in patients undergoing maintenance hemodialysis; the role of decreasing sweating of the eccrine sweat gland. Nephrology, Dialysis, Transplantation 1995; 12: 2269 – 73.

41. Gilkes JJH, Eady RA., Rees LH, Munro DD and Moorhead JF. Plasma immunoreactive melanotrophic hormones in patients on maintenance hemodialysis. Br Med J 1975; 1: 656-8.

42. Singh G, Singh SJ, Chakrabafty N et al.Cutaneous manifestations of chronic renal failure. Indian J Dermatol Venerol Leprol 1989; 55: 167-9.

43. Pico MR, Lugo – Somolinos A et al. Dept of Derm. University of Pureto Rico School of Medicine San Juan 00936 – 5067. Cutaneous alterations in patients with chronic renal failure. Int J dermatol 1992 ; 31(12): 860-3.

44. Morton CA et al: Acquired perforating dermatosis in a British dialysis population. Br J Dermatol 1996; 135: 671-3.

45. Haftek M . Acquired perforating dermatosis of diabetes mellitus and renal failure: Further ultra structure clues to its failure pathogenesis. J Cutan Pathol 1993; 20: 350-54.

46. Carter VH. Kyrle's disease: Clinical finding in five cases. Arch Dermatol 1968; 97 : 624 – 32.

47. Carter VH and Constantine VS. Kyrle's disease: Histopathological finding in five cases. Arch Dermatol 1968; 97 : 633 – 8.

48. Hood AF, Hardegan GL et al .Kyrle's disease in patients with chronic renal failure. Arch Dermatol 1982; 118 : 85 – 8.

49. Chang P, Fernandez V. Acquired perforating disease associated with chronic renal failure. Int J Dermatol 1992; 31 (2): 117 – 8.

50. Saray Y, Seckin D, Bilezikci B: Acquired perforating dermatosis: clinicopathological features in twenty-two cases. J Eur Acad Dermatol Venerol 2006; 20: 679 - 88.

51. Saleh HA, Lloyd KM. Kyrle's disease: Effectively treated with isotretnoin. J – Fla – Med Association 1993; 80 (6): 395 – 7.

52. Farrell AM. Acquired perforating dermatosis in renal and diabetic patients, Lancet 1997; 349 : 895 – 98.

53. Saldanha LF, Gonick HC, Rodriguez HJ et at. Silicon-related syndrome in dialysis patients. Nephron 1997; 77: 48-56.

54. Mehregan AH and Coskey RJ. Perforating folliculitis: Arch Dermatol 1968; 97 : 394 – 99.

55. Lever WF, Lever S.G. Degenerative diseases: Histopathology of the skin. J.B. Lippincott Company, Philadelphia, 1990 ; 5: 300-1.

56. Hudson RD, Apisarnthanarax P. Renal failure and perforating folliculitis JAMA 1982; 242 : 193-6.

57. Hurwitz RM, Weiss J, Melton ME et al .Perforating folliculitis in association with hemodialysis. Am J Dermatopathol 1982; 4 : 101-8.

58. White CR, Heskel NS, Pokorny DJ. Perforating folliculitis of Hemodialysis. Am J Dermatopathol 1982; 4 : 109-16.

59. Cochran RJ, Tucker SB, Wilkin JK. Reactive perforating collagenosis of diabetes mellitus and renal failure. Cutis 1983; 31: 55-8

60. Patterson JW. Progress in the perforating disorders. Arch Dermatol 1989; 125 : 1121 – 23

61. Schamroth JM, Kellen P, Grieve TP. Elastosis Perforans Serpiginosa in a patient with renal disease: Arch Dermatol 1986; 122: 82 – 4

62. Garcio – Bravo, Rodriguez – Pichardo, Camocho F. Uremic follicular hyperkeratosis. Clinical Experimental Dermatology 1985; 10: 448 - 54

63. Am Erel and Aligurer. Acquired reactive perforating disorder associated with chronic renal failure. Int J Dermatol 1994; 33: 42-43.

