# A CLINICAL STUDY OF THE CUTANEOUS MANIFESTATIONS OF CHRONIC RENAL FAILURE

## *Dissertation*

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# CERTIFICATE

This is to certify that the dissertation entitled **"A CLINICAL STUDY OF THE CUTANEOUS MANIFESTATIONS OF CHRONIC RENAL FAILURE"** is a bonafide work done by **Dr. K. Dhanalakshmi**, Post Graduate student of Department of Dermatology and Leprosy and Institute of STD, Madras Medical College and Government General Hospital, Chennai for the award of Degree of M.D. Dermatovenereoleprology (Branch XII-A) during the academic period of 2003-2006. This work has not previously formed the basis for the award of any degree or diploma.

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# INTRODUCTION

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 20$^{th}$ century have provided renal replacement therapy as a life-sustaining option for many individuals who otherwise may have died. For each year of the last 10 years, the number of individuals with end stage renal disease has grown approximately 20,000 per year.

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

# REVIEW OF LITERATURE

## DEFINITION:

Chronic renal failure is defined as the irreversible, substantial and usually long-standing loss of renal function causing ill health usually referred to as uremia.

End stage renal disease represents a clinical state in which there has been an irreversible loss of endogenous renal function 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[1]. Uremia 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 [2]

## 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 2001 report revealed diabetes mellitus to be the most common cause of end stage renal disease from 1993 – 97. Diabetes mellitus was responsible for more than 44% of new cases [2].

Etiology of chronic renal failure [3]

A) Congenital and inherited diseases

- Polycystic kidney disease
- Alports syndrome
- Congenital hypoplasia

B) Vascular diseases

- Arteriosclerosis (Hypertension)
- Vasculitis (Poly arteritis nodosa, Systemic lupus erythematosus, Scleroderma)

C) Glomerular diseases

- Proliferative Glomerulonephritis
- Crescentic Glomerulonephritis
- Membranous Glomerulonephritis
- Mesangiocapillary Glomerulonephritis
- Glomerulosclerosis
- Diabetic glomerulosclerosis
- Secondary Glomerulonephritis (Poly arteritis nodosa, Systemic lupus erythematosus, Amyloidosis)

D) Interstitial diseases

- Chronic pyelonephritis
- Vesico ureteric reflux
- Tuberculosis
- Analgesic nephropathy
- Nephrocalcinosis
- Schistosomiasis
- Unknown origin

E) Obstructive uropathy

- Calculus
- Retroperitoneal fibrosis
- Prostatic hypertrophy
- Pelvic tumors

F) Rare causes < 1% of the cases

- Alport's syndrome
- Hemolytic uremic syndrome
- Metabolic disorders

## PATHOPHYSIOLOGY OF CHRONIC RENAL FAILURE: [4, 6]

The exact pathogenesis of the clinical syndrome of uremia is unknown. The pathophysiology of uremic 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) [7.] The various uremic toxins [5]

are by-products of protein and aminoacid metabolism such as urea, guanido compounds, methyl guanidines, urates, hippurates,

end - products of nucleic acid metabolism, end products of aliphatic acid metabolism, 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 hypotheses. 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 uremic 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, glomerular filtration rate (GFR) 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 becomes impossible [5].

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, paraesthesia, 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 hypo albuminemia, urinalysis shows proteinuria, total 24 hr 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 anti-bodies, 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 UREMIA: [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 at least 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 treatment (drugs & dialysis) of renal failure.

## I. SPECIFIC CUTANEOUS MANIFESTATIONS OF CRF

Primary dermatologic manifestations associated with uremia are

*A.* SKIN CHANGES

### 1. Pruritus:

Uremia is the most common metabolic cause of pruritus and pruritus is the most common and troublesome cutaneous manifestation of uremia.

### Incidence:

Significant pruritus affects 15 – 49% 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 predominantly are 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 researches have concluded that end stage renal disease prutitus is

multifactorial.[9, 10] Some proposed causes of uremic 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]
- Uremic sensory neuropathy [17]– Johannson, Hlliges, & Stahle –Backdahl (1989) [18], identified and implicated a fine neuron specific immuno reactive nerve fiber laden with enolase, an acidic enzyme found in neurons, neuro endocrine 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 daltons. $\beta_2$ microglobulin, advanced glycosylation end products and parathyroid hormones are the middle molecules that have been evaluated, but their role is uncertain.

**Clinical presentation**:

Normal or Xerotic skin

Excoriations from scratching

Prurigo nodularis

LSC

**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 alleviate xerosis by depleting the skin of prutitic agent.

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 retinol content [14]

PUVA – 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 (5g 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]

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

xii. Nicerogoline 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. Trans-cutaneous 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]

xix. Mexiletine [35]

xx. Oral evening primrose oil [36, 37] and topical Tacrolimus [36, 37]

**2. Xerosis / Ichthyosis:**

Cutaneous dryness is the most frequent cutaneous abnormality in uremic patients. Significant xerosis occurs for unknown reasons in 50 – 75% 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. Sometimes variable degree of 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 with decreased sweating. [39, 40]
ii. Decrease in water content in the epidermis.
iii. Hyper or hypovitaminosis A– plasma and skin content of vit.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 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 dermatosis. Emollients may give symptomatic relief.

**3. Pigmentary alterations**: A multitude of uremia related changes are responsible for the pigmentary alterations.

- Pallor – it was common before the widespread use of erythropoietin. It is attributed to the significant anemia (reduced erythropoiesis and increased hemolysis)
- Sallow yellow discolouration is attributed to retained urochromes and carotene in the epidermis and subcutaneous tissue[2].
- Diffuse hyper pigmentation 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.
- An increased prevalence of hyper pigmented macules on the palms and soles has been reported in a large series of uremic patients.[43]

4. **Uremic 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 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**:

4 – 10% [63] of patients with chronic renal failure develop various perforating disorders. 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 micro deposition 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 chronic renal failure. 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 chronic renal failure.

**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 or itchy follicular or extra-follicular lesions.
- Hyperkeratotic verrucous plaques.
- Do not involve mucous membrane, palmar or plantar surfaces.

**Histopathological criteria** [47] are

- 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 intra-lesional glucocorticoids

Topical Tretnoin

Topical 5-FU

UVB [44, 52]

PUVA[44, 52]

Cryotherapy

Systemic isotretnoin

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 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] are

Widely dilated hair follicle 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. Uremic 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 glucocorticloids, topical retinoic acid, topical 5 Fluorouracil, UVB, control of serum phosphorus level.

6. **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 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. Hypocalcaemia occurs as a direct result of their hyperphosphatemia and is worsened by renal failure induced vit.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.

**HPE**:

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 includes free fatty acids, which causes accumulation of keto acids, metabolic products of fatty acids resulting 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 and colchicines
d) Intralesional corticosteroid – anti-inflammatory 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 for 5 years. It causes antagonism of the calcium – sodium ion pump.

***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 'challengers' and only after a critical lag time. Experimental sensitizing events and agents included nephrectomy and exposure to parathyroid hormone and vit. D. Substances used as challengers included egg albumin and metallic salts. Calciphylaxis was the end result.

**HPE**:

Calcification within the media of small and medium sized arterioles with external intimal

hyperplasia and fibrosis. 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, reduction of dialysate calcium concentration.
- ✓ Prevention of superimposed infections with wound care and debridement,of gangrenous tissue, antibiotics and hyper baric oxygen and pain management.

***Surgical***

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

**Complications:**

Ranges from moderate interference with activity to death.

- Non-healing ulcers and cutaneous gangrene
- Amputation
- Sepsis
- GI hemorrhage, infarction, and organ failure

**Prognosis**: Grave. [70]

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

**Causes 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**:

It is occasionally seen in patients with chronic renal failure of unknown etiology. It is thought to be an endocrinological complication of renal failure and dialysis. [75]

9**. Vascular disorders**:

i. **Microangiopathy** – severe microangiopathy has been revealed in skin biopsies from 75% of patients with chronic renal failure. [76]

**HPE**:

- 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 an ominous prognosis.

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

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

11. **Restless leg syndrome** is characterized by burning, painful paraesthesia of the dorsal or plantar surface of the feet and it is due to peripheral neuropathy.

*B*. ORAL MUCOSAL CHANGES:

Jaspers has reviewed oral changes, which occur 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 forearm and legs

- Diffuse alopecia of scalp [79]
- Fine dry and brittle hair
- Trichoclasia and trichorrhexis nodosa
- Hair discolouration

Microscopic examination of hair in uremia shows hair in telogen phase. With scanning electron microscope, uremic 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 1963. Although not pathognomonic of renal failure, they occur in 15-50 % [114] of patients on dialysis and disappear several months after successful renal transplantation. Half and half nails are characterized by a dark distal band that occupies 20 – 60% of the nail bed and by a white proximal band. The

distal dark band may range in color from reddish to brown. 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.
- 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. [82] It is the most useful onychopathologic indicator of renal failure.

***ii.*** Brown nail bed arc: [83]

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.

***iii.*** Mee's lines:

Single or multiple transverse white bands.

***iv.*** Muercke's lines:

Double white transverse lines that represent an abnormality in the vascular bed of the nail.

***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.

***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. [84]

II. SKIN MANIFESTATIONS DUE TO TREATMENT:

1. Pruritus

The incidence of renal pruritus in patients on long term hemodialysis has been shown to be as high as 50 – 90% [85, 34] Some patients complain of pruritus only during or soon after dialysis, whereas others report symptomatic exacerbation during the same period. Pruritus may also be a sign of inadequate dialysis. [86, 87]

2. Xerosis:

Significant xerosis occurs for unknown reasons in 50 – 75% of the dialysis population. Studies have shown no difference in the hydration of the stratum corneum or the trans epidermal water loss between patients on chronic dialysis and controls. However, simple emollient therapy has been shown to improve symptoms of pruritus in patients on chronic dialysis, perhaps through rehydration of the stratum corneum. [88]

Immuno-histochemical studies have shown neuron-specific enolase, immuno-reactive nerve fibres sprouting through the epidermis in dialysis patients, but not in control subjects indicating that abnormal pattern of cutaneous innervation may occur in dialysis patients which may account for their pruritus. [89]

3. Pigmentary changes

Brown diffuse hyper pigmentation is more evident in the areas exposed to sunlight found in about 60 – 78% [43] of dialysis patients. The incidence is greater in patients with longer duration of dialysis. Rare cases of diffuse bluish gray discoloration [90] of the skin and nails referred to as ‘argyria’ have been reported. Acquired hair and skin fairness, [91] a result perhaps of a disturbance of phenyl alanine metabolism, may occasionally be found in dialysis patients. A sudden deepening of pigmentation [92] during hemodialysis can develop in patients with severe hemolysis.

4. Keratotic pits of palms and soles
5. Chronic hemodialysis – related porphyria/ pseudoporphyria/ drug induced bullous dermatoses.

   In a considerable proportion of the patients with chronic renal failure, skin changes resembling porphyria cutanea tarda develop some months to years after the onset of maintenance hemodialysis. This can be either

   a. Real porphyria cutanea tarda
   b. Secondary porphyria cutanea tarda
   c. Porphyria cutanea tarda – like bullous dermatoses

**a. Porphyria cutanea tarda**: [93, 94] It is seen in minor proportion of patients. Chronic renal failure can influence hepatic porphyrin synthesis by reducing Uroporphyrinogen decarboxylase activity. This deficiency with impaired renal clearance of porphyrins leads to an accumulation of porphyrins. Increased plasma levels of uroporphyrin do not cross the dialysis membrane. Porphyria cutanea tarda can be diagnosed on the basis of increased total porphyrin levels with a predominant of uro I > III and heptocarboxy porphyrin III > I and fecal isocoproporphyrin. [95]

**Treatment**: Phlebotomy or chloroquine therapies are not usually advisable or effective in patients with chronic renal failure. Erythropoietin has been shown to be an effective treatment for porphyria cutanea tarda in chronic renal failure population, either alone or in combination with phlebotomy. [96, 97]

**b. Bullous dermatoses** [98] of hemodialysis or pseudoporphyria

It is a syndrome of cutaneous fragility and blistering. It is seen in higher proportion of chronic renal failure patients. It is a bullous disorder clinically and histopathologically

indistinguishable from porphyria. Gilchrist et al described it in the year 1975 and called it "bullous dermatoses of hemodialysis". Korting in the same year observed several uremic patients with skin changes mimicking porphyria cutanea tarda and coined the term "pseudoporphyria". It occurs in 1-18% [99] of patients on maintenance hemodialysis. Higher female: male ratio is observed. It is more often observed in adults. It occurs more frequently during the summer. It has been reported both in a patient undergoing peritoneal dialysis [100] and in a patient undergoing hemodialysis after reactivation of hepatitis C infection. [101]

**Clinical features:**

**Morphology**: It usually presents as vesicles/ bullae that resolve in few days. Erosions and atrophic scarring are seen. Sometimes milia and dyspigmentation are also observed. Sometimes the bulla may be filled with hemorrhagic fluid. Fragility of the skin is present.

**Pathogenesis**:- Due to unsatisfactory renal function, plasma porphyrins are elevated of which uroporphyrin and heptaporphyrins are the dominant fractions. But alterations in the ratio of the uro isomers or the presence of isocoproporphyrin cannot be expected.

- May be due to a non-porphyrin photo sensitizing chemical released by the polyvinyl chloride used in the plastic tubing for dialysis.

- Excess transfusion leads to iron overload which results in the development of porphyria cutanea tarda.

- Multiple transfusions lead to hepatitis C virus infection, which result in porphyria cutanea tarda.

- Effect of aluminum concentration from the environmental sources result in alteration of enzymatic process of heme biosynthesis resulting in overproduction of porphyrins.

**HPE**:

Kalman and Keechzes and Malcolm farr [102] in their study showed subepidermal bulla.

Edema in the dermis with scant perivascular lymphocytic infiltrate seen.

**Electron microscopy**:

Thickening of dermal venular walls and dermo-epidermal junction due to replicated basal laminae. Hypogranulated mast cells and granulofilamentous hyaline masses in the dermal connective tissue that appear to be secreted by adjacent fibroblast.

**Direct immuno fluorescence**:

Presence of IgG and inconsistent IgA, IgM, fibrin, complement around dermal venules with IgG and complement noted at dermo-epidermal junction or bulla floor.

***Note***: due to usage of erythropoietin and screening for Hepatitis C virus, there is decreased occurrence of pseudoporphyria.

c. **Drug induced bullous dermatoses**:

This disorder caused by exposure to photosensitizing drugs. It is clinically and histologically indistinguishable from both porphyria cutanea tarda and hemodialysis – related porphyria. Phototoxic bullous eruptions have been reported in uremic patients taking nalidixic acid, nabumetone, tetracycline, phenytoin, high dose frusemide and flutamide. [103,104] The diagnosis is based on a positive H/o photosensitizing drug ingestion. Resolution of bullous dermatoses usually occurs after the causative agent is discontinued.

**Treatment:** discontinuation of photosensitizing drug

avoidance of sunlight and visible light and topical sun block preparation

protection of exposed skin from mechanical trauma

N-acetyl cysteine, a glutathione precursor orally at a dose of 70 mg/kg p.o. Q 4h, brings resolution of blistering and fragility after 1-2 months of therapy

topical or systemic antibiotics to combat infection

6. Arteriovenous shunt dermatitis:

About 8% of the patients on chronic hemodialysis suffer from AV shunt dermatitis. [105]

***a.*** Arterio-Venous shunt dermatitis

It is characterized by irritant contact dermatitis from soaps, disinfectants and alcohol used for skin cleansing during hemodialysis. This dermatitis is most common in patients with pruritus.

**Treatment**:

- ✓ Mild topical steroids and substitution of normal saline for skin cleansing before hemodialysis.

***b.*** Dermopathy associated with venous hypertension of hand caused by hemodialysis shunt is much rare. It is characterized by swelling, induration, hyperpigmentation and even ulcer formation restricted to thumb and index finger. This disorder may be related to peri-capillary cuffs of fibrin due to venous hypertension. [106]

***c.*** Arterial steal syndrome:

It is uncommon but highly morbid complication of the vascular access necessary for hemodialysis. Production of an adequate vascular access required the formation of an arterio-venous cannula either by using native vessels (arterio-venous fistula) or by placing synthetic tubing (arterio-venous graft). Vascular access is typically placed in the upper extremities.

Arterial steal syndrome may develop if the inevitable proximal shunts of blood are significant enough to cause hand ischemia. Proximal shunting is attributed to the reversal of blood flow through distal arteries induced by the low-pressure system produced by arterio-venous connector.

**Symptoms**: pain, numbness, pulmonary ischemia result in digital gangrene, peripheral neuropathy or cutaneous atrophy

7. Vascular malformations:

Acroangiodermatitis or pseudo kaposis sarcoma [38] is a benign vascular proliferation that develops distal to an AV shunt and may resolve following thrombus or surgical ligation of the shunt.

**Morphology**: purplish nodules or papules slowly evolving into scaly crusted violaceous patches.

**Histology**: vascular and fibroblast proliferation in the superficial dermis. Vascular slits, mitotic figures and extravasated RBCs may be seen.

It may improve if the shunt or AV fistula is removed.

8. Contact dermatitis: both allergic and irritant contact dermatitis may occur to dialysis tubing, nickel (needles) and topical medicaments. [105]
9. Nail changes:
    - Half and Half nails
    - Splinter haemorrhages
    - Onycholysis
10. Hair changes:
    - Alopecia
    - Discoloration of hair
    - Fine brittle hair
    - Hair shaft abnormalities
11. Infections: Increased carriage of staphylococcus aureus [105] has been found in patients

undergoing peritoneal dialysis and hemodialysis and may predispose patients to folliculitis, furunculosis or catheter site infections.

12. Premalignant conditions:
    - Multiple actinic keratoses may occur in skin exposed to sun and appear as scaly, rough red plaque. [107]
    - Porokeratosis – characterized by crater shaped keratin may develop on the access region for hemodialysis. [108]
13. Malignancy:

Basal cell carcinoma is the most common skin cancer in uremia occurring in about 4% of maintenance dialysis patients. Painless, non-inflamed smooth, translucent nodule, which can show numerous telengiectatic vessels near its surface. Nodules often ulcerate and form a crust. It may invade nearby structures such as bones, nerves or brain.

14. Nephrogenic fibrosing dermopathy [110,111] is a recently described disorder which resembles scleromyxedema clinically with normal immunoglobulin and no paraprotein. It has been found only in patients with renal disease. Most affected individuals have been on hemodialysis and many have re-started dialysis after failure of a renal transplant. It also has been described in a few patients with acute renal failure.

**Etiology**: unknown.

**Clinical features**: progressive development of erythematous, sclerotic dermal plaques on the arms and legs with sparing of the head and neck. Pruritus is a common feature.