64. Rapini RP, Hebert AA, Drucker RC. Acquired Perforating Dermatosis. Arch Dermatol 1989; 125 : 1074 – 78.

65. De Graaf P, Ruiter DJ, Scheffer E et al. Metastatic skin calcification: Dermatologica 1980; 161: 28 – 32

66. Ross CN, Cassidy MJ et al .Proximal cutaneous necrosis associated with

small vessel calcification in renal failure: QJ Medicine 1991; 79 (289): 443 – 50.

67. Selye H. Calciphylaxis: University of Chicago press 1962; 24: 1-16

68. Parfitt PM. Soft tissue calcification in uremia: Arch Int Med 1969; 124 : 544-8.

69. Aida Lugo Somolinos, Sanchez JL et al – Calcifying panniculitis associated with polycystic kidney disease and chronic renal failure. J Am Acad Dermatol 1990; 22: 743 – 7.

70. Roe SM, Graham LD et al .Calciphylaxis, Early recognition and Management. Ame – Surg 1994; 601 (2): 31 – 6.

71. Worth R.L. Calciphylaxis - Pathogenesis and therapy. J Cutan Med Surg 1998; 2 : 245-52.

72. Hafner J .Uremic small artery disease with medial calcification and intimal hyperplasia (so called calciphylaxis): A complication of chronic renal failure and benefit from parathyroidectomy. J Am Acad dermtol 1995; 33 : 954 – 7.

73. Walker RP. Meta-static soft calcification presenting as a tongue mass. Otolaryngology and Head and Neck surgery 1993; 109: 540 – 2

74. Enelow et al . Perforating papules in chronic renal failure. Arch Dermatol 1998; 134: 98 – 99.

75. Freeman RM, Lawton RL, Fearing MO. Gynecomastia, an endocrinological complication of hemodialysis. Annals of Internal Medicine 1968; 69 : 67 – 72.

76. Gilchrest BA, Rowe JW, and Mihm ML. Clinical and histological cutaneous finding in uremia. Evidence for a dialysis resistant transplant responsive microangiopathy. 1980; 34: 1271 –75.

77. Jaspers MT. Unusual oral lesions in a uremic patient: Oral surgery, Oral medicine and Oral pathology 1975; 39: 934 – 44.

78. Astback J, Fernstrom A, Hylander B, Arvidson K, Johansson O.Taste buds and neuronal markers in patients with chronic renal failure. Perit Dial Int 1999; 19: S315- S23.

79. Sarris. E . Diffuse alopecia in a hemodialysis patient caused by a low molecular weight heparin, tinzapirin. American journal of kidney disease 2003; 15: 41-3.

80. Ralph Daniel et al. Nails in systemic disease, Dermatology Clinics, Symposium on the nail 1985; 3: 474 – 6.

81. Philip G. Lindsay. The Half and Half Nail : Arch Int Med 1967; 119: 483 – 7.

82. Fantini, F. Baraldi et al . Cutaneous innervation in chronic renal failure patients. Acta Dermatovenerologica ,Stock holm 1992; 72: 102 – 5.

83. Lubach D, Strubbe J and Schmidt J. The 'half and half nail' phenomenon in chronic hemodialysis patients. Dermatologica 1982; 164: 350-3.

84. Steward WK and Raffie EJ. Brown nail bed arcs and chronic renal disease. Br Med J 1972; 1 : 784 – 6.

85. Caputo R, Gelmetti C and Cambiaghi S. Severe self-healing nail dystrophy in a patient on peritoneal dialysis. Br J Dermatol 1997; 194: 274-5.

86. Bencini PL, Montagnino G, De Vecchi A, Tarantino A, Crosti C, Caputo R, et al.Cutaneous manifestations in renal transplant recipients. Nephron 1983; 34: 79-83

87. Chugh KS, Sharma SC, Singh V, Sakhuja V, Jha V, Gupta KL. Spectrum of dermatological lesions in renal allograft recipients in a tropical environment. Dermatologica 1994; 188: 108-12

88. Barba A, Tessari G, Boschiero L, Chieregato GC. Renal transplantation and skin diseases: I of the literature and results of a 5 year follow up of 285 patients.Nephron 1996; 73: 131-6

89. Lugo-Janer G, Sanchez JL, Santiago-Delphin E. Prevalence and clinical spectrum of skin diseases in kidney transplant recipients. J Am Acad Dermatol 1991; 24: 410-4