**HPE**: resembles that of scleromyxedema, with proliferation of fibroblast in the dermis and subcutaneous septae, accompanied by increased dermal and septal collagen and mucin.

Course: persistent

Treatment: No effective treatment

15. Cutaneous reaction to treatment with recombinant human erythropoietin. A papulous skin reaction as well as generalized increased pruritus following 2-3 months of treatment.

16. Perforating pseudoxanthoma elasticum

17. Cutaneous calcinosis in hemodialysis

**HISTOPATHOLOGICAL CHANGES OF UREMIA IN SKIN**:

They have been studied and they include [112]

***Epidermal***

- moderately thickened stratum corneum
- reduction of prickle cell layers of pyknotic nuclei
- vacuolated cytoplasm of the epidermal cells
- flattening of dermo epidermal junction

***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:*** [3]

Specific management of cutaneous lesions is already discussed individually. The 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.

## AIMS OF THE STUDY

1. To study the various cutaneous manifestations and their incidence in patients with chronic renal failure.
2. To study the age and sex incidence of the individual cutaneous manifestations.

3. To study the incidence and types of cutaneous infections in chronic renal failure.
4. To study the treatment-related (medical and dialysis) dermatologic manifestations of chronic renal failure.
5. To correlate between the skin manifestations of systemic disorders with chronic renal failure.

## MATERIALS AND METHODS

This study was done for 2 years from December 2003 to December 2005. at nephrology ward, Government general hospital, Chennai, as well as at Dermatology outpatient department (referral cases).

During this period, the patients were screened for the evidence of cutaneous manifestations of chronic renal failure. Of these, 75 patients who had the presence of skin manifestations were selected and studied. All the 75 patients were known cases of chronic renal failure diagnosed at nephrology department/ medical department who presented with various stages of renal failure.

All patients were thoroughly investigated with routine hematologic and biochemical investigations. When appropriate, radiographs, USG and renal biopsy were done. All these patients were managed with drugs and dialysis according to the severity of renal failure.

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, skin lesions due to the treatment 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. Culture of skin scrapings for growth of fungal agents
c. Tzanck smear when indicated in viral infections
d. Pus culture and sensitivity
e. Skin biopsy for HPE in selected cases.

## OBSERVATIONS

The number of patients studied with chronic renal failure was 75.

**Age incidence**:

The age of the patients ranged from 16-70 years with a mean of 36 years.

**Sex incidence**:

Out of 75 patients, males were 51 and females 24, with Male: Female ratio of 2.1: 1.

**TABLE - I**

| sex | no. of patients studied with crf | incidence |
|---|---|---|
| Male | 51 | 68% |
| Female | 24 | 32% |
| Total | 75 | |

## I. INCIDENCE OF SPECIFIC CUTANEOUS MANIFESTATIONS OF CHRONIC RENAL FAILURE:

A**. SKIN**:

1. Pruritus

Out of 75 patients, 39 males and 15 females suffered from pruritus (fig 1). The total incidence in both sexes was 72%. 12 of the patients had excoriations due to pruritus (fig. 3b). 4 of them developed prurigo nodularis (fig 1b, fig 1c) and another 3 developed lichen simplex chronicus.

**TABLE - II**

| **sex** | **no. of persons with pruritus** | **incidence %** |
|---|---|---|
| Male | 39 | 52 |
| Female | 15 | 20 |
| Total | 54 | 72 |

11 patients showed improvement in pruritus following dialysis, no change in 24, and worsened in 19.

## SPECIFIC CUTANEOUS MANIFESTATIONS OF UREMIA

### PRURITUS

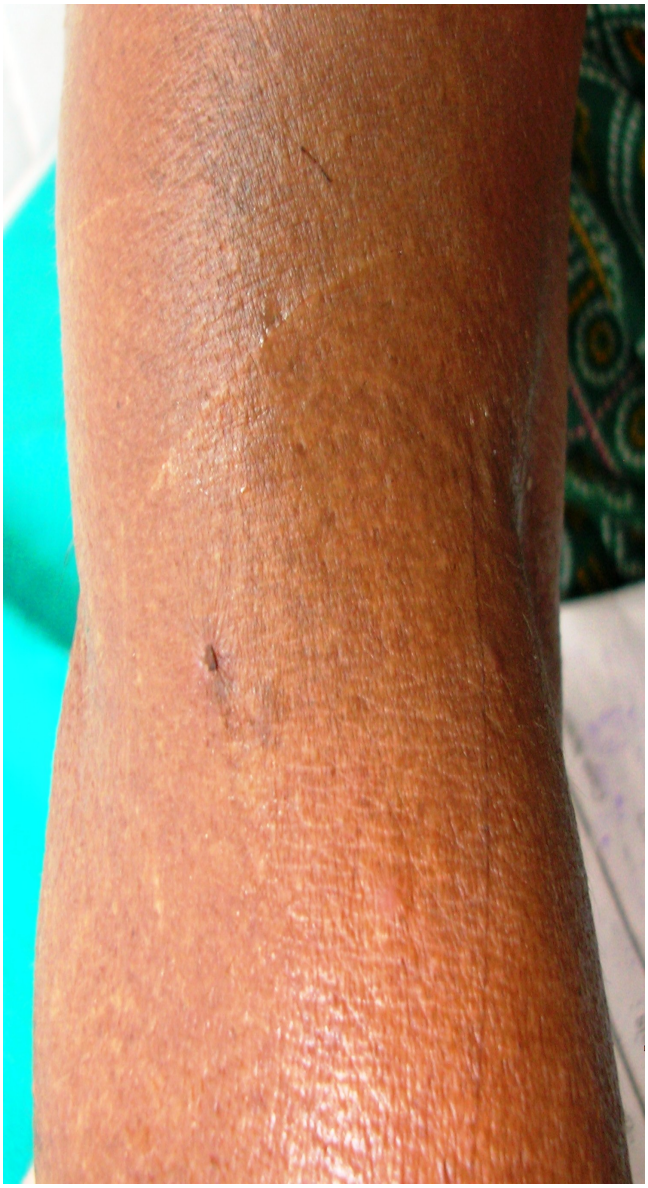

***Fig 1a***
Pruritus with scratch marks

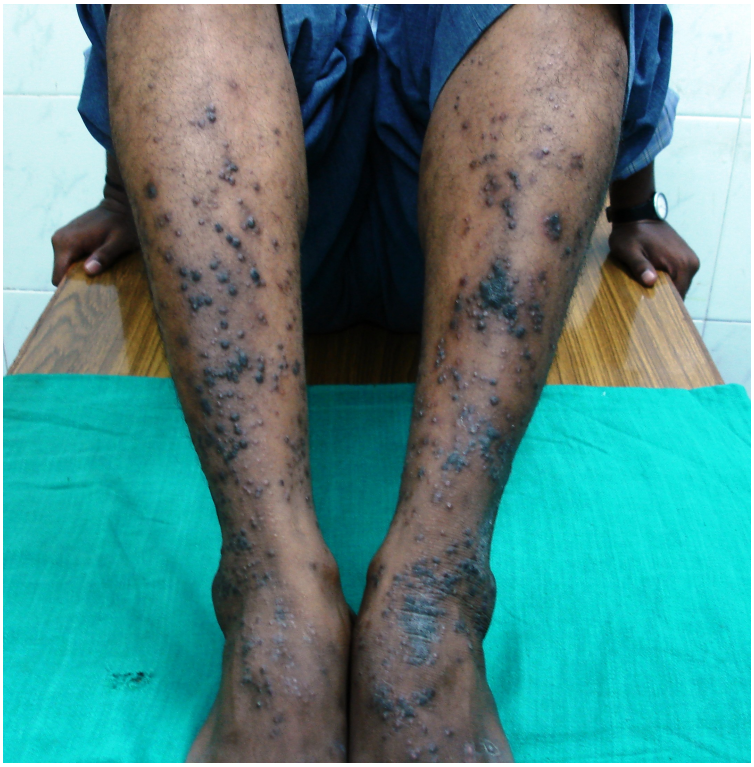

***Fig 1b***
Prurigo nodularis over the lower legs

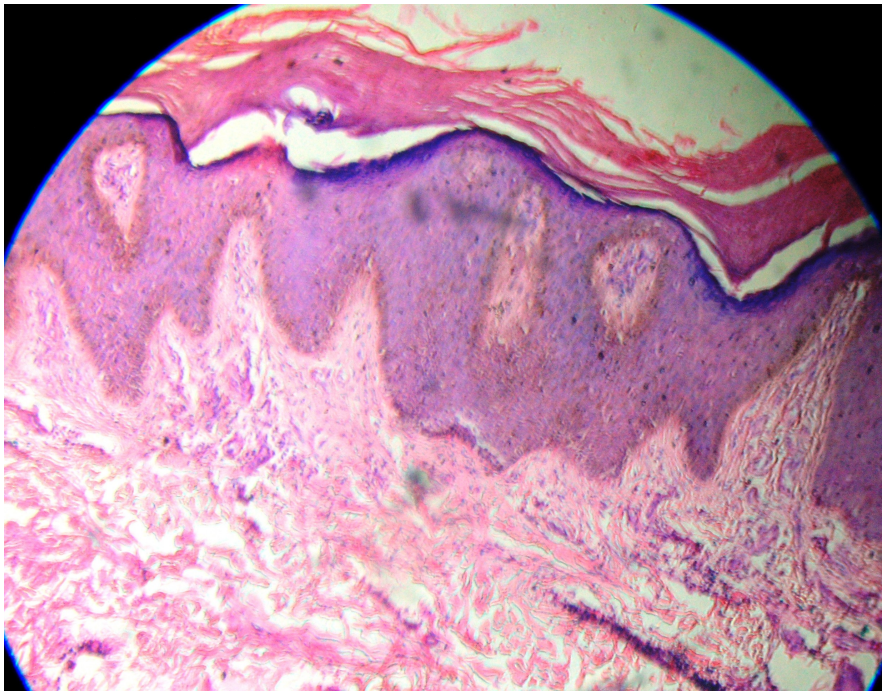

***Fig. 1c***
Histopathology – Prurigo nodularis showing vertical orientation of collagen in the papillary dermis & irregular acanthosis in the epidermis

2. Xerosis / ichthyosis:

34 patients developed dryness of skin (fig 2a); Ichthyosis (fig 2b) was noted in 15 patients, and acquired plantar hyperkeratosis in 3 males.

**TABLE - III**

| clinical features | no. of patients | | incidence % | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| Xerosis | 23 | 11 | 30.6 | 14.6 |
| Ichthyosis | 8 | 7 | 10.6 | 9.3 |
| Plantar hyperkeratosis | 3 | 0 | 4 | 0 |
| Total | 34 | 18 | 45.3 | 24 |

3. Pigmentary alterations:

Among pigmentary alterations 16 had diffuse hyper pigmentation (fig 3b), 12 were pale, 8 were of yellowish hue (fig. 3a) and 4 had pigmented macules over palms (fig. 3c) and soles (fig. 3d). The total number of patients with pigmentary alterations was 40. The incidence was found to be 53.3%.

**XEROSIS**

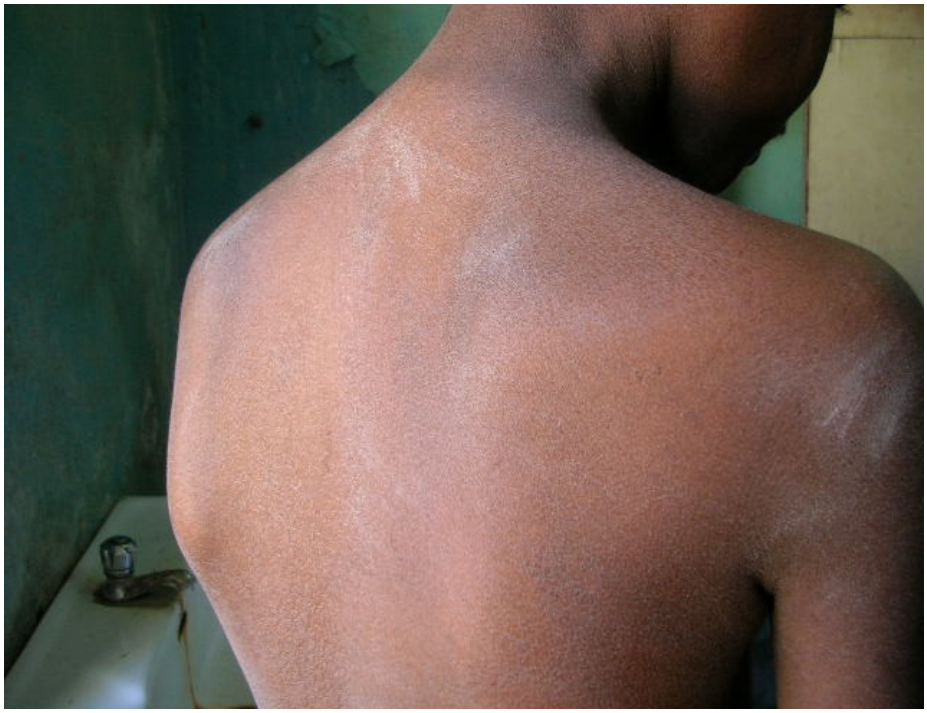

***Fig 2a***
Dryness of skin over the back

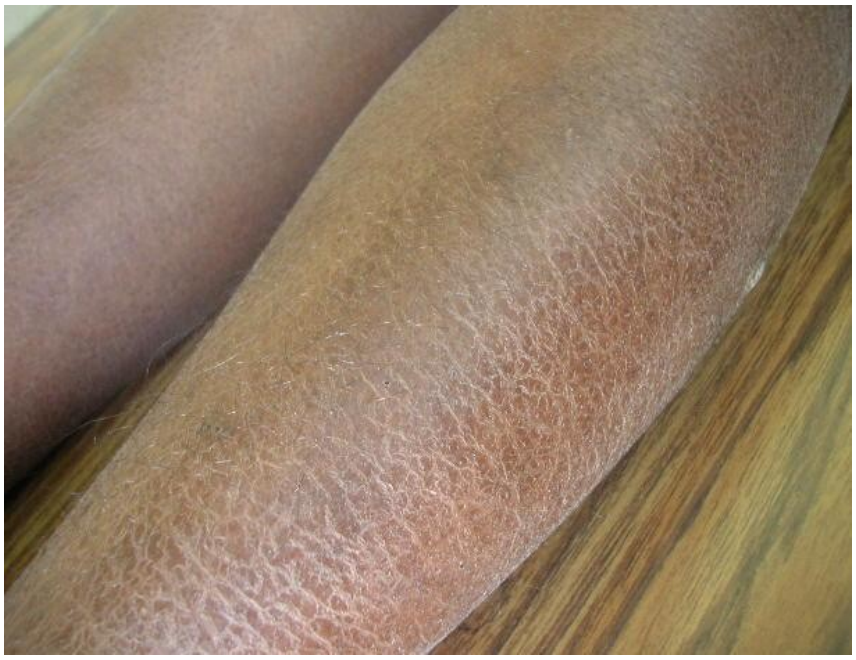

***Fig 2b***
Icthyosis over the lower legs

**PIGMENTARY CHANGES**

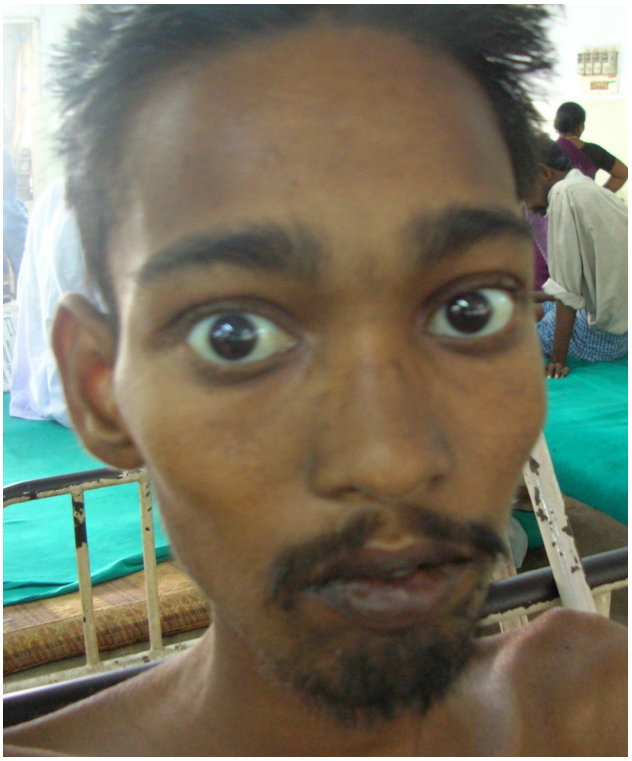

***Fig 3a***
Sallow yellow discolouration

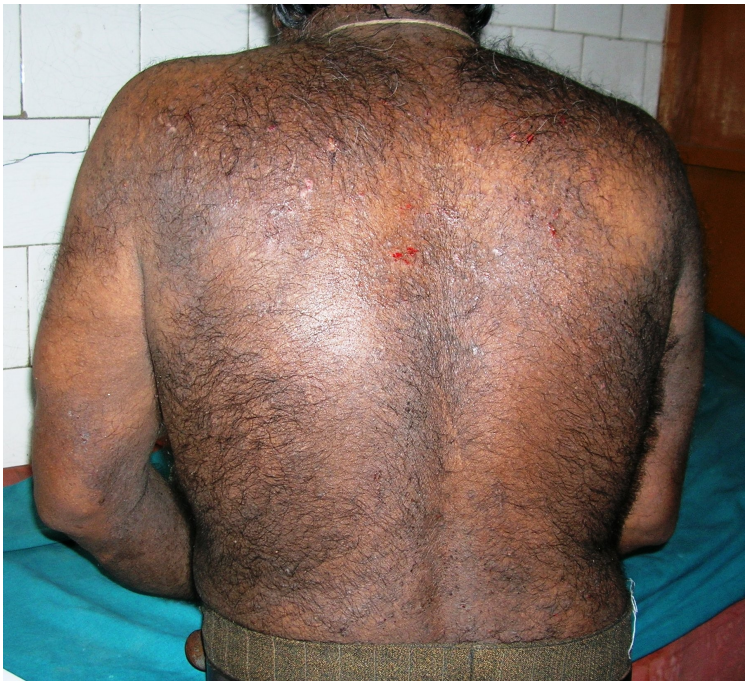

***Fig 3b***
Diffuse hyperpigmentation with excoriation marks

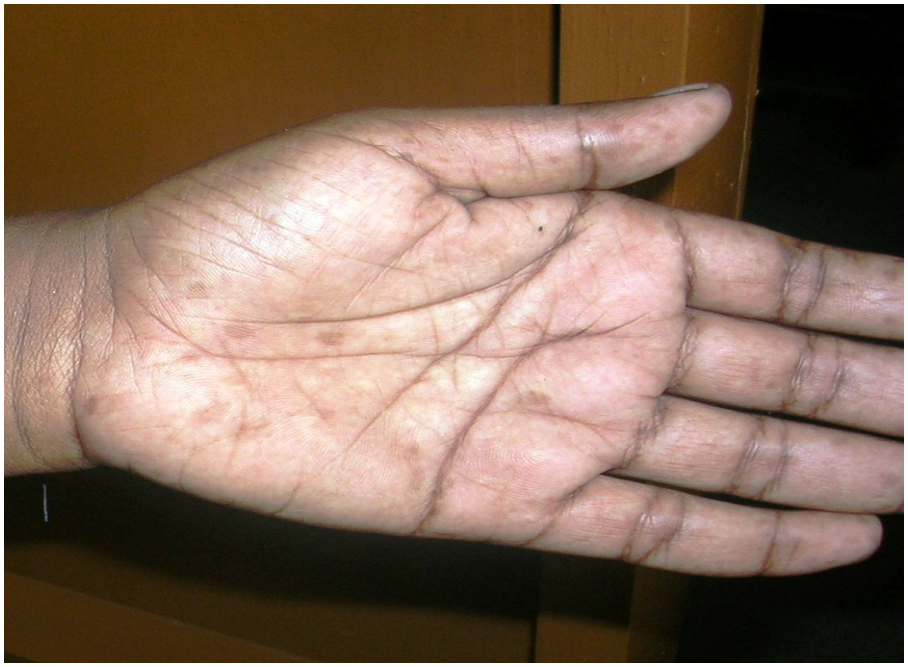

***Fig 3c***
Hyperpigmented macules over the palm

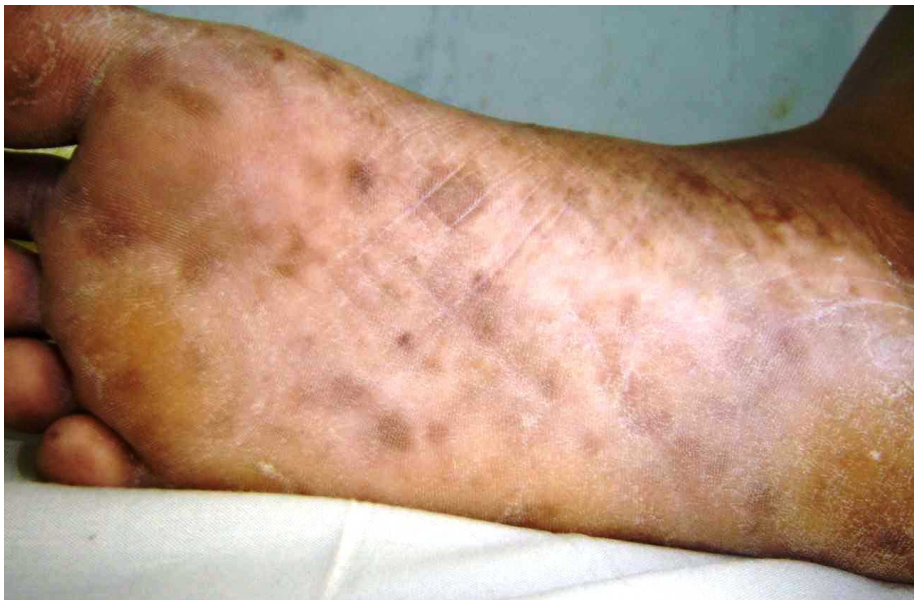

Fig 3d
Hyperpigmented macules over the sole

**TABLE - IV**

| Clinical features | No. of patients | |
|---|---|---|
| | male | female |
| Yellow discoloration | 3 | 5 |
| Diffuse hyper pigmentation | 11 | 5 |
| Hypermelanotic macules of palms and soles | 2 | 2 |
| Pallor | 7 | 5 |
| Total | 23 | 17 |
| Incidence % | 30.6 | 22.6 |

4. Uremic frost: Not noted
5. Perforating dermatosis: 12 patients presented with the clinical morphology of perforating dermatosis. With the help of Histopathological findings, Kyrle's disease (fig. 4a, 4b) was seen in 3 patients, perforating folliculitis in 4 (fig 4c, 4d) . Others showed features of nodular prurigo and prurigo simplex.

**TABLE -V**

| clinical features | no. of patients | |
|---|---|---|
| | Male | Female |
| Kyrle's disease | 1 | 2 |
| Perforating folliculitis | 2 | 2 |
| Others | 2 | 3 |

Total number of patients with perforating dermatosis was 7, and the incidence was found to be 9.3%.

**PERFORATING DISORDERS**

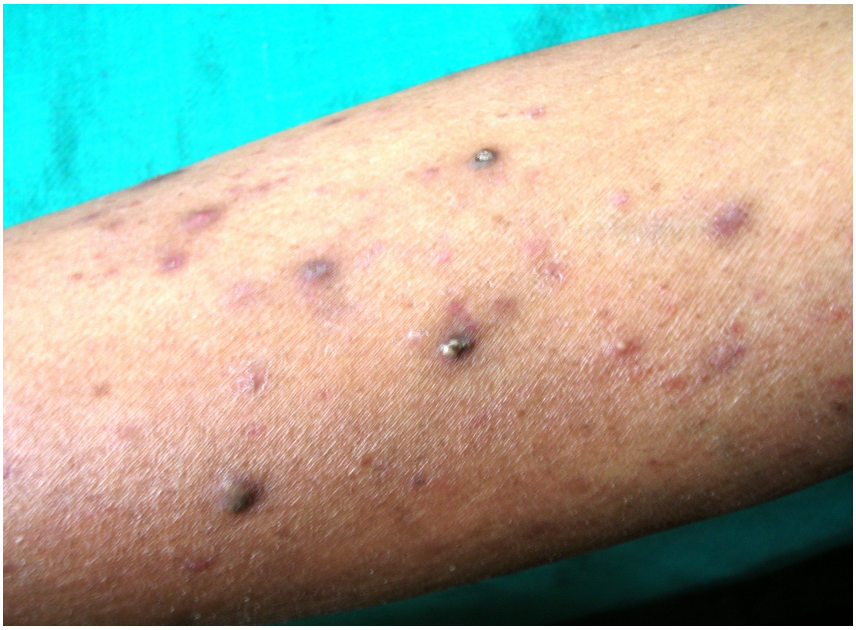

***Fig 4a***
Kyrle's disease over the upper extremity

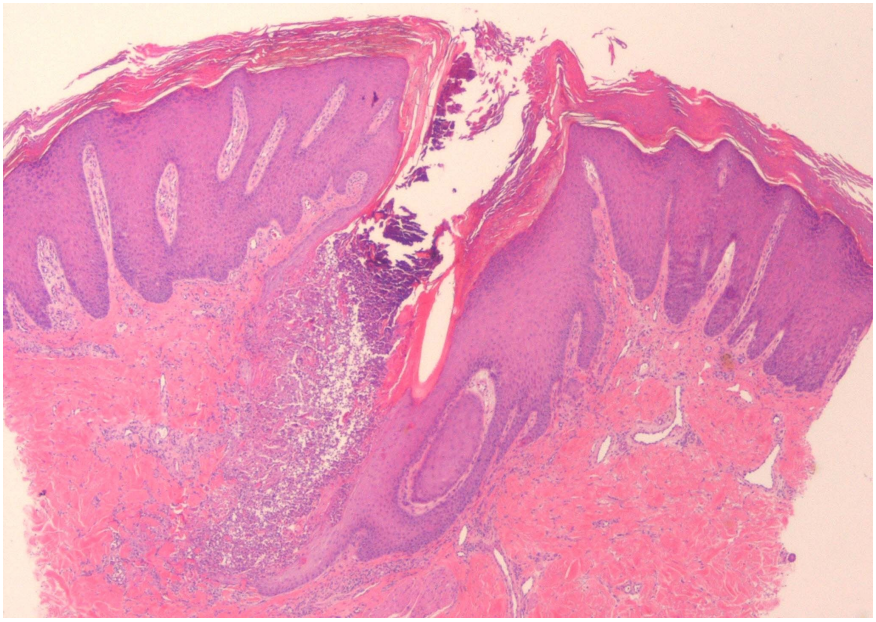

***Fig 4b***
Histopathology of Kyrle's disease showing basophilic debris in an epidermal invagination. Plug is in direct contact with the dermis.

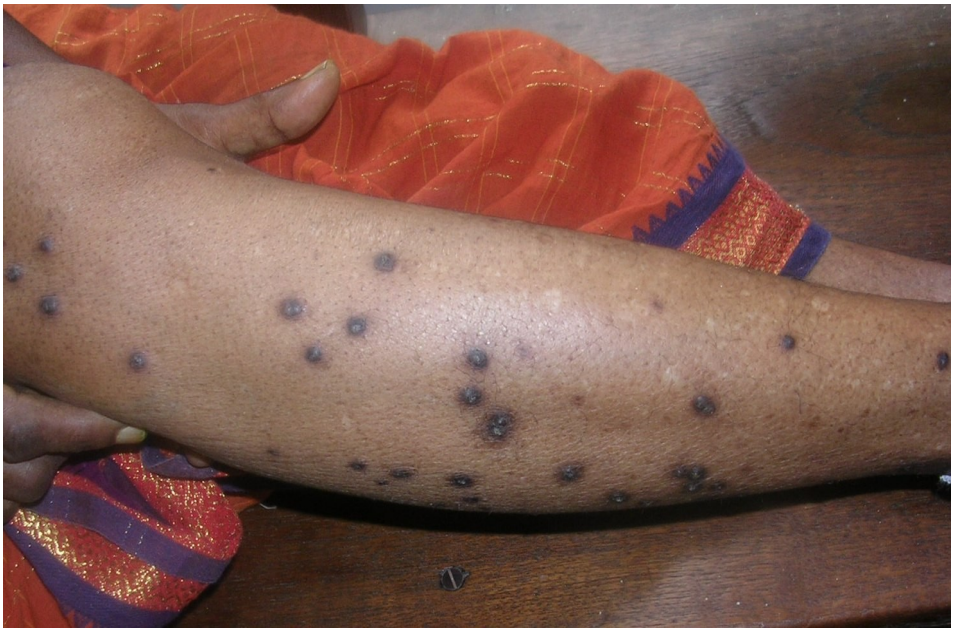

***Fig 4c***
Perforating folliculitis over the lower leg

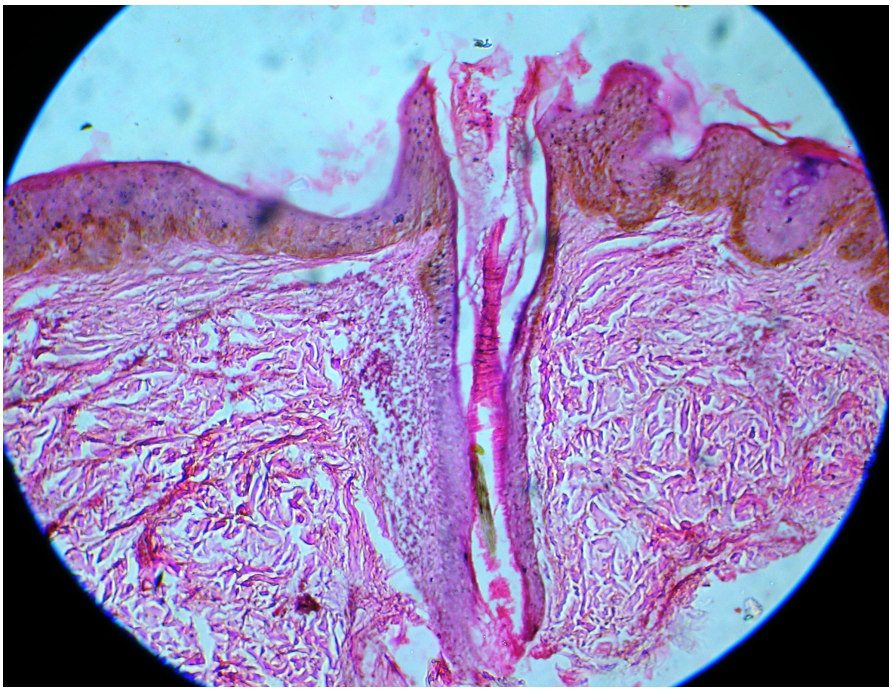

***Fig 4d***
Histopathology of peforating folliculitis with perforation of the follicular epithelium and degenerative collagen fibres extruding through the dermis.

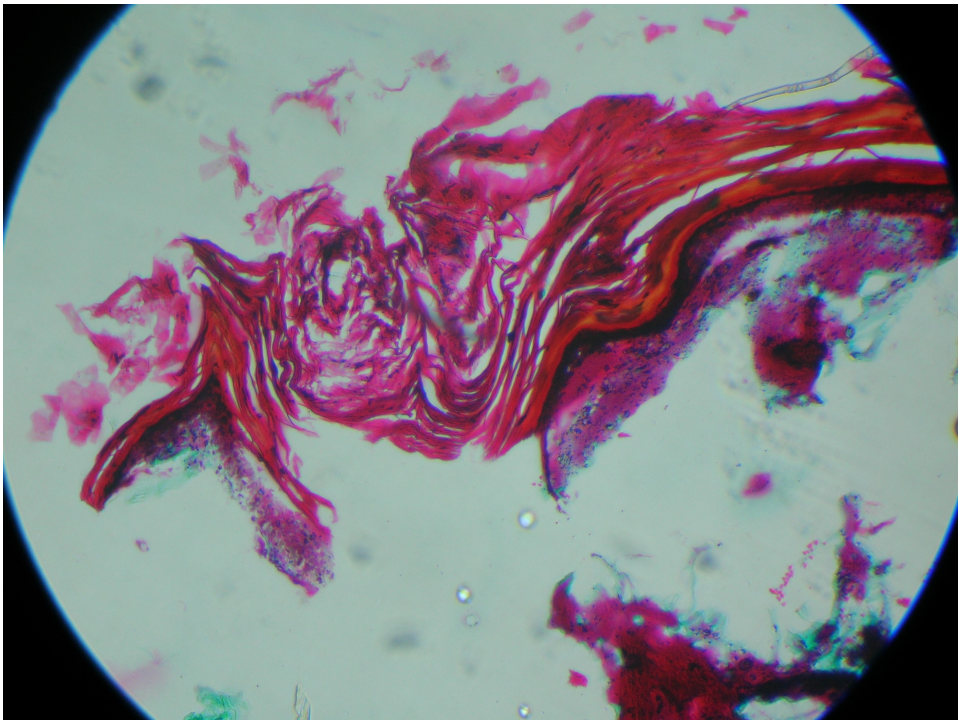

***Fig 4e***
Histopathology of perforating folliculitis – trichrome stain showing elimination of collagen fibres through the follicular wall

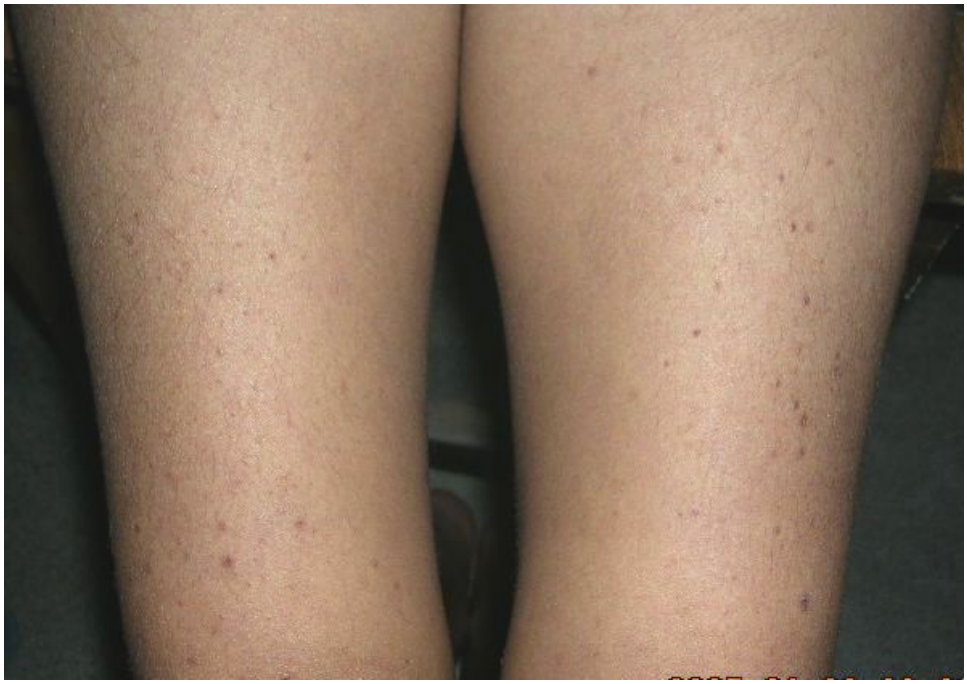

***Fig 5***
Purpura over the thighs

6. Metastatic calcification: not noted.
7. Purpura (fig. 5) : over legs were noted in 9 patients. In male patients, the reason was mainly due to underlying thrombocytopenia. But in females, 3 were diagnosed to have Henoch-Schonlein purpura; one had cryoglobulinemia and another had ITP.

**TABLE - VI**

| **Sex** | **No. of patients with purpura** | **Incidence %** |
|---|---|---|
| Male | 3 | 4 |
| Female | 6 | 8 |
| Total | 9 | 12 |

8. Gynaecomastia – Not noted
9. Vascular disorders: Digital gangrene (fig. 6) present over fingers was noted in 2 patients.
10. Poor wound healing (fig. 7) : following trauma was seen in 4 patients.
11. Restless leg syndrome: Two patients had burning pain over the soles of the feet.