90. Vijaykumar R, Fernando E, Rajendran S, Jayakumar M, Muthusethupathi MA. Dermatological manifestations in renal transplant recipients. Transpl Proc 1998; 30: 3135

91. Gulec AT, Demirbilek M, Seckin D, Can F, Saray Y, Sarifakioglu E, et al. Superficial fungal infections in 102 renal transplant recipients: A case-control study.J Am Acad Dermatol 2003; 49: 104-14

92. Koranda FC, Dehmel EM, Kahn G, Penn I. Cutaneous complications in immunosuppressed renal homograft recipients. JAMA 1974; 229: 419-24

93. Dyall SD, Trowell H, Dyall SML. Benign human papillomavirus infection in renal transplant recipients. Int J Dermatol 1991; 30: 785-9

94. Rudlinger R, Smith IW, Bunney MH, Hunter JA. Human papillomavirus infection in a group of renal transplant recipients. Br J Dermatol 1986; 115: 681-92

95. Brown JH, Hutchinson T, Kelly AM, McGeown MG. Dermatologic lesions in a transplant population. Transplantation 1988; 46: 530-32

96. Hoxtell EO, Mandell JS, Murray SS, Schuman LM, Goltz RW. Incidence of skin carcinomas after renal transplantation. Arch Dermatol 1977; 113: 436-8.

97. Gilchrist B.A, Rowe W.J.,Mihm C.M: Clinical and histological skin

changes in chronic renal failure: evidence for a dialysis resistant transplant responsive microangiopathy; The Lancet 1980: 1271-75.

98. Diouf B, Niang A, Ka EH, Badaine M, Mo-reiva Diop T. Chronic renal failure in one Dakar Hospital Department Dakar Med 2003; 48(3): 185-8.

99. Udayakumar P, Balasubramanian S, Ramalingam KS, Lakshmi C, Srinivas CR, Mathew AC. Cutaneous manifestations in patients with chronic renal failure. Indian J Dermatol Venerol Leprol 2006; 72: 119-25.

100. Silverberg NB, Singh A, Laude TA. Cutaneous manifestations of chronic renal failure in children of colour. Paediatr Dermatol 2001; 18: 199-204.

101. Cohen GS. Renal disease. In: Lynch MA, editor. Barket's oral medicine: Diagnosis and treatment, 9th edition. Philadelphia: Lippincott- Raven: 1997; 3: 487-509.

102. Kafaie P, Najafi F, Noorbala MT. Journal of Pakistan Association of Dermatologists 2010; 20: 15-18.

103. Fine A, Zacharias J, Kidney Int 2002; 61: 2210-7.

104. Falodun O, Ogunbigi A, Salako B, George AK. Skin changes in patients With chronic renal failure. Saudi J Kidney Dis Transpl. 2011; 22: 268-72.

ABBREVIATION

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CRF - Chronic Renal Failure

RT - Renal Transplantation

RTR - Renal Transplant Recipients

ESRD - End Stage Renal Disease

OPD - Out Patient Department

DEJ - DermoEpidermal Junction

HPE - HistoPathological Examination

ITP - Idiopathic Thrombocytopenic Purpura

SLE - Systemic Lupus Erythematosus

DPN - Dermatosis Papulosa Nigra

DM - Diabetes Mellitus

GFR - Glomerular Filtration Rate

PROFORMA

PROFORMA

Clinical study of skin manifestations in chronic renal failure and renal transplantation

1. Name :
2. Age / Sex :
3. Address :
4. OP No. :
5. Category of patients : Cutaneous manifestations
    a. Associated with chronic renal failure
    b. Associated with renal transplantation
6. Complaints regarding skin manifestations :

Complaints	Duration	Site
a) Pruritus		
b) Pigmentation		
c) Purpuric spots		
d) Hair changes		
e) Nail changes		
f) Poor wound healing		
g) Any other skin changes		