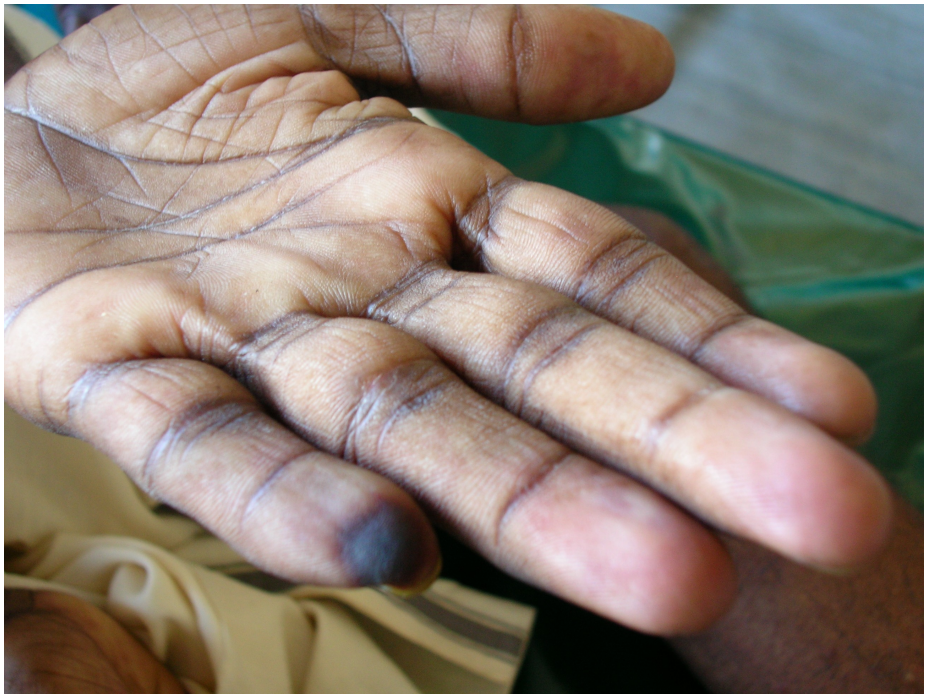

***Fig 6***
Gangrene over the little finger

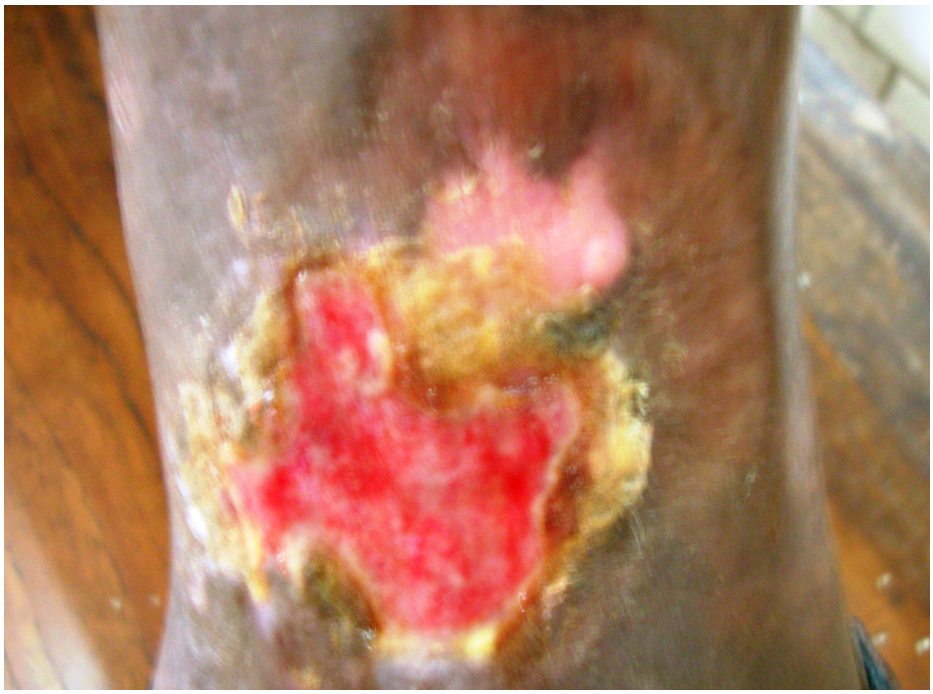

***Fig 7***
Poor wound healing in a chronic leg ulcer following trauma

B. **MUCOSAL CHANGES**:

Stomatitis (fig. 8) was noted in 12 patients. 3 of them had oral ulcers (fig. 9), 2 had leukokeratosis of oral mucosa. The total number of patients with mucosal changes was 17, and the incidence was found to be 22.6

**TABLE -VII**

| **clinical features** | **no. of patients** | |
|---|---|---|
| | Male | Female |
| Stomatitis | 8 | 4 |
| Oral ulcers | 1 | 2 |
| Leukokeratosis of oral mucosa | 1 | 1 |
| Total | 10 | 7 |
| Incidence | 13.3 | 9.3 |

C. **HAIR ABNORMALITIES**: 14 had sparse hair (fig. 10) and 8 had brittle hair. The total number of patients with hair abnormalities was 22. The incidence was found to be 29.3%.

**TABLE - VIII**

| **clinical features** | **no. of patients** | |
|---|---|---|
| | Male | Female |
| Diffuse alopecia | 6 | 8 |
| Brittle hair | 4 | 4 |
| Total | 10 | 12 |
| Incidence | 13.3 | 16 |

**MUCOSAL CHANGES**

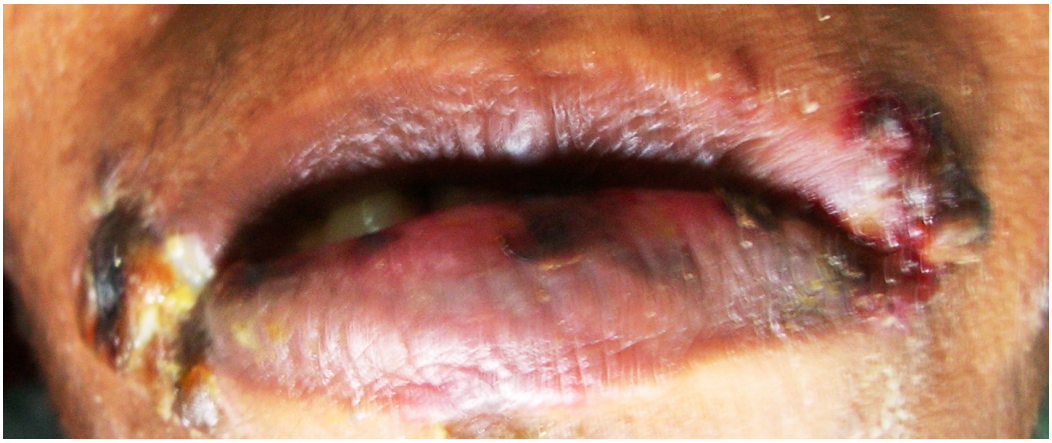

***Fig 8***
Showing stomatitis

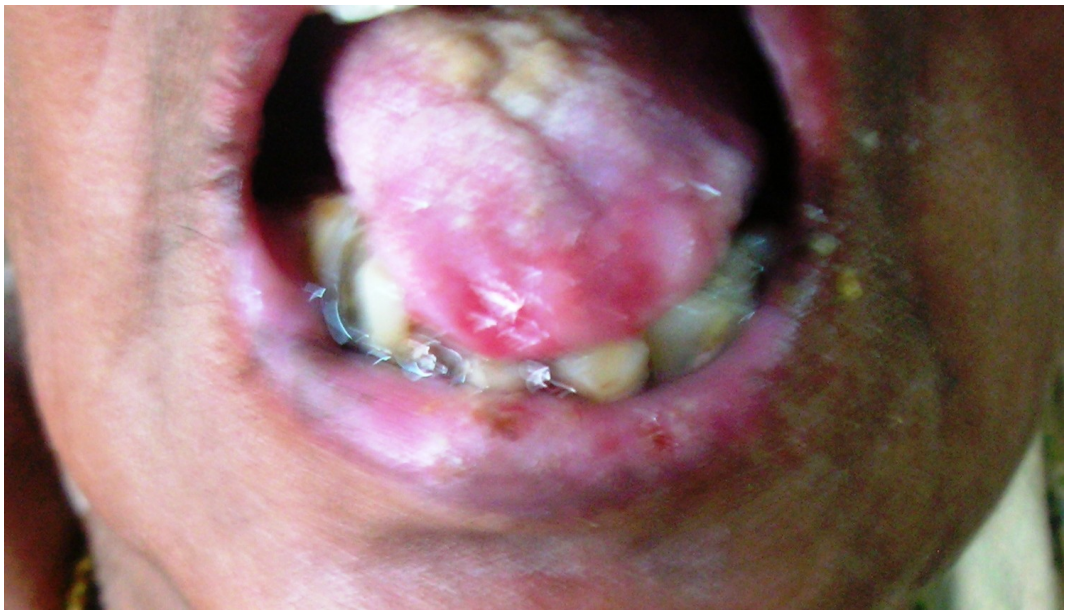

***Fig 9***
Shows ulcer over the labial mucosa and tongue

## HAIR ABNORMALITIES

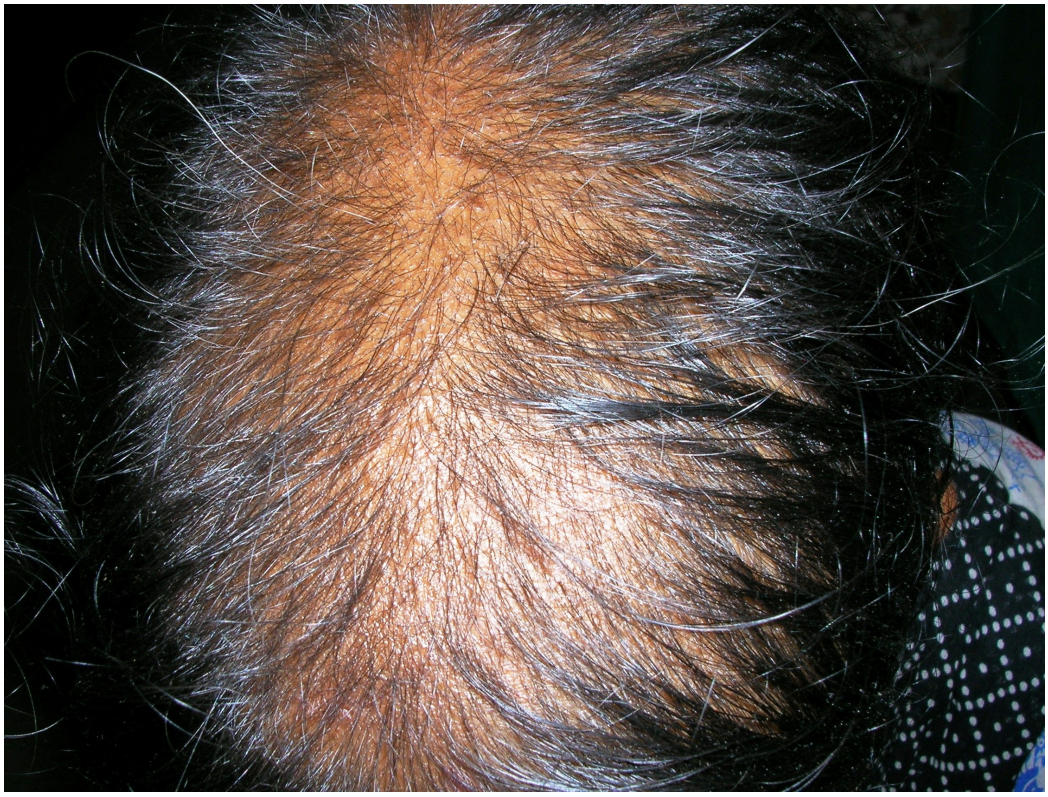

***Fig 10***
Shows diffuse loss of hair

D. **NAIL CHANGES**: Among 75 patients, 18 had 'half and half nails' (fig. 11 & 12), 8 had brown nail bed arc (fig. 13). Other nail features such as Mee's lines and Muercke's lines were not noted. 4 had shiny nails (fig. 14) , probably secondary to scratching, 3 had onychodystrophy (fig. 15) (nail scraping was done and examined under 10% KOH and found to be negative), 2 had melanonychia (fig.16) and one patient had blue nails (fig. 17), not

associated with Raynaud's phenomenon or cyanosis

**TABLE – XI**

| clinical features | no. of patients | |
|---|---|---|
| | Male | Female |
| Half and half nail | 12 | 6 |
| Brown nail bed arc | 5 | 3 |
| Shiny nails | 1 | 3 |
| Onychodystrophy & onycholysis | 4 | 1 |
| Melanonychia | 2 | 0 |
| Blue nails | 1 | 0 |
| Total | 25 | 13 |
| Incidence % | 33.3 | 17.3 |

**NAIL CHANGES**

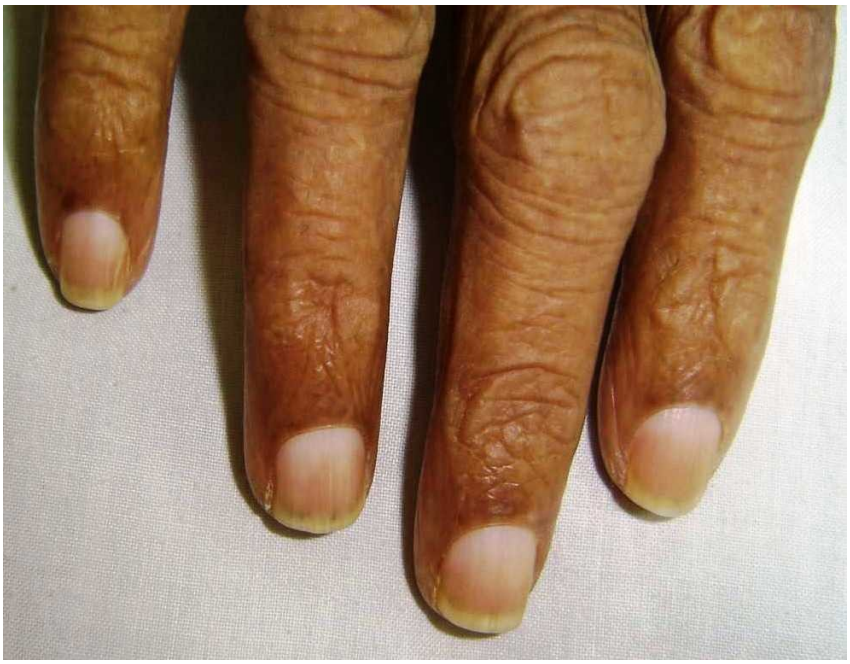

***Fig 11***
Half and half nails in finger nails

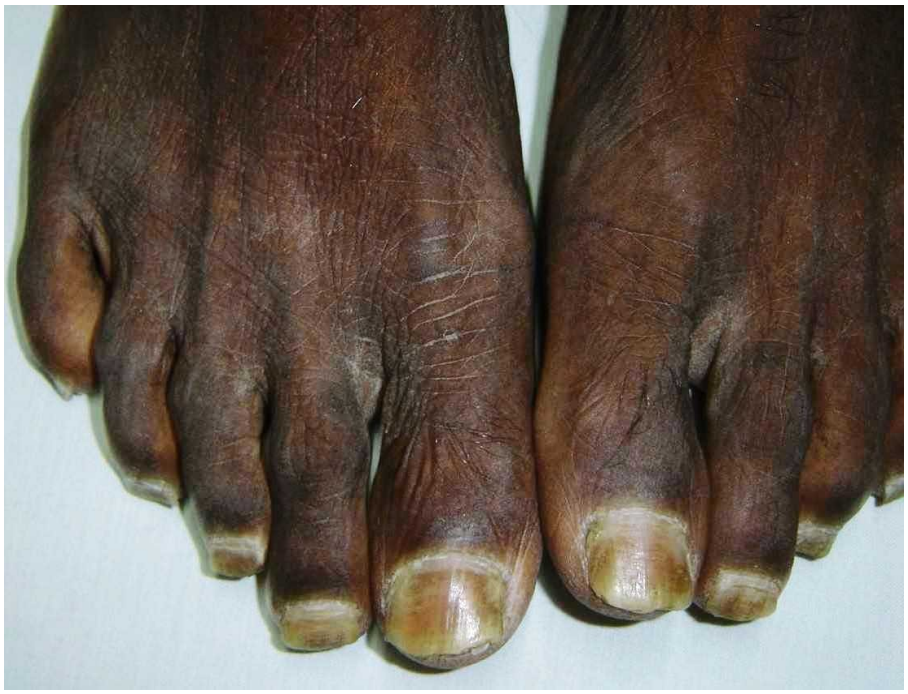

***Fig 12***
Half and half nails in toe nails

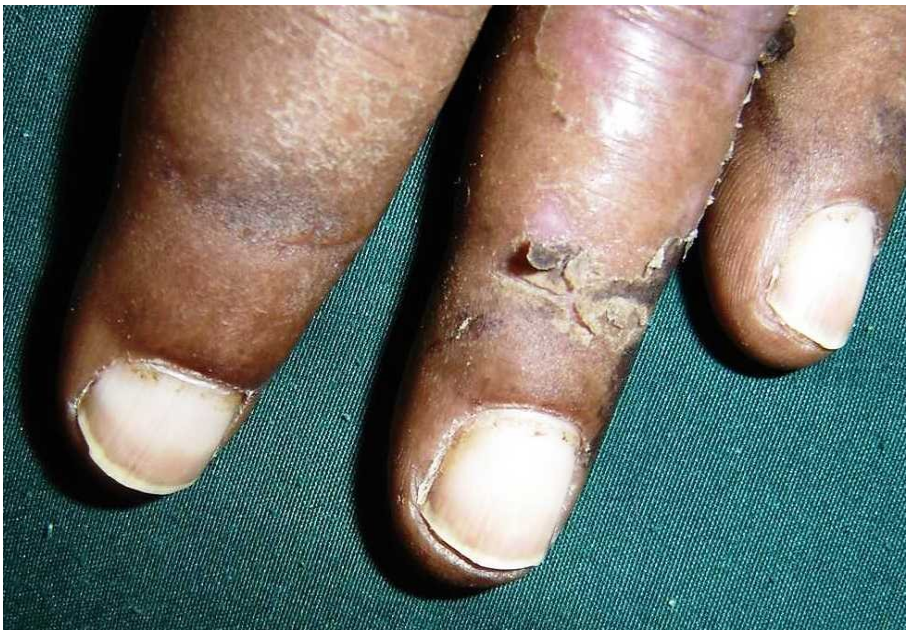

***Fig 13***
Brown nail bed arc in finger nails

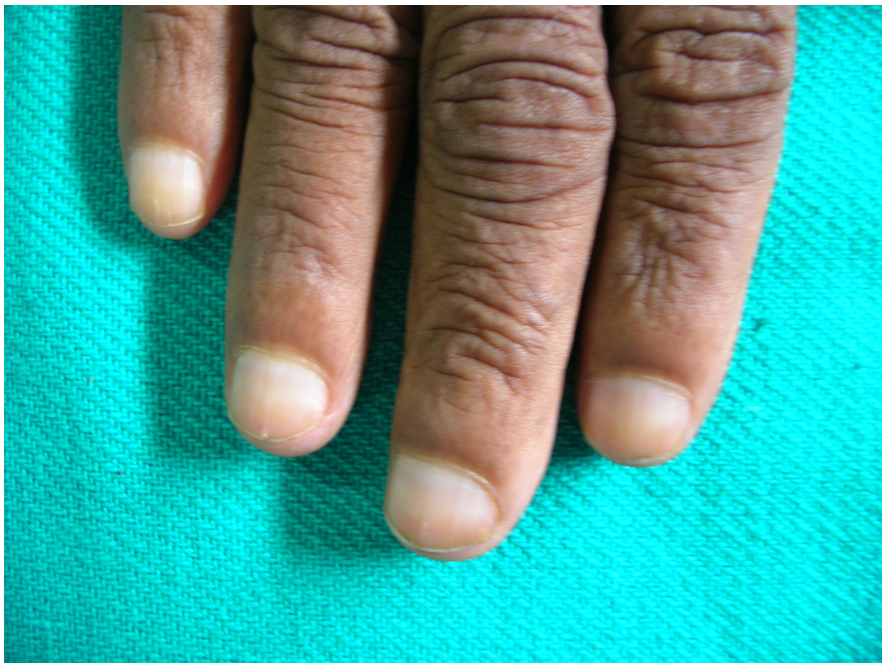

***Fig 14***
Shiny nails due to scratching

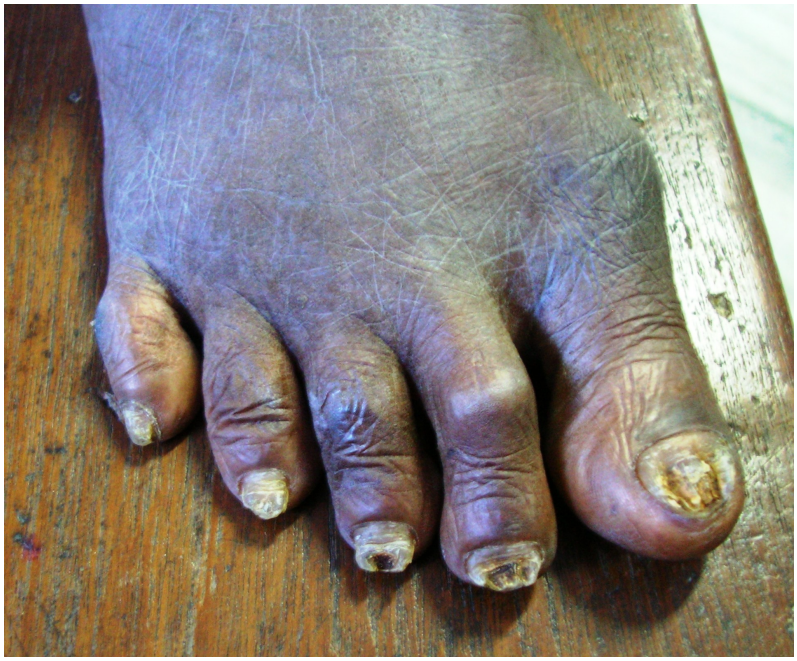

***Fig 15***
Onychodystrophy of toe nails

***Fig 16***
Longitudinal melanonychia over the finger nails

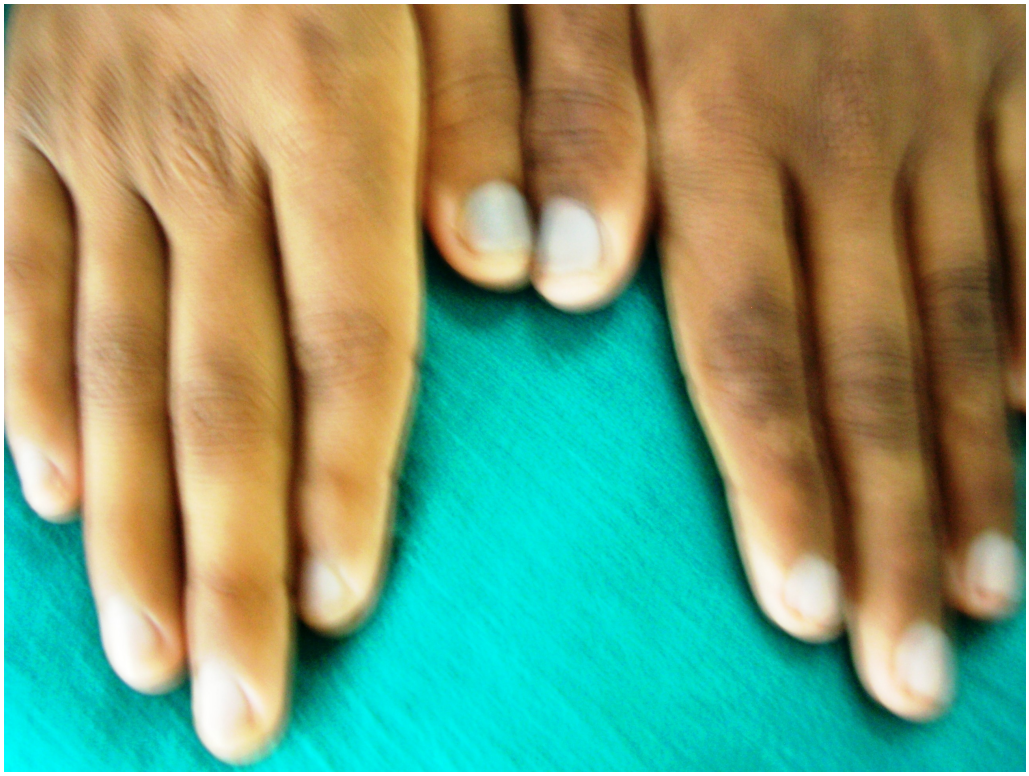

***Fig 17***

Blue nails seen over the fingers, most evident over the thumbs

SPECIFIC CUTANEOUS MANIFESTATIONS OF CRF

**TABLE - X**

| s.no | SPECIFIC CUTANEOUS MANIFESTATIONS | NO. OF PATIENTS | | TOTAL | INCIDENCE % |
|---|---|---|---|---|---|
| | | Male | Female | | |
| A | SKIN CHANGES | | | | |
| 1. 1 | Pruritus | 39 | 15 | 54 | 72 |
| 2. | Xerosis/ ichthyosis | 34 | 18 | 52 | 69.3 |
| 3. | Pigmentary alterations | 23 | 17 | 40 | 53.3 |
| 4. | Uremic frost | 0 | 0 | 0 | 0 |
| 5. | Perforating disorder | 3 | 4 | 7 | 9.3 |
| 6. | Metastatic calcification | 0 | 0 | 0 | 0 |
| 7. | Purpura | 3 | 6 | 9 | 12 |
| 8. | gynaecomastia | | | | |
| 9. | Vascular disorders | 1 | 1 | 2 | 2.6 |
| 1 | Poor wound healing | 3 | 1 | 4 | 5.3 |

| | | | | | |
|---|---|---|---|---|---|
| 1<br><br>1. | Restless leg syndrome | 1 | 1 | 2 | 2.6 |
| B | MUCOSAL CHANGES | 10 | 7 | 17 | 22.6 |
| C | HAIR ABNORMALITIES | 10 | 12 | 22 | 29.3 |
| D | NAIL ABNORMALITIES | 25 | 13 | 38 | 50.6 |

## II. INCIDENCE OF SKIN MANIFESTATIONS DUE TO TREATMENT (MEDICAL AND DIALYSIS):

Apart from pruritus, pigmentary alterations nail and hair changes, keratotic pit of palms (fig. 18a) noted in 3 patients. Arteriovenous shunt dermatitis was noted in a patient and eczema around cannula site was noted in 2 patients (fig. 18b).

**TABLE XI**

| **sex** | **bullous dermatosis** | **keratotic pits of palms** | **av shunt dermatitis** |
|---|---|---|---|
| Male | 0 | 3 | 0 |
| Female | 0 | 0 | 1 |
| Total | 0 | 3 | 1 |
| Incidence | 0 | 4 | 1.3 |

## CUTANEOUS MANIFESTATIONS DUE TO TREATMENT (MEDICAL AND DIALYSIS)

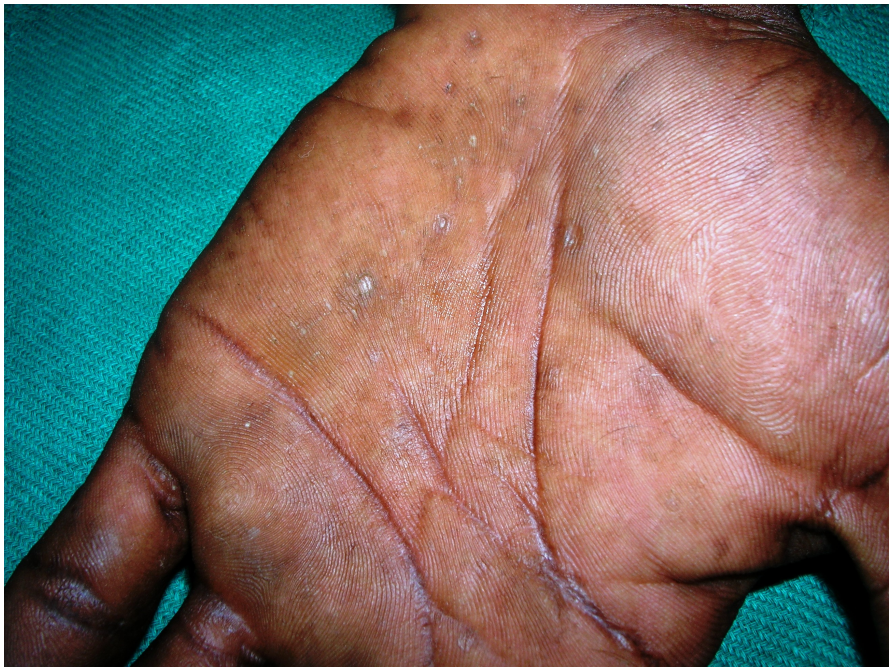

***Fig 18a***
Keratotic pits over the palm

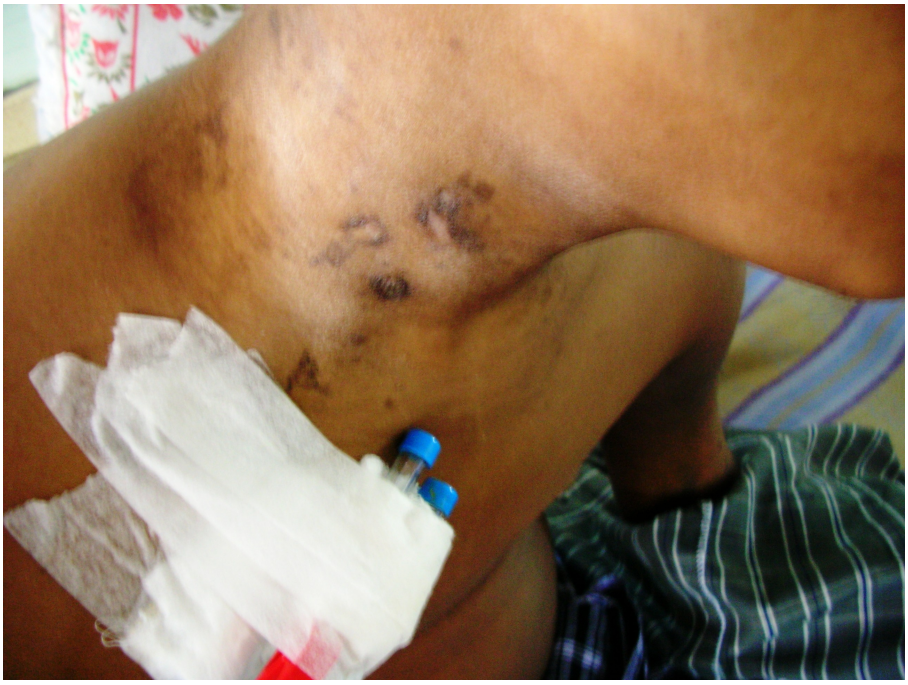

***Fig 18b***
Eczema around the IJV cannulation site

## III. INCIDENCE OF CUTANEOUS INFECTIONS NOTED IN CRF:

BACTERIAL INFECTIONS:

Furunculosis (fig. 19) was seen in 3 patients and infected leg ulcers in 2 patients. Pus culture revealed staphylococcal aureus in 2 patients.

VIRAL INFECTIONS:

Herpes simplex labialis was seen in 3 patients. One patient had herpes zoster (fig 20a), Tzanck smear revealed multinucleated giant cells (fig. 20b). Verruca vulgaris was noted in 4 patients. Palmar (fig. 20 c) wart was seen in 1 patient.

FUNGAL INFECTIONS:

Pityriasis versicolor (fig. 21a) was seen in 6 patients. Among dermatophyte infections, 4 had tinea cruris, 2 had tinea corporis (fig. 21b) and 1 with extensive dermatophytosis. Scraping for

direct microscopic visualization of fungal elements with 10% KOH was done and found to be positive for all cases. Culture was positive in one case. The organism grown in culture was Trichophyton rubrum. Oral candidiasis (fig. 21c) was noted in 2 patients. Vulvovaginal candidiasis was seen in 2 patients.

PARASITIC INFESTATIONS:

Scabies (fig. 22) was seen in 2 patients.

Total number of patients with cutaneous infections and infestations were found to be 33, and the incidence was 43.8 %.

CUTANEOUS INFECTIONS IN CRF

**TABLE - XII**

| **cutaneous infections** | | **no. of patients** | **total** | **incidence** |
|---|---|---|---|---|
| Bacterial infections | Furunculosis | 3 | 5 | 6.6 |
| | Infected leg ulcers | 2 | | |
| Viral infections | HS labialis | 3 | 9 | 12 |
| | Herpes zoster | 1 | | |
| | Verruca vulgaris | 4 | | |
| | Plane wart | 1 | | |
| Fungal infections | Pityriasis versicolor | 6 | 17 | 22.6 |
| | Dermatophytosis | 7 | | |
| | Oral candidiasis | 2 | | |
| | Candidial vulvovaginitis | 2 | | |
| Parasitic infestations | Scabies | 2 | 2 | 2.6 |
| Total | | | 33 | 43.8 |