7. General Examination
    a. anemia
    b. edema
    c. hydration
    d. pulse rate
    e. BP
    f. CVS
    g. RS
    h. P/A
    i. CNS
    j. Fundoscopy

k. P/R in male
l. P/V in female

8. Dermatological Examination:
    a. Cutaneous manifestations specific for renal failure
        i. Skin changes
            1. Pruritus
            2. Pigmentary disturbances
            3. Xerosis / ichthyosis
            4. Perforating dermatosis
            5. Purpura, ecchymoses, haematoma
            6. Metastatic calcification – calcinosis cutis, calciphylaxis
            7. Uremic frost
            8. Poor wound healing
            9. Gynecomastia
            10. Scratch marks
        ii. oral mucosal changes
        iii. nail changes
        iv. hair changes
    b. Cutaneous manifestations specific for renal transplantation
        i. Infections
            1. Viral
            2. Bacterial
            3. Fungal
            4. Parasitic
        ii. Premalignant / Malignant lesions
            1. Actinic keratoses
            2. Squamous cell carcinoma
            3. Basal Cell carcinoma
            4. Kaposi sarcoma

5. Melanoma
6. Other Malignancies

c. Other associated cutaneous manifestations

9. Investigations
   a. Renal
      i. urine analysis
      ii. urine culture
      iii. blood Hb%
      iv. blood TC
          DC
          ESR
      v. platelet count
      vi. blood - urea
          - sugar
      vii. serum - creatinine
          - electrolytes
          - alk. phosphatase
      viii. USG abdomen
      ix. Duplex doppler scan of renal arteries
      x. MR angiography
      xi. renal biopsy
   b. Skin
      i. skin biopsy
      ii. Tzanck smear
      iii. scraping for fungus - 10% KOH
          - Culture

MASTER CHART

S.No	Name	Age	Sex	SPECIFIC CUTANEOUS MANIFESTATIONS OF CRF														SPECIFIC CUTANEOUS MANIFESTATIONS OF RENAL TRANSPLANTATION					SKIN CHANGES CONTRIBUTED TO THE ETIOLOGY OF CRF					INCIDENCE OF ASSOCIATED SKIN CONDITIONS									
				Pruritus	Xerosis/ichthyosis	Pigmentary alterations	Uremic frost	Perforating disorders	Metastatic calcification	Purpura	Gynaecomastia	Vascular disorders	Poor wound healing	Restless leg syndrome	Mucosal changes	Hair abnormalities	Nail abnormalities	Bacterial infections	Viral infections	Fungal infections	Parasitic infections	Premalignant and malignant conditions	DM	SLE	Scleroderma	Vasculitis	ITP	Lichen planus	Psoriasis	Erythroderma	Eczema with sensitization	Stasis eczema	Vitiligo	Phrynoderma	Urticaria	Seborrheic keratosis / DPN	Erythema nodosum
1	Mariammal	55	F	P	P										P		P						P													
2	Saral	40	F	P	P					P							P																			
3	Subbaiyah	35	M	P				P															P													
4	Kuppusamy	49	M	P		P										P	P						P													
5	Karuppasamy	65	M	P	P	P																	P												P	
6	Pokkisam	52	F	P	P	P									P								P													
7	Nethaji	32	M	P											P	P																P				
8	Lawerence	56	M	P	P												P																	P	
9	Kuttidurai	53	M	P	P	P																	P									P				
10	Avudaiappan	3O	M												P	P	P															P				
11	Mookammal	68	F	P	P												P																	P	
12	Ponnikaniammal	65	F	P		P									P	P	P																P			
13	Karuppasamy	38	M			P		P									P																			
14	Ramalingam	31	M	P											P													P							
15	Balasubramaniyan	25	M			P									P	P		P																		
16	Alithurai	42	M	P		P									P																	P				
17	Kalyani	46	F		P	P										P		P					P													
18	Kaliyammal	28	F			P									P	P								P												
19	Marimuthu	65	M		P	P											P															P				
20	Irudhayadurai	45	M		P			P									P																			
21	Arumugasundari	45	F	P						P						P	P																			
22	Parvathy	55	F		P												P															P				
23	Kannan	34	M	P											P	P	P		P																	
24	Paramasivam	70	M	P	P	P																													P	
25	Duraipalam	48	M			P		P							P		P				P															
26	Alliyammal	55	F		P	P										P	P																			
27	Krishnan	58	M	P		P									P																	P			P	
28	Suryanarayana	68	M	P		P									P																					
29	Beer mydeen	47	M		P									P	P		P						P													

30	Marimuthu	44	M		P			P																															
31	Ramalingam	47	M	P											P		P																						
32	Ramzan beevi	36	F												P	P	P	P																				
33	Asaikani	43	M		P	P												P																				
34	Krishnammal	45	F	P												P	P																				P		
35	Essakiammal	23	F			P									P	P									P													
36	Kadarkarai	43	M		P	P																																
37	Sundari	45	F		P										P	P								P										P				
38	Lakshmi	46	F		P										P		P																			P		
39	Muthulakshmi	56	F	P	P	P									P									P														
40	Vandimalayan	60	M	P	P	P											P							P										P		P		
41	Selvi	25	F	P	P												P																	P				
42	Shahul hameed	32	M	P									P		P																			P				
43	Zakeer husain	32	M	P												P				P														P				
44	Krishnan	58	M		P	P										P				P																		
45	Nallusamy	43	M	P		P											P																	P				
46	Karuppasamy	50	M	P		P											P																					
47	Sornapillai	57	M	P	P	P											P																					
48	Thangapandi	65	M		P											P																			P		
49	Arumugasankar	16	M	P											P		P																		P			
50	Rosline	60	F	P	P	P																														P		
51	Gopalakrishnan	63	M		P											P																						
52	Chellammal	50	F		P	P		P									P																					
53	Vanaja	44	F		P	P								P			P																					
54	Ramalingam	47	M	P	P	P																														P		
55	Ayyanar	35	M	P	P									P			P																			P		
56	Muthukumar	33	M	P	P															P										P								
57	Petchiammal	35	F		P	P		P		P							P																					
58	Midhar mydeen	39	M	P											P		P			P									P									
59	Utchimakali	55	F		P	P		P																														
60	Azad kani	43	M		P	P														P																	
61	Gomathinayagam	40	M	P		P													P																			
62	Muthaiyah	55	M	P	P	P																																
63	Komala	29	F					P							P	P			P																P			
64	Thomas	60	M	P		P										P																		P				
65	Murugan	35	M	P	P					P							P											P										
66	Chellammal	47	F	P		P										P	P																					P
67	Jeyaraman	23	M	P				P																														
68	Mathi	41	F	P	P					P							P									P												
69	Rahamathulla	41	M	P	P														P																			
70	Chellammal	65	F		P	P									P		P												P							P	
71	Marimuthu	65	M		P	P		P																													P	

72	Deivanai	45	F	P						P						P	P						P														
73	Samuvel	65	M	P		P											P																				
74	Vandimalayan	60	M	P		P											P																				
75	Pitchaipillai	62	M	P		P											P																				
76	Samgodson	20	M	P						P			P																								
77	Velu	67	M	P	P																										P						
78	Paramasivam	45	M	P		P											P												P								
79	Sadasivam	58	M			P											P												P								
80	Maharasiammal	70	F	P	P	P											P															P				P		
81	Ganesh	40	M	P		P									P		P		P																		
82	Senthilnayagar	31	M	P						P							P			P																	
83	Sheik mohamed	33	M	P	P	P											P																				
84	Thangammal	37	F	P		P											P																				
85	Ganesan	58	M	P	P												P																				
86	Sivasakthi	20	F	P				P									P																				
87	Petchiammal	35	F	P		P											P								P												
88	Petchiammal	55	F		P	P											P						P														
89	Ayyanpillai	48	M	P	P					P							P																				
90	Madathi	17	F	P						P							P																			P		
91	Shanmugasundari	24	F					P									P		P																P		
92	Parvathi	53	F	P		P				P							P																				
93	Muthuselvi	20	F	P				P									P																				
94	Fathima	40	F	P	P												P			P																	
95	Suriyanarayanan	69	M	P	P	P											P																				
96	Selvaraj	34	M	P		P						P																									
97	Gopalakrishnan	70	M	P		P											P																				
98	Seethai	66	F	P	P	P											P																			P	
99	Dhanappan	23	M	P						P							P		P																		
100	Simsom	26	M	P	P	P							P							P																	

P- Present