## CUTANEOUS INFECTIONS AND INFESTATIONS IN CRF

## BACTERIAL INFECTION

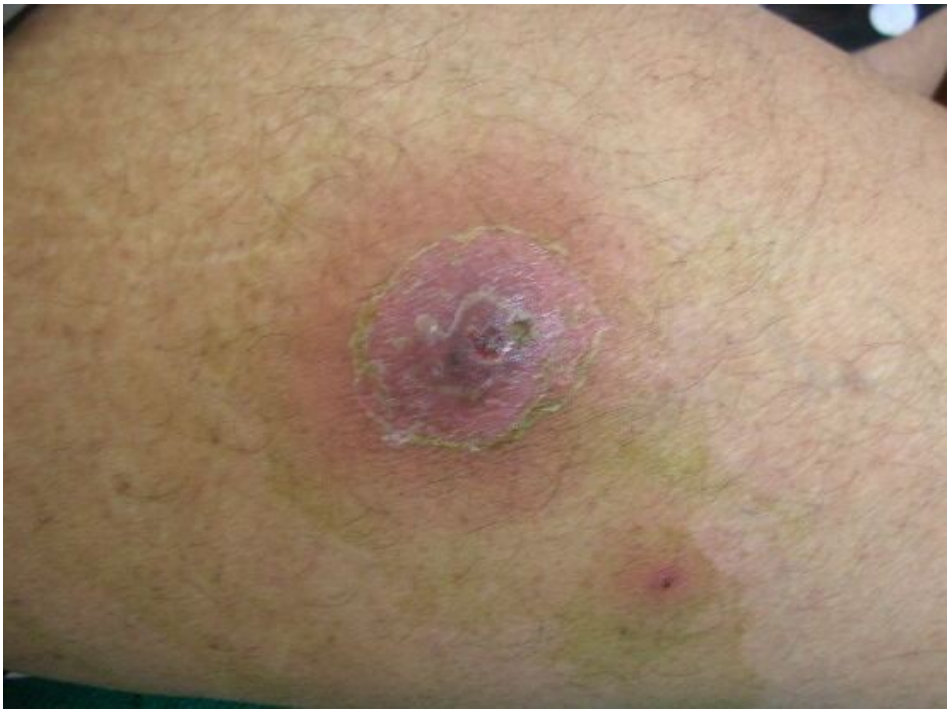

***Fig 19***
Furuncle present over the thigh

## VIRAL INFECTIONS

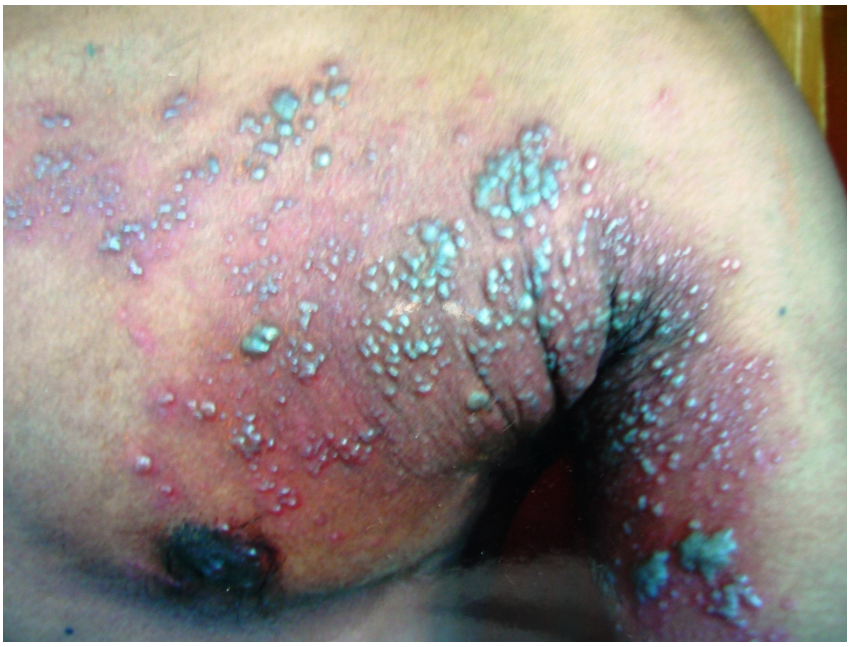

***Fig 20a***
Herpes zoster – T1 dermatome

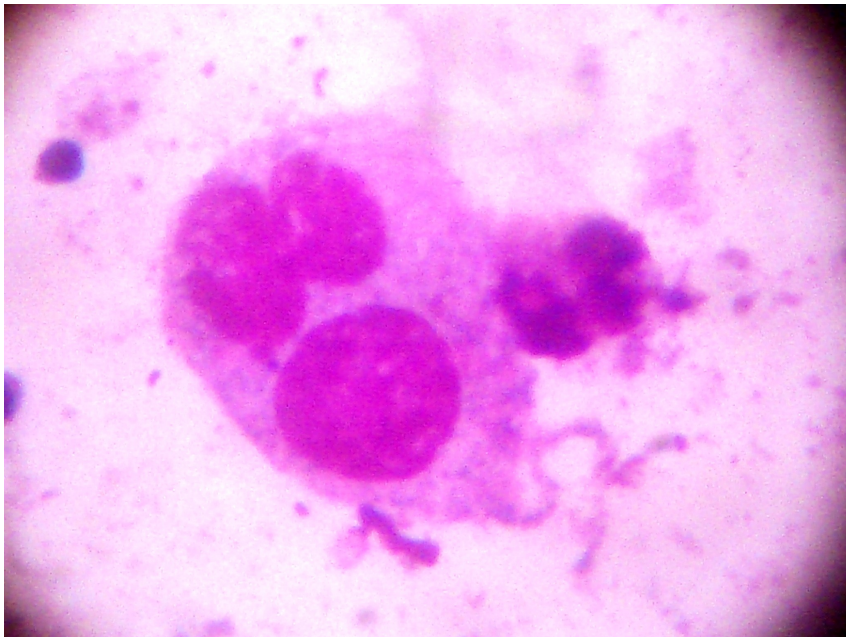

***Fig 20b***
Multinucleated giant cells seen in the above patient

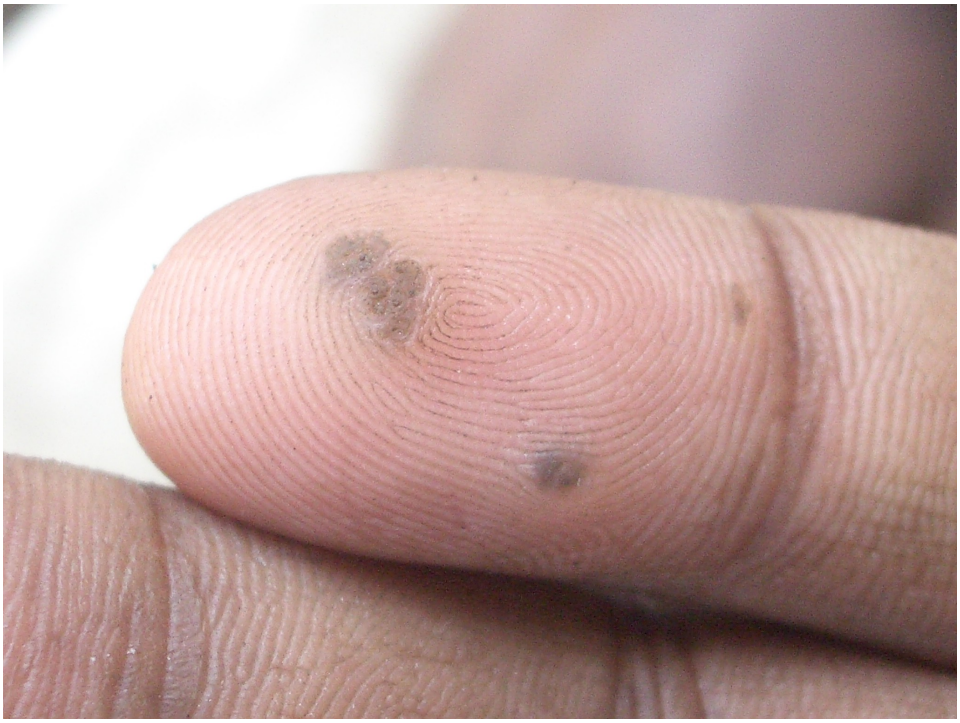

***Fig 20c***
Shows palmar wart

## FUNGAL INFECTIONS

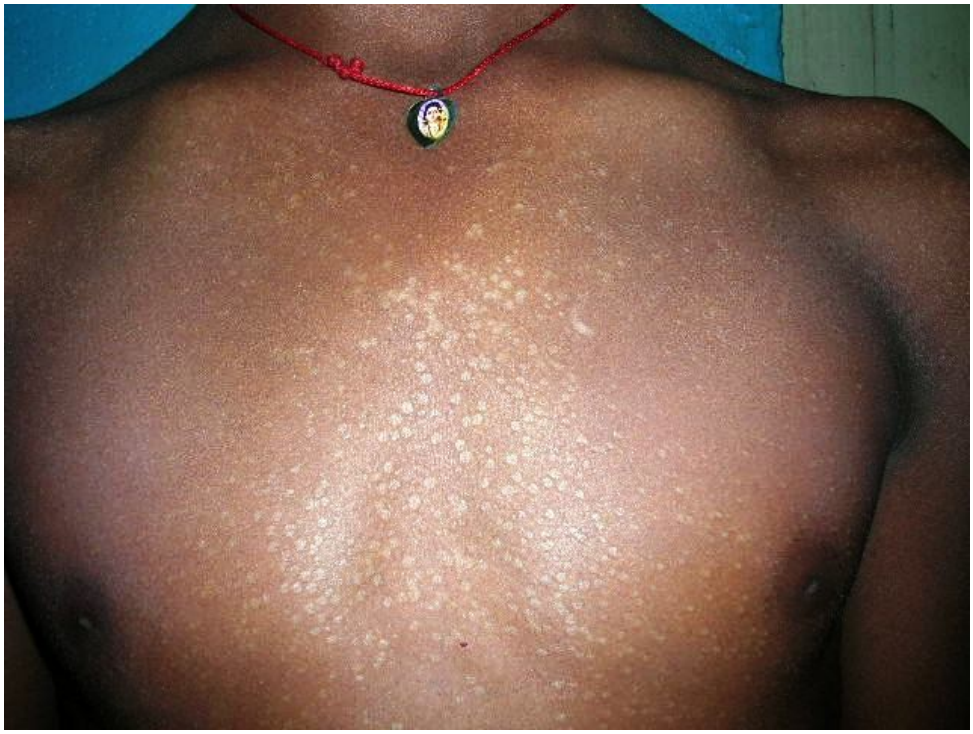

***Fig 21a***
Pityriasis versicolor over the chest

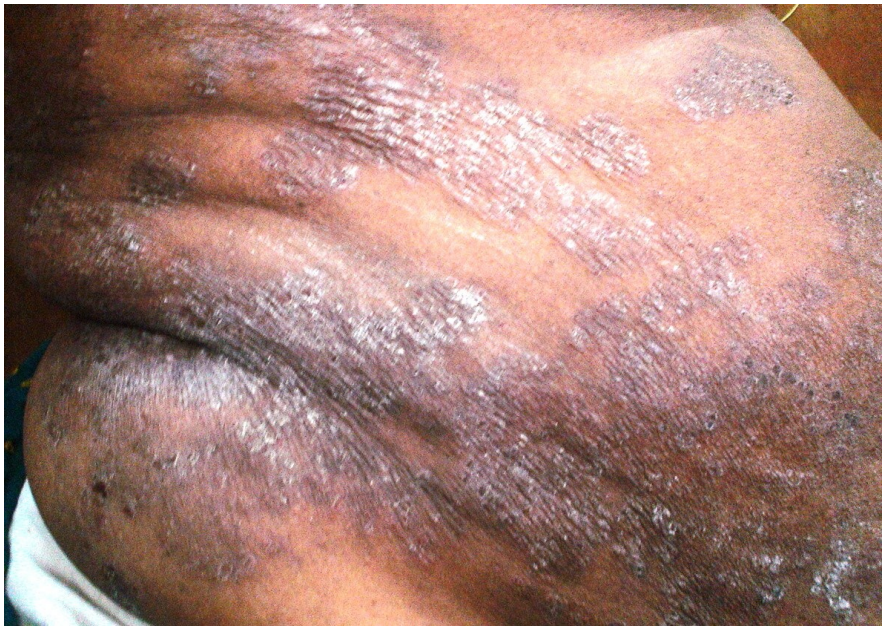

***Fig 21b***
Showing Tinea corporis

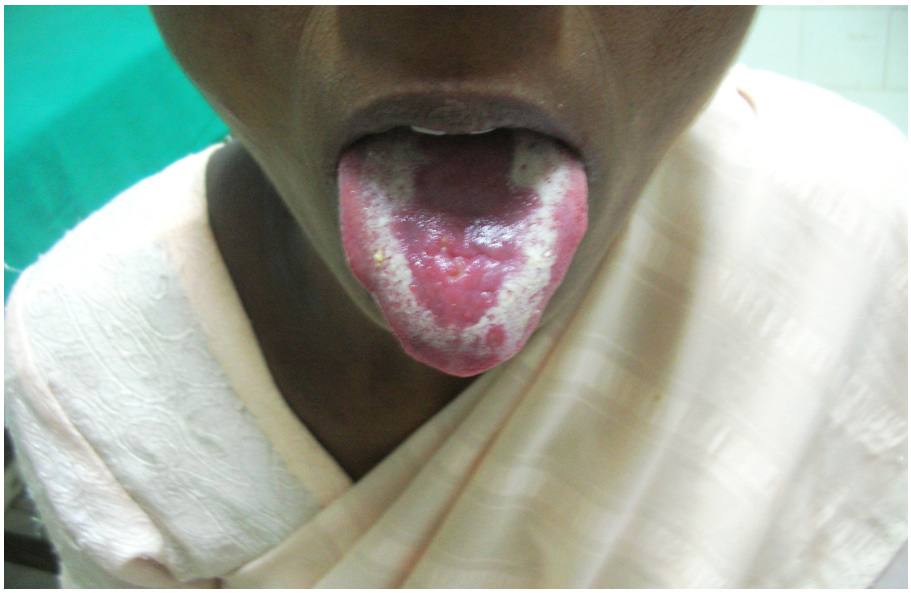

***Fig 21c***
Oral candidiasis seen over the tongue

## PARASITIC INFESTATIONS

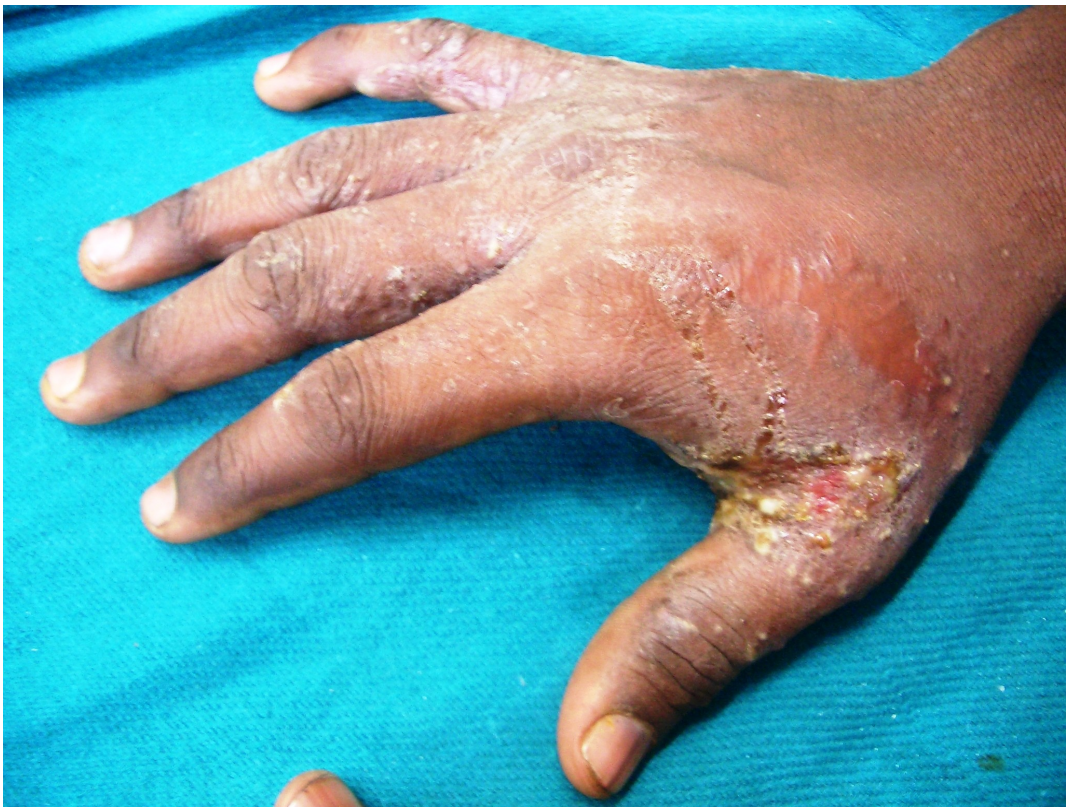

***Fig 22***
Showing scabies

## IV. INCIDENCE OF ASSOCIATED SKIN LESIONS:

These were classified into

1. Skin lesions contributing to the etiology of CRF

Skin changes of diabetes mellitus like acanthosis nigricans, perforating folliculitis, peripheral neuropathy were noted in 10 patients. Skin changes of systemic lupus erythematous (fig. 23) like malar rash, erythematous scaly plaques, discoid rash and diffuse alopecia of the scalp were noted in 3 patients. Cutaneous findings of scleroderma like hide-bound skin, sclerodactyly salt and pepper pigmentation (fig. 24), and pitted scars were noted in 2 patients. 2 patients presented with vasculitic ulcer on (fig. 25) lower legs. 5 patients presented with purpura that had differing etiologies like ITP, cryoglobulinemia, HSP. One case of Ellis van creveld syndrome (fig. 26) with cortical medullary disease presented with cutaneous changes. One case of tuberous sclerosis with renal involvement presented with cutaneous changes like angiofibroma (fig. 27), shagreen patch, ashleaf macules.

SKIN CHANGES CONTRIBUTED TO ETIOLOGY OF CRF

**TABLE – XIII A**

| **diseases** | **no. of patients** | | **total** | **incidence** |
|---|---|---|---|---|
| | Male | Female | | **%** |

| | | | | |
|---|---|---|---|---|
| Diabetes mellitus | 6 | 4 | 10 | 13.3 |
| SLE | 0 | 3 | 3 | 4 |
| Scleroderma | 0 | 2 | 2 | 2.6 |
| Vasculitis | 2 | 0 | 2 | 2.6 |
| ITP | 0 | 1 | 1 | 1.3 |
| Cryoglobulinemia | 0 | 1 | 1 | 1.3 |
| HSP | 0 | 3 | 3 | 4 |
| Ellis van creveld | 0 | 1 | 1 | 1.3 |
| Tuberous sclerosis | 0 | 1 | 1 | 1.3 |

**ASSOCIATED SKIN LESIONS**

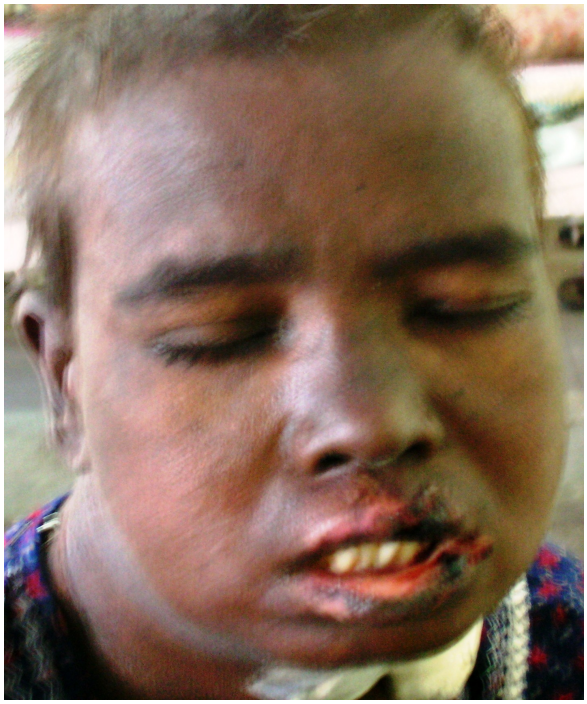

***Fig 23***
Systemic lupus erythematosus patient with lupus nephritis

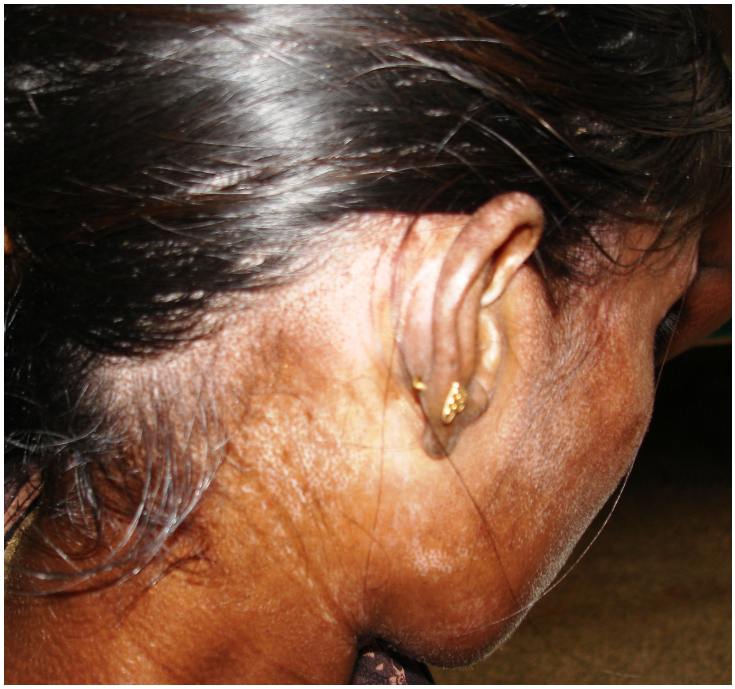

***Fig 24***
Salt and pepper pigmentation noted in a scleroderma patient

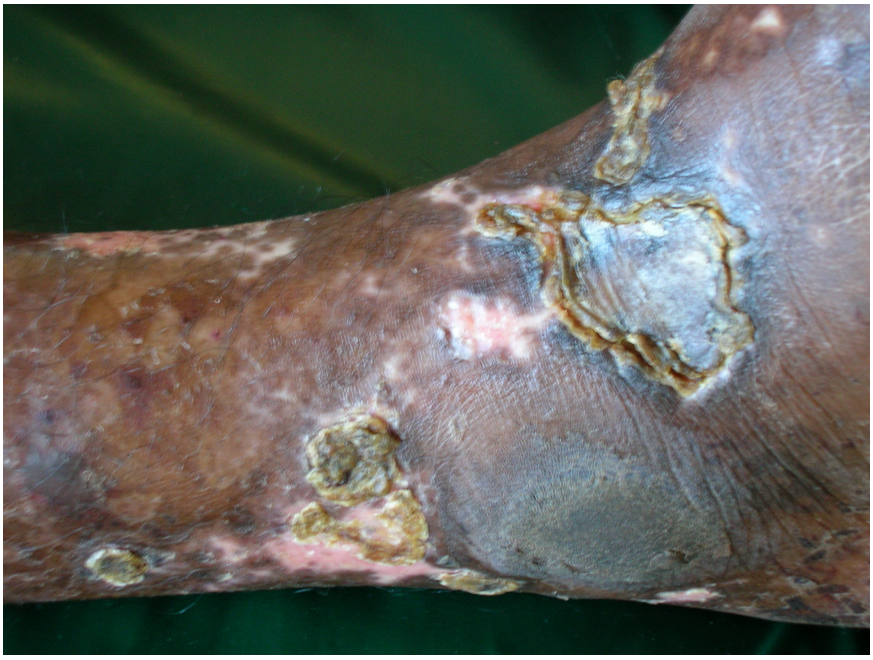

***Fig 25***
Vasculitic ulcer

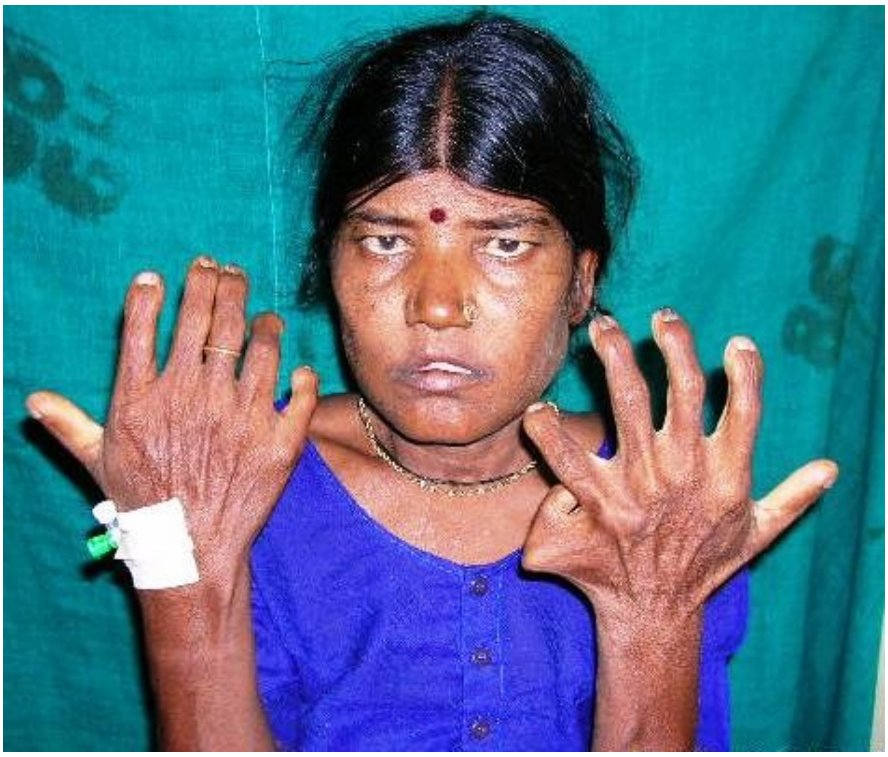

***Fig 26***
Ellis van creveld syndrome with cortical medullary disease

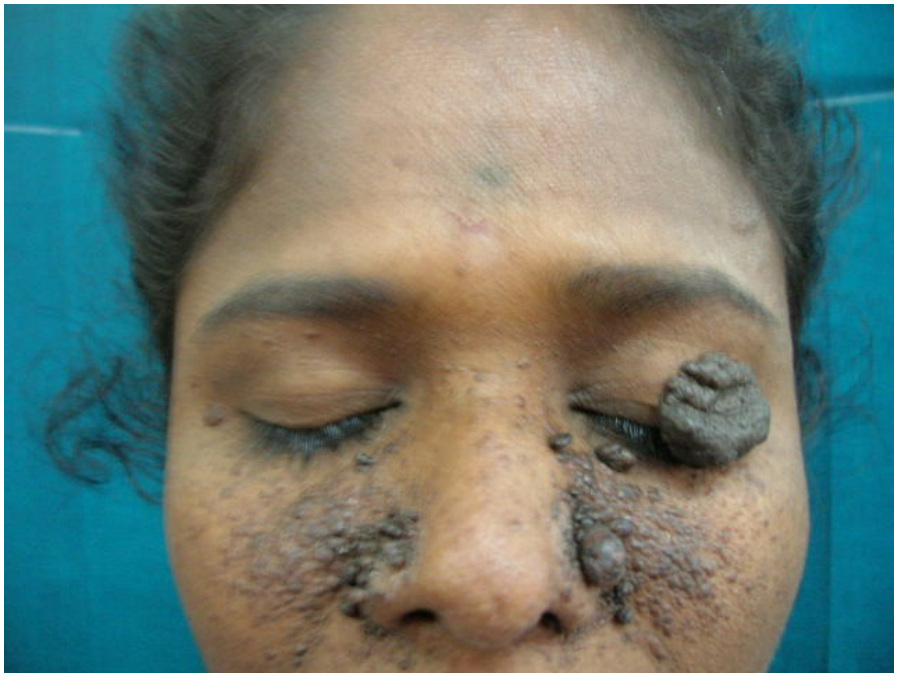

***Fig 27***
Angiofibroma in tuberous sclerosis patient with renal involvement

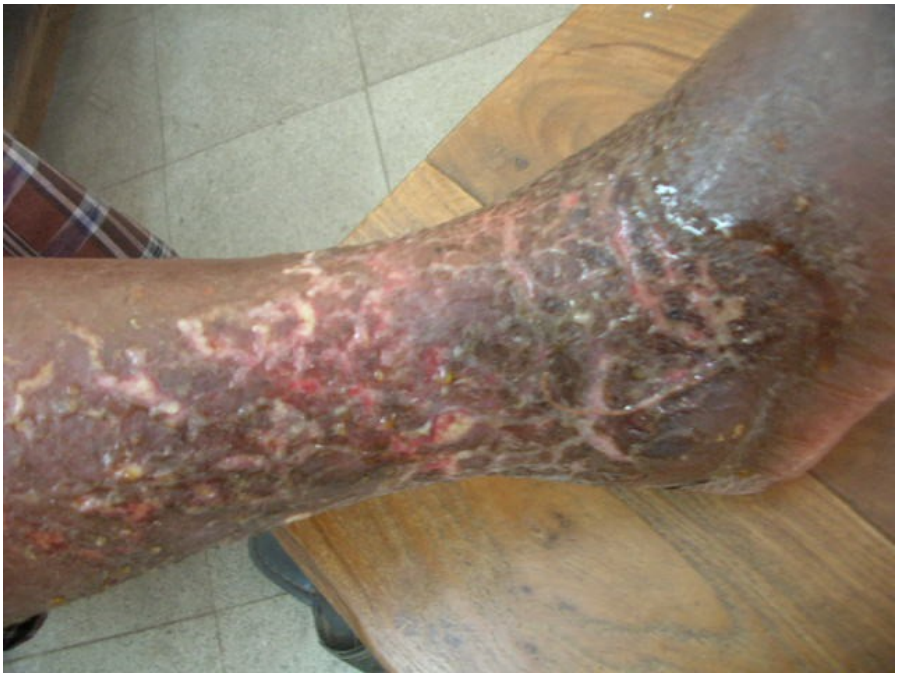

Fig 28
Stasis eczema in an uremic patient

2. Skin lesions associated with CRF

Non-specific skin diseases associated with these patients were LP, erythroderma, eczema with sensitization, stasis eczema (fig. 28), vitiligo, phrynoderma, bullous pemphigoid (fig. 29), pellagroid dermatitis (fig.30)

INCIDENCE OF ASSOCIATED SKIN LESIONS

**TABLE – XIII-B**

| **diseases** | **no. of patients** | | **total** | **incidence** |
|---|---|---|---|---|
| | Male | Female | | **%** |
| Lichen planus | 2 | 1 | 3 | 4 |
| Bullous pemphigoid | 1 | 0 | 1 | 1.3 |
| Erythroderma | 1 | 0 | 1 | 1.3 |
| Eczema with sensitization | 1 | 0 | 1 | 1.3 |
| Stasis eczema | 3 | 1 | 4 | 5.3 |
| Pellagroid dermatitis | 1 | 0 | 1 | 1.3 |
| Vitiligo | 2 | 2 | 4 | 5.3 |
| Phrynoderma | 3 | 1 | 4 | 5.3 |

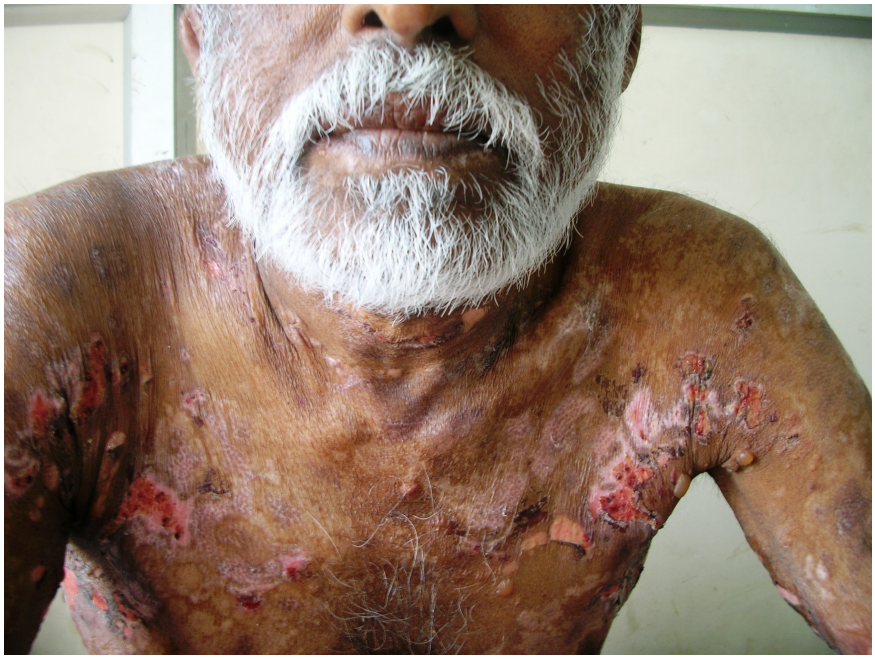

***Fig 29***
A bullous pemphigoid patient with chronic renal failure

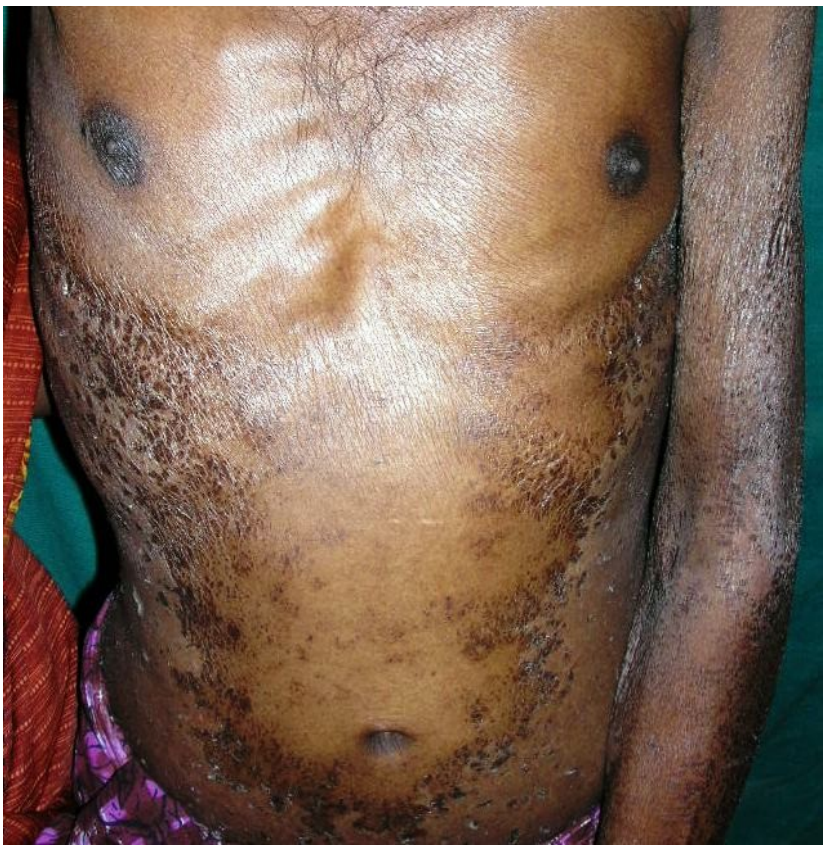

***Fig 30***
Pellagroid dermatitis in an alcoholic with CRF

# DISCUSSION

In this study including 75 patients with CRF, the mean age was around 36 years, which is in par with the literature of 30-60 yrs[2]. There was a male preponderance with male: female of 2.1: 1 in this study which goes in par with the literature. [2]

## I. SPECIFIC CUTANEOUS MANIFESTATIONS OF CRF:

A. SKIN CHANGES:

1. Uremic pruritus was seen in 72% and is between the reported ranges of 50 - 90% [35, 86] in one study and 40 – 70% [113] in another study. 14.6% of the patients with pruritus improved with dialysis, 25.3% worsened after dialysis and 32% had no change, which also is in par with the literature where 25% [8] developed pruritus during dialysis and 42% [8] had severe pruritus during dialysis. These suggest that dialysis may be a trigger for pruritus.

2. Xerosis was seen in 34 patients involving both trunk and extremities. Ichthyosis was seen in 15 patients, mostly involving lower extremities. All patients with xerosis also had associated pruritus. The incidence of xerosis was found to be 45.2% which lies nearer to the literature of 50 – 75%

3. Pigmentary alterations: Diffuse pigmentation over sun-exposed areas which is reported in 60-78%[43] of uremic patients was seen only in 21.3% in this study. Pallor of the skin was seen in 16%. Sallow grey pigmentation was noted in 8 patients. Hypermelanotic macules of the palms and soles were seen in 4 patients, whereas considerable cases have been reported in the literature[43]. The total incidence of patients showing pigmentary changes was 53.3%.

4. Perforating dermatoses: This was seen in 12 patients clinically. Skin biopsies were done for histopathologic evaluation. Using clinical and histopathologic correlation, Kyrle's

disease was found in 3 patients; Perforating folliculitis in 4 patients and features of nodular prurigo and prurigo simplex in other 5 patients. The incidence of perforating disorders in this study was 9.3% which lie in the range of 4-10% [63] of patients in the literature.

5. Purpura: was noted in 7 patients giving an incidence of 9.3%. Mild thrombocytopenia or marked platelet dysfunction could have contributed to the occurrence of purpura in some patients. Henoch-Schonlein purpura, ITP, cryoglobulinemia as etiologies of CRF presented with purpuric lesions over lower legs.

Interesting findings noted were – digital gangrene was seen in 2 patients, poor wound healing following trauma was noted in 4 patients and restless leg syndrome was diagnosed in 2 patients.

B. MUCOSAL ABNORMALITIES:

Oral mucosal lesions were seen in 17 patients with incidence of 22.6%. Uremic stomatitis was the commonest mucosal change seen in 12 patients with severe end stage renal disease. Oral ulcers over the buccal mucosa were seen in 3 patients. Leukokeratosis was seen as whitish plaques in the oral mucosa noted in 2 patients. Except for the hemorrhagic lesions, all the other oral mucosal changes were seen in this study.

C. HAIR ABNORMALITIES:

About 18.6% of the patients reported diffuse loss of hair resulting in sparse hair. Brittle dry hair was seen in 8 patients in this study.

D. NAIL CHANGES:

Half and half nails reported to occur in 15-50% [114] of uremic patients were seen in 24% of patients in this study. Brown nail bed arcs were seen in 10.6% as compared to 35% [83] in

one study. Thus the incidence of specific nail changes was comparatively lower in this study except for half and half nail. Other changes noted are shiny nails, probably due to scratching, melanonychia, onycholysis, onychodystrophy. Blue nails were seen in a patient during hemodialysis. [90] This was a rare finding reported in the literature. Mee's and Muercke's lines were not seen.

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

## II. SKIN CHANGES DUE TO TREATMENT

(MEDICAL AND DIALYSIS):

Arteriovenous shunt dermatitis was noted in 1.3 % only, low compared to the literature of 8% [105]. The low incidence may be due to proper wound care and good antibiotic coverage. Eczema around cannula site was noted in 2 patients. Dialysis induced pruritus and pigmentary alterations were seen in small percentage of the patients. Keratotic pits of palms were noted in three patients, which have been reported considerably in few studies[43,38]. Drug induced bullous dermatosis, pseudo porphyria, pseudo Kaposi's sarcoma; vascular malformations were not seen in this study.

## III. CUTANEOUS INFECTIONS IN CRF:

Fungal infections were found to be most common in this study. Dermatophytosis and pityriasis versicolor were the two common superficial mycoses. Extensive dermatophytosis was seen in one patient. Oral candidiasis was noted in 2 patients. Candidial vulvovaginitis was noted in 2 patients of which one was associated with diabetes mellitus.

Viral infections were the next highest in incidence, with verruca vulgaris found in

significant number of patients. Herpes simplex labialis and Herpes zoster were reported in association with severe pain.

Bacterial infections were low in incidence. This may be due to adequate antibiotic coverage in the ward. Staphylococcus aureus was grown in culture.

Classical scabies was seen in 2 patients.

The increased incidence of cutaneous infections of 43.8% could be due to an increased susceptibility to infections as a result of impaired immunity seen in uremia. There was no case of immunosuppression-induced tumors noted during the study.

## IV. ASSOCIATED SKIN LESIONS:

Certain skin changes helped in identifying the etiological causes of renal failure in this study. Skin lesions of systemic lupus erythematosus like malar rash, erythematous scaly plaques, atrophic depigmented plaques, diffuse alopecia were seen in 3 patients. Characteristic facies with pinched up nose, small mouth, sclerodactyly and salt and pepper pigmentation, hide-bound skin with digital pitted scars were noted in 2 patients. All of them had renal involvement and the cutaneous manifestations provided clue to the etiology of renal failure. Skin lesions of diabetes mellitus showing acanthosis nigricans, and vulvovaginitis were seen in 10 patients. Vasculitic ulcers were noted in 2 patients. Purpura was noted as a clinical manifestation occurring in proven cases of Idiopathic thrombocytopenic purpura, Henoch shonlein purpura and cryoglobulinemia. Ellis van creveld syndrome with renal finding of cortical medullary disease presented as end stage renal disease.

Other associated skin lesions were lichen planus, which was seen in 3 patients, all of

them were negative for hepatiris C virus infection indicating no etiological relationship in the particular patients; erythroderma in one patient, eczema with sensitization in one patient and stasis eczema in 4 patients. Pellagroid dermatitis was noted in an alcoholic patient. Vitiligo and phrynoderma were noted in 4 patients each. Bullous pemphigoid was seen in a patient without any associated history of drug intake such as frusesmide.

# CONCLUSION

This clinical study of cutaneous manifestations of chronic renal failure was done during the period December ’03 to December ‘05 revealed the following

1. Most of the specific cutaneous manifestations of chronic renal failure were seen in this study. Pruritus and xerosis were the most common among the specific cutaneous manifestations of chronic renal failure. Pigmentary alterations and nail abnormalities were the next. Mucosal and hair abnormalities were noted in good percentage of cases. Nearly 10% had perforating dermatosis and purpura. Interesting findings noted in this study were digital gangrene, poor wound healing, and restless leg syndrome.

2. Skin changes due to treatment reported were arteriovenous shunt dermatitis, keratotic pits of palms in small percentage and blue nails in a patient during hemodialysis, other than pruritus and pigmentary alterations.

3. Cutaneous infections and infestations were seen in 43.8 % of the cases. This high incidence could be due to impaired immunity resulting in increased susceptibility to infections in chronic renal failure patients. Fungal infections were the most common, followed by viral, bacterial and parasitic infestations.

4. Associated skin changes of systemic diseases helped in finding varying etiologies of chronic renal failure such s diabetes mellitus, systemic lupus erythematosus, scleroderma, vasculitis, Henoch schonlein purpura, idiopathic thrombocytopenic purpura. A case of

cortical medullary disease in Ellis van creveld syndrome was reported with cutaneous changes. A case of tuberous sclerosis with renal involvement and skin changes was seen. Other associated skin changes were not related to the etiology and were found to be just coincidental.

# PROFORMA

## A CLINICAL STUDY OF THE CUTANEOUS MANIFESTATIONS OF CHRONIC RENAL FAILURE

1. NAME:
2. AGE / SEX:
3. ADDRESS:
4. WARD No.:
5. EVALUATION OF RENAL FAILURE:
    a) Etiology
    b) Duration

6. TREATMENT FOR RENAL FAILURE:
    a) Drugs
    b) Dialysis
    c) Duration

7. 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

8. GENERAL EXAMINATION:
    a) anaemia
    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

9. 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 due to treatment

Due to dialysis

1. Pruritus
2. Bullous dermatoses
3. Vascular malformations
4. AV shunt dermatitis
5. Nail changes
6. Hair changes
7. Keratinization disorder
8. Neoplasms

10. INVESTIGATIONS

a) Renal

1. urine analysis
2. urine culture
3. blood Hb%
4. blood TC

   DC

   ESR
5. platelet count
6. blood – urea

- sugar

7. serum – creatinine
    - electrolytes
    - alk. Phosphotase
8. USG abdomen
9. duplex Doppler scan of renal arteries
10. MR angiography
11. renal biopsy

b) Skin

1. skin biopsy
2. tzanck smear
3. scraping for fungus – 10% KOH
    - Culture
    -

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# MASTER CHART

| Sl. no. | case no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | 20 | 35 | 30 | 17 | 21 | 41 | 45 | 50 | 32 | 30 | 35 | 50 | 24 | 49 | 46 | 55 | 26 | 29 | 16 | 52 |
| | Sex | M | M | F | M | M | F | M | M | F | M | F | M | F | M | M | M | M | F | M | M |
| | Duration ( in years) | 1 | 2 | 2 | 1 | 3 | 3 | 5 | 2 | 2 | 3 | 1 | 1 | 2 | 3 | 2 | 3 | 2 | 4 | 1 | 3 |
| I | **Cutaneous infections and infestations** | | | | | | | | | | | | | | | | | | | | |
| | **Specific lesions due to CRF** | | | | + | | | + | | | | | | | | + | | | | | + |
| | Fungal infections | | | + | | | | | | | + | | | | | | | + | | | |
| | Viral infections | | | | | | | | | | | | | | | | | | | | |
| A | **Skin changes** | | | | | | | | | | | | | | | | | | | | |
| 1 | Bacterial infections | + | | | | | | | | | | | | | | | | | | | |
| 2a | Pruritus | | + | + | + | | + | + | + | + | + | + | + | | + | | | | | | + |
| 2b | Parasitic infestations | | | + | | | + | + | + | + | | + | + | | + | + | + | | + | | + |
| | Xerosis | | | + | | | | | + | + | | + | | | | | | | | | |
| | Ichthyosis | | | | | | | | | | | | | | | | | | | | |
| 3 | **Associated skin lesions** | | | | | | | | | | | | | | | | | | | | |
| 4 | ***Contributing etiology of CRF*** | | | | | | | | | | | | | | | | | | | | |
| 5 | Pigmentary alterations | + | + | + | | + | + | + | | + | + | + | + | + | | + | | | + | + | + | |
| 6 | Uremic frost | | | | | | | | | | | | | | | | | | | | |
| 7 | Diabetes mellitus | | | | | | | + | + | | | + | | | | | | | | | |
| 8 | Perforating dermatoses | | | | | | | | | | + | | | + | | | | | | | |
| 9 | Systemic lupus erythematosus | | | + | | | | | | | | | | | | | | | | | |
| 10 | Metastatic calcification | | | | | | | | | | | | | | | | | | | | |
| 11 | Scleroderma | | | | | | | | | | | | | | | | | | | | |
| B | Purpura | | + | | | + | + | | | + | | | | | | | | | + | | |
| C | Vasculitis | | | | | | | | | | | | | | + | | | | | | |
| D | Gynaecomastia | | | | | | | | | | | | | | | | | | | | |
| | ITP, Cryoglobulinemia | | | | | | | | | | | | | | | | | | | | |
| | Vascular disorders | | | | | | | | | | | | | | | | | | | | |
| | Henoch Schonlein Purpura | | | | | | + | | | + | | | | | | | | | | | |
| | Poor wound healing | | | | | | | | | | | | | | | | | | | | |
| | Ellis Van Creveld syndrome | | | | | | | | | | | | | | | | | | | | |
| | Restless leg syndrome | | | | | | | | | | | | | | | | | + | | | |
| | Tuberous sclerosis | | | | | | | | | | | | | | | | | | | + | |
| B | **Mucosal changes** | | + | | | + | | + | | | + | | | + | + | | | | | | |
| | ***Other associated skin lesions*** | | | | | | | | | | | | | | | | | | | | |
| C | **Hair abnormalities** | | + | + | | + | | | | | + | + | | + | | | | + | | + | |
| D | Bullous pemphigoid | | | | | | | | | | | | | | | | | | | | |
| | **Nail abnormalities** | + | + | + | + | + | | | + | + | + | + | + | | + | | + | | | + | + |
| | Lichen planus | | | | | | | | | | | | | | | | | | | | |
| II | **Skin changes due to treatment** | | | | + | | | + | | | | | | | | + | | | | | + |
| 1 | Pseudoporphyria | | | | | | | | | | | | | | | | | | | | |
| 2 | Vascular malformations | | | | | | | | | | | | | | | | | | | | |
| 3 | AV shunt dermatitis | | | | | | | | | | | | | | | | | | | | |
| 4 | Keratotic pits of palms | + | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | |

| | case no. | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | 19 | 25 | 43 | 47 | 40 | 39 | 50 | 22 | 36 | 40 | 42 | 41 | 42 | 51 | 24 | 70 | 38 | 35 | 22 |
| | Sex | M | F | M | M | M | M | M | F | M | M | M | M | M | M | F | M | M | F | M |
| | Duration ( in years) | 2 | 7 | 2 | 2 | 3 | 2 | 2 | 1 | 3 | 5 | 3 | 3 | 2 | 3 | 1 | 4 | 2 | 3 | 3 |
| | **Specific lesions due to CRF** | | | | | | | | | | | | | | | | | | | |
| | **Skin changes** | | | | | | | | | | | | | | | | | | | |
| | Pruritus | | | + | + | | + | + | | + | + | + | | + | + | + | + | + | + | |
| | Xerosis | | + | + | + | | + | + | | | + | + | + | | + | | + | + | + | |
| | Icthyosis | | | | | | | + | | | | | | | | | + | | + | |
| | Pigmentary alterations | | + | + | | | + | | + | + | | | | + | | + | | + | + | + |
| | Uremic frost | | | | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Perforating dermatoses | + | | | | | | | + | | | | | | | | | | | | |
| Metastatic calcification | | | | | | | | | | | | | | | | | | | | |
| Purpura | | + | | | | | | | | | | | | | + | | | | | |
| Gynaecomastia | | | | | | | | | | | | | | | | | | | | |
| Vascular disorders | | | | | + | | | | | | | | | | | | | | | |
| Poor wound healing | | | | | | | | | | | | + | | | | | | | | |
| Restless leg syndrome | | | | | | | | | | | | | | | | | | | | |
| **Mucosal changes** | | | + | | | + | | + | | | | | | + | + | | | | | |
| **Hair abnormalities** | | + | | | | | | + | + | | | | | | + | | + | + | + | |
| **Nail abnormalities** | | + | | + | | + | + | + | + | + | | + | | | + | | + | | + | |
| **Skin changes due to treatment** | | | | | | | | | | | | | | | | | | | | |
| Pseudoporphyria | | | | | | | | | | | | | | | | | | | | |
| Vascular malformations | | | | | | | | | | | | | | | | | | | | |
| AV shunt dermatitis | | | | | | | | | | | | | | | | | | | | |
| Keratotic pits of palms | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |

| case no. | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 19 | 25 | 43 | 47 | 40 | 39 | 50 | 22 | 36 | 40 | 42 | 41 | 42 | 51 | 24 | 70 | 38 | 35 | 22 |
| Sex | M | F | M | M | M | M | M | F | M | M | M | M | M | M | F | M | M | F | M |
| Duration ( in years) | 2 | 7 | 2 | 2 | 3 | 2 | 2 | 1 | 3 | 5 | 3 | 3 | 2 | 3 | 1 | 4 | 2 | 3 | 3 |
| **Cutaneous infections and infestations** | | | | | | | | | | | | | | | | | | | |
| Fungal infections | + | | | | + | | | | | + | + | | + | | | | | + | |
| Viral infections | + | | | + | | + | | | | | | | | | | | | | + |
| Bacterial infections | | | | | | | | | | | | | | | | | | + | |
| Parasitic infestations | | | | | | | | | + | | | | | | | | | | |
| **Associated skin lesions** | | | | | | | | | | | | | | | | | | | |
| ***Contributing etiology of CRF*** | | | | | | | | | | | | | | | | | | | |
| Diabetes mellitus | | | + | | | | | | | | | | | | | | + | + | |
| Systemic lupus erythematosus | | + | | | | | | | | | | | | | | | | | |
| Scleroderma | | | | | | | | | | | | | | | | | | | |
| Vasculitis | | | | | | | | | | | | | | | | | | | |
| ITP, Cryoglobulinemia | | + | | | | | | | | | | | | | + | | | | |
| Henoch Schonlein Purpura | | | | | | | | | | | | | | | | | | | |
| Ellis Van Creveld syndrome | | | | | | | | | | | | | | | | | | | |
| Tuberous sclerosis | | | | | | | | | | | | | | | | | | | |
| ***Other associated skin lesions*** | | | | | | | | | | | | | | | | | | | |
| Bullous pemphigoid | | | | | | | | | | | | | | | | | | | |
| Lichen planus | | | + | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |

| case no. | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 23 | 19 | 68 | 43 | 41 | 45 | 24 | 50 | 25 | 40 | 18 | 24 | 19 | 47 | 27 | 31 | 24 | 28 | 40 |
| Sex | F | F | M | M | M | M | F | M | M | M | M | M | F | M | M | M | M | F | F |
| Duration ( in years) | 2 | 1 | 3 | 2 | 4 | 2 | 2 | 2 | 3 | 2 | 2 | 3 | 3 | 2 | 6 | 1 | 2 | 2 | 3 |
| **Specific lesions due to CRF** | | | | | | | | | | | | | | | | | | | |
| **Skin changes** | | | | | | | | | | | | | | | | | | | |
| Pruritus | + | | + | | + | + | + | | + | + | | + | | + | + | + | + | | + |
| Xerosis | | | + | | | + | | + | | | + | | | | | | | | + |
| Icthyosis | | | | | | | | | | | | | | + | | | | | |
| Pigmentary alterations | + | + | | + | + | | + | | + | | | + | | | + | | + | + | |
| Uremic frost | | | | | | | | | | | | | | | | | | | |
| Perforating dermatoses | | | | | | | | | | | | | | | + | | | | |
| Metastatic calcification | | | | | | | | | | | | | | | | | | | |
| Purpura | | | | | | | | | | | | | | | | + | | + | + |
| Gynaecomastia | | | | | | | | | | | | | | | | | | | |
| Vascular disorders | | | | | | | | | | | | | | | | | | | |
| Poor wound healing | | | | + | | | | | | | | | | | | | | | |
| Restless leg syndrome | | | | | | | | | | | | | + | | | | | | |
| **Mucosal changes** | | + | | | | | | | | | | | + | | | | | | |
| **Hair abnormalities** | | | | | | | + | | | | | | | | + | | + | + | |
| **Nail abnormalities** | + | | | | + | | + | | | | | + | | | + | | + | + | |
| **Skin changes due to treatment** | | | | | | | | | | | | | | | | | | | |
| Pseudoporphyria | | | | | | | | | | | | | | | | | | | |
| Vascular malformations | | | | | | | | | | | | | | | | | | | |
| AV shunt dermatitis | | | | | | | + | | | | | | | | | | | | |
| Keratotic pits of palms | | | | | | | | | | + | + | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |

| case no. | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 23 | 19 | 68 | 43 | 41 | 45 | 24 | 50 | 25 | 40 | 18 | 24 | 19 | 47 | 27 | 31 | 24 | 28 | 40 |
| Sex | F | F | M | M | M | M | F | M | M | M | M | M | F | M | M | M | M | F | F |
| Duration ( in years) | 2 | 1 | 3 | 2 | 4 | 2 | 2 | 2 | 3 | 2 | 2 | 3 | 3 | 2 | 6 | 1 | 2 | 2 | 3 |
| **Cutaneous infections and infestations** | | | | | | | | | | | | | | | | | | | |
| Fungal infections | | | + | | | + | | + | | | | | + | | | | | | + |
| Viral infections | | | | | | | | | + | | + | | | | | | + | + | |
| Bacterial infections | | | | | | | | + | | | | | | | | | | | |
| Parasitic infestations | | | | | | | | | | | | | | | | | | | |
| **Associated skin lesions** | | | | | | | | | | | | | | | | | | | |
| ***Contributing etiology of CRF*** | | | | | | | | | | | | | | | | | | | |
| Diabetes mellitus | | | | | | | | | | | | | | | | | | | + |
| Systemic lupus erythematosus | | | | | | | | | | | | | | | | | | | |
| Scleroderma | | | | | | | + | | | | | | | | | | | | |
| Vasculitis | | | | | | | | | | | | | | | | | | | |
| ITP, Cryoglobulinemia | | | | | | | | | | | | | | | | | | | |
| Henoch Schonlein Purpura | | | | | | | | | | | | | | | | | | + | |
| Ellis Van Creveld syndrome | | | | | | | | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Tuberous sclerosis | | | | | | | | | | | | | | | | | | | |
| | ***Other associated skin lesions*** | | | | | | | | | | | | | | | | | | | |
| | Bullous pemphigoid | | | + | | | | | | | | | | | | | | | | |
| | Lichen planus | | + | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |

| Sl. no | case no. | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | 50 | 18 | 65 | 48 | 47 | 29 | 34 | 39 | 28 | 43 | 23 | 26 | 28 | 41 | 25 |
| | Sex | M | F | M | M | F | F | F | M | M | M | F | M | F | F | M |
| | Duration ( in years) | 8 | 1 | 4 | 3 | 1 | 2 | 7 | 3 | 2 | 2 | 2 | 1 | 3 | 2 | 2 |
| **I** | **Specific lesions due to CRF** | | | | | | | | | | | | | | | |
| **A** | **Skin changes** | | | | | | | | | | | | | | | |
| 1 | Pruritus | + | | + | + | + | + | + | + | + | + | | + | + | + | + |
| 2a | Xerosis | + | | + | + | + | | | + | | + | | | | + | |
| 2b | Icthyosis | | | + | | | | + | | | | + | | | | |
| 3 | Pigmentary alterations | | | | | + | + | | + | + | | | | + | | |
| 4 | Uremic frost | | | | | | | | | | | | | | | |
| 5 | Perforating dermatoses | | | | | + | | | | | | | | | | |
| 6 | Metastatic calcification | | | | | | | | | | | | | | | |
| 7 | Purpura | | | | | | + | | | | | | | | | |
| 8 | Gynaecomastia | | | | | | | | | | | | | | | |
| 9 | Vascular disorders | | | | | | | + | | | | | | | | |
| 10 | Poor wound healing | | | | | | | | | | | | | | + | |
| 11 | Restless leg syndrome | | | | | | | | | | | | | | | |
| B | **Mucosal changes** | | + | | + | | | | | | | + | | | | + |
| C | **Hair abnormalities** | | | | | | | + | | + | | | | + | | |
| D | **Nail abnormalities** | | | | | + | + | | | + | | + | + | | | |
| **II** | **Skin changes due to treatment** | | | | | | | | | | | | | | | |
| 1 | Pseudoporphyria | | | | | | | | | | | | | | | |
| 2 | Vascular malformations | | | | | | | | | | | | | | | |
| 3 | AV shunt dermatitis | | | | | | | | | | | | | | | |
| 4 | Keratotic pits of palms | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |

| Sl. no | case no. | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | 20 | 35 | 30 | 17 | 21 | 41 | 45 | 50 | 32 | 30 | 35 | 50 | 24 | 49 | 46 |
| | Sex | M | M | F | M | M | F | M | M | F | M | F | M | F | M | M |
| | Duration ( in years) | 1 | 2 | 2 | 1 | 3 | 3 | 5 | 2 | 2 | 3 | 1 | 1 | 2 | 3 | 2 |
| **III** | **Cutaneous infections and infestations** | | | | | | | | | | | | | | | |
| 1 | Fungal infections | | | | | | | | + | | | | | | | |
| 2 | Viral infections | | | | | | | | | | + | | + | | | |
| 3 | Bacterial infections | | | | | | | | | | | | | | | |
| 4 | Parasitic infestations | | | | | | | | | + | | | | | | |
| **IV** | **Associated skin lesions** | | | | | | | | | | | | | | | |
| A | ***Contributing etiology of CRF*** | | | | | | | | | | | | | | | |
| 1 | Diabetes mellitus | | | | + | + | | | + | | | | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Systemic lupus erythematosus | | | | | | | | | | | | | | | |
| 3 | Scleroderma | | | | | | | | | | | + | | | | |
| 4 | Vasculitis | | | | | | | | | | | | | | | |
| 5 | ITP, Cryoglobulinemia | | | | | | | | | | | | | | | |
| 6 | Henoch Schonlein Purpura | | | | | | | | | | | | | | | |
| 7 | Ellis Van Creveld syndrome | | | | | | | | | | | | | | | |
| 8 | Tuberous sclerosis | | | | | | | | | | | | | | | |
| B | ***Other associated skin lesions*** | | | | | | | | | | | | | | | |
| 1 | Bullous pemphigoid | | | | | | | | | | | | | | | |
| 2 | Lichen planus | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |