Dermatologic Manifestations in Renal Failure

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Key Points

- The three most common kidney diseases that lead to end-stage of chronic renal failure (CRF) are:
- Vascular nephropathy
- Obstructive nephropathy
- Diabetic nephropathy

Of note, the latter is the main cause of CRF in American and Spanish populations [1]

- Most skin disorders are seen in patients undergoing HD, probably owing to the fact that it is the most frequently used renal replacement therapy worldwide [2]
- Skin disorders in chronic renal failure are benign, but almost all of them show a significant impact on the quality of life of affected patients [3, 4]
- The prevalence of dermatoses in chronic renal failure is close to 100% [5–7]

Introduction

Chronic renal failure (CRF) is a major public health problem worldwide [3]. (It is defined as an abnormality in renal structure or function, with health implications present for at least 3 months. It is classified according to three variables: glomerular filtration rate (GFR), its etiology, and the amount of albuminuria [8].

Administration of kidney replacement therapy is based on the GFR. Patients with GFR less than 15 mL/min should be admitted to a replacement kidney function plan with any of the existing methods [8]. Replacement of renal function is currently performed by three modalities: hemodialysis (HD), peritoneal dialysis (PD), and renal transplant. Most skin disorders are seen in patients undergoing HD, probably because it is the most frequently used renal replacement therapy worldwide since it has been proved to prolong the life expectancy of patients with CRF [2].

The three most common kidney diseases that lead to end-stage CRF are vascular nephropathy, obstructive nephropathy, and diabetic nephropathy. The latter is the main cause in American and Spanish populations [1].

Of note, this chapter does not discuss dermatologic conditions that are common after transplantation in immunosuppressed patients; this information is available in another chapter.

These patients are considered to have a chronic inflammatory status caused by multiple factors, some of which include the underlying disease, a

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permanent fistula or catheter, the membranes used for HD or PD, and the drugs and supplements that they receive [9].

From a dermatologic point of view, there is a high frequency of dermatoses associated with this condition. They can be divided as specific and nonspecific, the latter having the highest prevalence, but all of them showing a significant impact on patients quality of life [3].

Skin changes reported in patients with CRF are diverse [3]. Most skin disorders are benign and do not affect the course of CRF [4]. Sometimes skin disorders can predict the initiation of a renal replacement plan, or may be precipitated by it [3, 4].

Epidemiology

Few worldwide publications describe the prevalence and characteristics of skin alterations observed in patients with CRF and in patients receiving HD. Pico et al. (1992) registered a 100% prevalence of skin lesions in patients with CFR while Bencini et al. (1998) reported 79% prevalence [5–7]. In accordance with these studies, Udayakamur et al. (2006) conducted a study of dermatoses in 100 patients receiving HD, for which the prevalence was 82% [5, 6]. We recently conducted a study in Uruguay about the prevalence of dermatoses in 200 patients in HD, which found a prevalence of 98%.

Multiple factors are described to explain the greatest amount of dermatoses affecting patients with CRF, and these are briefly mentioned in Chart 44.1.

Practically, skin changes in CRF are classified into four groups depending on the relationship with the renal disease or the renal treatment, as described in Chart 44.2.

Chart 44.1 Multiple factors described to explain the greatest amount of dermatoses affecting patients with CRF

Factors described to explain the dermatoses affecting patients with chronic renal failure
Skin dehydration (specially epithelial) with malfunction of the eccrine sweat glands [5, 8]
Dysregulation of calcium and phosphorus metabolism [6]
Chronic systemic proinflammatory condition; for patients receiving hemodialysis, postulating the permanent fistula or catheter as a possible active element [4, 6]
Type of hemodialysis membrane used, which is a questionable concept [9]
Urochrome skin storage [4, 11]
Hypovitaminosis D [5, 8]
Hypervitaminosis A [5, 8]
In hemodialysis patients, higher amount of melanocyte-stimulating hormone β because of poor excretion via hemodialysis [12, 13]
Accelerated erythropoiesis [3, 8]
Altered hemostasis, among other factors mostly by high concentration of urea [10, 11]
Heparin use [10, 11]
Protein malnutrition [5, 10]
Altered cellular immunity [5, 14]
Iron deficiency [3, 8]

Chart 44.2 Classification of skin changes in chronic renal failure according to the relationship with the renal disease or the renal treatment [10]

Causes of skin changes in chronic renal failure
The disease itself that is generating the kidney malfunction
Kidney disease itself
Established treatment
Drugs that the patients receive

Cutaneous Manifestations of Chronic Renal Failures

From a dermatologic point of view, a high frequency of dermatoses and skin lesions are associated with this condition. For practical purposes, these dermatoses can be grouped into nonspecific (with higher prevalence) and specific. All of them have a significant impact on patients' quality of life [9, 14].

Nonspecific dermatoses are listed in Chart 44.3 and the specific dermatoses are in Chart 44.4.

Besides the aforementioned, there exist iatrogenic dermatoses caused by treatment and adverse drug reactions [6, 10].

Xerosis, bruising, and itching are ubiquitous in this population and are considered multifactorial xerosis, pale skin, and itching were the most prevalent findings according to an Indian study

Chart 44.3 Dermatoses grouped as "nonspecific" in chronic renal failure [8, 9, 14]

Nonspecific dermatoses in chronic renal failure
Xerosis
Pruritus
Dyschromia
Ecchymosis
Gynecomastia
Cutaneous infections
Skin cancer
Mucosal alterations
Faneral disorders

Chart 44.4 Dermatoses grouped as "specific" in chronic renal failures [4, 8–10, 14]

Specific dermatoses in chronic renal failures
Acquired perforating dermatoses (APD)
Bullous dermatoses
Calcification disorders
Nephrogenic systemic fibrosis (NSF)
Specific nail changes
Uremic frost

conducted in 99 patients [4, 10, 14]. This correlates with our findings according to a Uruguayan study, conducted in 2015, of dermatoses in 200 patients receiving HD.

Nonspecific Cutaneous Entities with Higher Prevalence in Patients with Chronic Renal Failure

This grouping mechanism is currently considered controversial since these skin changes could be either coincidental or associated with factors other than CRF, such as the etiologic condition causing renal failure [12].

Xerosis

Xerosis, or dry skin, is a common skin disorder described as the most common skin disorder found among patients with CRF, especially in patients receiving regular HD [4, 9, 10]. It is characterized clinically by rough, scaly, and often itchy skin [2]. A frequency between 50% and 70% in patients undergoing HD is reported [4–6, 8, 10, 11].

Pruritus

Pruritus is one of the most distinctive and troublesome symptoms among patients with CRF, but seems to be absent in patients with acute renal disease [5, 6, 8, 10]. A prevalence rate of 50% has been found in different studies [5, 8–10]. Pruritus has been associated with the degree of renal impairment of the patient and is considered an inflammatory systemic disease rather than a skin disorder per se [5, 9, 15]. It may be accompanied by xerosis but there is no direct correlation between these two entities [15].

The prevalence in patients undergoing HD is between 58% and 90% [5, 11, 15, 16].

Various publications describe that severe pruritus improves after HD, others report no improvement, while some describe patients who report its aggravation after starting HD [5, 9, 10, 16]. Pruritus seems to be more severe in patients with diabetes mellitus (DM) [5, 6].

Dyschromia

Two types of pigmentary changes are described: diffuse hyperpigmentation and citrine yellowish tint [5, 6].

Thomas et al. reported that dyschromia occurs in 32% of HD patients while others refer to prevalence between 25% and 75%, this percentage being higher in patients on maintained HD [10]. In our experience, the prevalence was 31.2% in the 200 patients receiving HD studied.

Diffuse hyperpigmentation is a relatively common early sign and is located in sun-exposed areas [14, 15].

Pallor is observed more frequently in patients receiving sustained HD, with an incidence from 40% to 60% reported. It is difficult to quantify and is defined as an unusual lightness of skin color when compared with normal hue [16], it is attributed to chronic anemia and dysfunctional erythropoiesis [3, 8, 12, 13]. For some authors, pallor is a hallmark in patients with CRF and adds significant morbidity. It correlates with the hemoglobin level, presenting higher incidence in patients with levels lower than 8 g% [6].

Ecchymosis

Ecchymosis prevalence varies from 10% to 60% [5, 10, 11]. It is clinically observed as a

subcutaneous lesion characterized by deposits of extravasated blood [16].

Gynecomastia

Gynecomastia has a reported prevalence of 40% in patients undergoing HD [5]. The development of this clinical sign seems to occur 1 or 2 months after starting HD, and spontaneous regression is seen in most cases within a year [17].

Cutaneous Infections

A prospective Indian study of patients undergoing HD reported a prevalence of 26.26% of bacterial, viral, fungal, and parasitic infections, bacterial ones being the most common among diabetic patients [5, 10, 15].

The most common are the fungal infections such as tinea versicolor and onychomycosis; the latter also most prevalent in patients with DM [5, 6]. In Nigeria a high prevalence of tinea versicolor is reported, the predominant location being upper extremities and not in the "classic" areas where sebum production is increased [11].

The most prevalent viral infections reported are warts, herpes simplex, and herpes zoster (VHZ), although in some studies no statistically significant differences were found compared with the general population [5, 7]. Herpes reactivation has been reported more frequently in this population, and supplements with vitamin D and iron have been linked to a lower incidence [18].

Skin Cancer

Immunosuppression in these patients would predispose to higher prevalence of skin cancer, basal cell carcinoma (BCC being) the most frequently reported, although its prevalence has not been compared with that in the general population [5]. In our recent experience the prevalence of BCC and squamous cell carcinoma (SCC) was similar (4% and 4.5%, respectively). One partial possible explanation for the increase in SCC in this study is the fact that we conducted our study in Uruguay, where population is predominantly Caucasian with a high degree of sun exposure as a result of the latitude and social behavior regarding tanning habits. However, in the Uruguayan population BCC is more frequent than SCC. This would favor skin carcinogenesis in susceptible individuals with low phototypes [19]. This study shows that the relationship between the prevalence of BCC and SCC in the HD population would resemble what happens in renal transplant patients in whom the BCC/SCC ratio is reversed [20] (see Box 44.1).

Box 44.1 BCC and SCC in the HD Population of Uruguay [19]

The authors conducted a study in 2015 about the prevalence of dermatoses in 200 patients receiving hemodialysis. This study allowed the diagnosis of melanoma in two patients, one of them with Breslow thickness of 0.73 mm and the other of 1.3 mm. The reported incidence in Uruguay, where the study was conducted, is 5.2 cases per 100,000 population per year. There are no literature reports on the prevalence of melanoma in hemodialysis patients, this being much higher than that reported in the general population of this country.

Mucosal Alterations

A prevalence of 90% is reported for oral mucous membrane disorders among patients with CRF. Macroglossia ("uremic tongue"), xerostomia, and ulcerative stomatitis are the most frequent findings [5, 10, 21].

Other mucous membrane disorders are angular cheilitis, furred tongue, and uremic breath, the latter being caused by a high concentration of urea in saliva and ammonium degradation [5, 11].

Faneral Disorders

Diffuse hair loss and diffuse alopecia with dull hair are described as distinctive features among patients with CRF [4, 12].

A Brazilian study reported that the prevalence of hair loss and dull hair was between 26% and 33% [11].

Ungular disorders described are koilonychias, subungual hyperkeratosis, onycholysis, Mee's lines (leukonychia transverse bands), Muehrcke's lines (double white cross band),

splinter hemorrhage, absence of lunula, and Beau's lines [5, 22]. The prevalence of these entities, plus Lindsay nails (better known as "half and half nails"), is estimated to be 71.4% of patients with CRF [11, 23].

Specific Skin Entities Characteristic of Patients with Chronic Kidney Disease

The prevalence of these entities has been studied in patients receiving HD, but not in patients with CRF. In a case–control study conducted in Egypt a prevalence of 3% was reported among 128 patients receiving HD [12]. These figures do not match with our previously mentioned study, where prevalence was 14%. This difference could be explained in part by the exclusion in the Egypt study of various dermatoses included in our study, such as fistula dermatoses and Lindsay nails.

Acquired Perforating Disorders

Several perforating disorders have been described in patients with CRF. They can be primary or acquired and include perforating folliculitis, Kyrle's disease, reactive perforating collagenosis, and acquired perforating disorder (APD) [5, 8, 10, 13].

The term APD or perforating disorder in kidney disease is used for the description of follicular hyperkeratotic papules in these patients [5, 13]. APD is an acquired skin disease characterized by transepidermal elimination of dermal material with minimal damage to adjacent structures [5, 7, 13, 14, 19].

The reported incidence among patients with CRF varies between 4.5% and 11% [9, 13, 14]. Higher prevalence is described in patients of African descent and patients with DM [7, 9, 13, 19].

Bullous Dermatoses

Bullous dermatoses in renal failures include porphyria cutanea tarda (PCT), pseudoporphyria, and bullous cutaneous drug reactions. The latter is not specific of patients with CRF. The prevalence of these three entities varies from 1.2% to 18% [19].

Porphyria Cutanea Tarda

PCT is a disorder in heme biosynthesis resulting in vesicles and blister rash on sun-exposed areas [14]. It can be divided into inherited or acquired. In acquired PCT the deficient enzyme is located in the liver [8, 13, 14].

The reported incidence of PCT is in the range of 1.8–3%. It was considered a common condition in patients receiving HD in the pre-erythropoietin era, whereby iron overload was common [8, 9, 13, 14].

In PCT the standard HD cannot remove uroporphyrins. These levels in patients with CRF without PCT are similar to the ones found in PCT patients with normal renal function. Currently PCT occurs in anemic HD patients with erythropoietin resistance that requires red blood cell transfusions. In such patients, treatment is based on reducing iron stores and plasma levels of porphyrins [14, 19].

Pseudoporphyria

Pseudoporphyria is a photodistributed vesicobullous disorder with clinical and histologic features similar to those of PCT but without any biochemical porphyrin abnormalities [8, 13, 14, 19, 24].

Calcification Disorders

Disorders of calcification are a heterogeneous group of diseases whose common denominator is the deposit of calcium. Calcium salt deposits in the skin and soft tissues are known as calcinosis cutis [13, 25]. In the context of a patient with chronic kidney disease it is subclassified as benign nodular calcification (BNC) [14]. When intravascular calcium reservoir occurs and is accompanied by initial fibroplasia, vascular occlusion, and soft tissue necrosis, the diagnosis is calciphylaxis, also known as calcifying uremic arteriopathy [7, 9, 14].

Calciphylaxis is a frequently lethal entity because of progressive skin necrosis secondary to calcification of small blood vessels [9, 13, 14]. BNC and calciphylaxis occur more frequently in patients with CRF. While calciphylaxis is more common in patients with CRF, it has also been reported in other entities such as in renal transplant recipients, Crohn's disease,

cirrhosis, rheumatoid arthritis, inflammatory bowel disease, neoplasms, systemic lupus erythematosus, human immunodeficiency virus (HIV) infection, and primary hyperparathyroidism [13, 14]. Kidney failure is not a requirement for the development of this phenomenon [8, 25].

The overall incidence of calciphylaxis in HD patients is estimated at between 1% and 4%, women being more commonly affected [8, 13].

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) is a systemic condition with prominent cutaneous manifestations encompassed in fibrosing sclerosis-like disorders, observed in patients with renal disease after exposure to contrast agents based on gadolinium during an imaging procedure [14, 26]. It is a chronic and progressive disease without cure [19, 26, 27].

NSF today is well known by dermatologists and nephrologists, being easily recognized by clinical presentation [14, 27]. While most patients suffering from this condition are undergoing HD, it has also been described in patients receiving peritoneal dialysis and those patients receiving HD because of acute renal failure [7, 14, 19, 27, 28]. The estimated prevalence of NSF among patients with CRF is 0.5–6% [26]. The dominant feature is its presentation during kidney failure, both acute and chronic [14, 28].

Specific Nail Changes

Lindsay nails or "half and half nails" is the most frequent ungual alteration in CRF patients, with an approximate prevalence reported in HD patients from 21% to 40% [4, 5, 8, 10, 22]. In the general population the prevalence is 1.4% [5].

Uremic Frost

Uremic frost is one of the most infrequent skin changes that occurs in patients who suffer an acute episode of severe uremia [5, 8]. It was a common finding in the pre-HD era [5, 6].

Dermatoses on the Arteriovenous Shunt

Udayakumar et al. (2006) reported a prevalence of 8% in patients receiving prolonged HD [5, 6]. The authors found three dermatoses of this topography during the examination of 200 patients on HD.

Kaposi's Pseudosarcoma

Few cases are reported of this entity close to the region of an artificially constructed arteriovenous fistula. They are described as purple nodules or plaques that evolve slowly to lilaceous scaly crusted plaques near the fistula [5].

Adverse Drug Reactions

A higher incidence is described in this population, mainly due to the simultaneous administration of multiple drugs and drugs with prolonged half-life [5].

Recent advances in treatment have improved the quality and life expectancy of these patients, resulting in changes in the frequency and characteristics of skin disease [10].

Etiopathogenic Mechanisms

Xerosis

Cutaneous xerosis may be explained as a dysfunction and reduction in size of eccrine sweat glands, suggesting an alteration in the secretion product that results in epithelial dehydration. The high diuretic regime in these patients could also be involved [4–6, 8, 14, 21]. In the study conducted by Udayakumar et al. (2006), 37% of the patients also had associated pillar-like keratosis lesions on extensor surfaces, xerosis being more severe in patients who also had DM [5]. In our experience, xerosis was found in 79.4% of 200 patients receiving HD. These figures coincide with previous studies in Brazil and in the United States [3, 5]. This Uruguayan study researched the relationship between DM and xerosis with no statistically significant data as reported in the Brazilian study, where 72.5% of patients had DM [3].

Pruritus

The etiopathogenesis and pathophysiology of pruritus is complex, since several uremic and

nonuremic factors contribute to its development [5, 10, 25]. In this sense, two hypotheses are described: the immunologic and the opioid hypothesis. The first one is based on considering uremic pruritus as a systemic disease. This idea is based on the proven benefits of the treatment with ultraviolet B (UVB) and thalidomide or calcineurin inhibitor intake such as tacrolimus [9]. UVB radiation attenuates the development of T-helper 1 (Th1) cells for Th2 differentiation, which leads to decreased production of interleukin (IL)-2. In addition, serum levels of proinflammatory markers such as C-reactive protein and IL-6 are increased in CRF patients with pruritus compared with those without pruritus, confirming the inflammatory nature of the condition. Opioid hypothesis proposes that pruritus is part of a change in the endogenous opioid system, overexpressing μ-opioid receptors in dermal skin cells and lymphocytes. This overexpression, with a concomitant decrease of κ-opioid receptors, could cause increased β-endorphin serum in patients with CRF, which would explain the development of pruritus. Use of κ-receptor agonists such as nalfurafine, or naltrexone, a μ-receptor antagonist, improves pruritus in this population [9].

Other possible biological theories proposed to explain pruritus in patients with CRF are urochrome skin reservoir, uremic toxemia, dysregulation of calcium and phosphorus metabolism, proliferation of mast cells with increased levels of histamine, allergy to HD components, and reaction to hypovitaminosis D and hypervitaminosis A [4–6, 8, 10, 11]. Pruritus has been linked to xerosis, although several studies failed to find such a relationship [13]. In HD patients, high plasma histamine levels may be due to allergic sensitization to various components of the HD's membrane and an altered renal excretion of histamine [5, 13]. Parathyroid hormone and divalent ions such as calcium; phosphorus, and magnesium have also been implicated in the pathogenesis of uremic pruritus, since itching is present in severe secondary hyperparathyroidism [5, 7, 10, 19, 29]. The lack of a consistent relationship between levels of parathyroid hormone, calcium, phosphorus, and uremic pruritus indicates that there would be other more important factors involved in the pathogenesis [9, 10, 13, 29]. A study in Brazil revealed a statistically significant correlation between pruritus and elevated levels of phosphorus and magnesium [11]. A Japanese study 1,773 patients in HD identified male gender, high levels of blood urea/nitrogen, β2-microglobulin, hypercalcemia, and hyperphosphatemia as independent risk factors for the development of severe pruritus, whereas a low level of calcium and intact parathyroid hormone were associated with reduced risk [30].

In our experience, factors described in the literature that could influence the presence of pruritus in this particular population could not be proven statistically, including DM, HD membrane type, calcemia, phosphoremia, C-reactive protein level, and intake of vitamin supplements. On the other hand, we emphasize a significant relationship between vitamin D deficiency (in plasma) and the presence of pruritus. Vitamin D deficiency has been linked to pruritus in HD patients [4, 6].

Dyschromia

Diffuse Hyperpigmentation

Pigmentary alterations are attributed to an increase of melanin pigment in the basal layer of the epidermis and superficial dermis, owing to the greater amount of melanocyte-stimulating hormone because of poor HD excretion [12, 13, 25, 26]. Higher prevalence of this entity has been reported in patients who also had positive serology for hepatitis C virus (HCV) [7].

Sallow Skin

Carotenoid, lipochrome, and urochrome deposits in dermal layer and subcutaneous tissue are thought to be responsible for the yellowish sallow dyschromia so characteristic of these patients [3, 12, 13, 27].

Ecchymosis

Ecchymosis is explained by defects in hemostasis, which generate vascular fragility and platelet

dysfunction, to which is added the use of heparin during HD [5, 8, 10, 13]. High concentrations of urea alter platelet aggregation and increase guanidinosuccinic acid levels, which inhibits platelet activity induced by adenosine diphosphate [11].

Gynecomastia

Gynecomastia occurs in the early stages of HD and is explained by a "feedback" after starting treatment. Both in CRF and protein malnutrition, pituitary and testicular function remain suppressed. When protein supplies increases after starting treatment with HD, a second "pubertal" push generates a transient gynecomastia [5, 10]. It has also been attributed to accumulation of prolactin, which inhibits the release of follicle-stimulating hormone and luteinizing hormone, resulting in decreased production of estrogen and progesterone [8].

Cutaneous Infections

HD patients have impaired cellular immunity because of their smaller number of T cells, which could explain the high percentage of infections in this population [9, 14, 15].

Skin Cancer

Patients with CRF receiving HD have been reported have an increased risk of any cancer [31]. Prevalence of skin cancer in CRF patients compared with the general population has not been reported [5]. By contrast, kidney transplant recipients with a higher skin cancer prevalence are well studied, with an SCC-versus-BCC incidence ratio of 3.8:1 and an annual incidence calculated at 6.5%, increasing to 10.5% at more than 10 years post transplantation. Duration of immunosuppression, older age at transplantation, presence of actinic keratosis, male sex, and outdoor occupation are significantly associated with both SCC and BCC in kidney transplant recipients [32]. In transplant recipients, immunosuppressive drugs severely impair the body's immune functions. Among the cell types affected are T lymphocytes, natural killer cells, and dendritic and other antigen-presenting cells. The end result is disrupted immune surveillance. Thus, a microenvironment is created that is conducive to unrestricted tumor growth [33]. In our opinion, the same situation is likely to occur in CRF patients as this population is considered as being in a chronic immune-suppressed state [5]. As described earlier, this concept agrees with the findings of our study wherein the prevalence of SCC was slightly greater than that of BCC in HD patients. In addition, this population is at greater risk for developing virus-induced neoplasms.

Nonmelanocytic skin cancer behaves more aggressively in chronically immunosuppressed individuals. The exact mechanism whereby this aggressive phenotype is achieved remains elusive [33].

Faneral Disorders

Dull hair is believed to be due to decreased secretion of sebum [5, 10]. On the other hand, all abnormalities in the hair are considered as related to the administration of heparin, hypervitaminosis A, accumulation of toxins, iron deficiency, and drugs frequently used in HD patients such as β-blockers, methyldopa, cimetidine, allopurinol, and indomethacin [11].

Acquired Perforating Dermatoses

The pathophysiology of APD remains unclear at present, although removal of transepidermal material is thought to be the final pathway. One of the most accepted theories explains the phenomenon as resulting from diabetic microangiopathy that would prevent proper healing; however researchers have recognized that this theory cannot explain cases of APD in patients without DM [13, 14]. It is suggested that minimal trauma such as scratching triggers tissue necrosis and that the necrotic material is removed by transepidermal elimination [14, 19]. This theory is supported by

the fact that lesions exhibit the Koebner phenomenon several times. Saray et al. reported that among 11 patients with coexistent APD and DM, none developed lesions of APD until nephropathy occurred. Other authors propose that the underlying renal disease would be the cause of skin diseases; while other another described that the dermal material is a foreign body reaction to an unknown dermal substance [15].

Bullous Dermatoses

Porphyria Cutanea Tarda

From a pathophysiologic point of view, porphyria is caused by enzyme deficiency related to heme biosynthesis, resulting in blocking heme synthesis and the subsequent accumulation of toxic porphyrins. In PCT the deficient enzyme is uroporphyrinogen decarboxylase, which causes the accumulation of porphyrins, especially water-soluble uroporphyrin, in both liver plasma and skin. The skin porphyrin deposit causes oxygen free radicals when exposed to UV radiation, resulting in photosensitivity, blistering, and scarring. Iron plays an essential role in the development of symptoms of PCT because this metal encourages early enzymatic function for the synthesis of heme and inhibits the already poor decarboxylase uroporphyrinogen. Moreover, iron promotes the oxidation of the porphyrin precursors [14]. In PCT the standard HD cannot remove uroporphyrins [14, 19].

Alcohol, estrogens, HCV, hepatitis B virus (HBV), and HIV are thought to precipitate further uroporphyrinogen decarboxylase dysfunction, possibly through an iron-dependent mechanism [8, 9, 14, 19].

Pseudoporphyria

Pseudoporphyria can develop as a consequence of photosensitizing drugs (including naproxen, furosemide, nalidixic acid, bumetanide, tetracyclines, and amiodarone), excessive exposure to ultraviolet A (UVA) (in the case of tanning beds), or CRF without another precipitant factor. It is more likely to occur when other precipitants are present in a patient receiving HD, such as photosensitization [8, 13]. The mechanism of induction is unknown [14].

Proposed factors that may elicit pseudoporphyria in a patient with CRF and receiving HD include diuretics, aluminum hydroxide, polyvinyl chloride HD tubing, hemosiderosis, silicone particles, erythropoietin, and susceptibility to oxygen free radicals. Keczkes et al. (1976) described five patients with CRF who had bullous dermatoses, all of whom were taking furosemide. The causal role of erythropoietin is discussed because many cases of pseudoporphyria were reported before its use. In addition, through reducing iron stores, it can alleviate pseudoporphyria. Possible aggravating circumstances in some of the case reports of peritoneal dialysis-associated pseudoporphyria include probable HVC infection and the use of nifedipine, a known photosensitizer [34].

Disorders of Calcification

Benign Nodular Calcification

The factors that predispose to such calcification include an increase in calcium and phosphorus products in serum, the degree of secondary hyperparathyroidism, the level of magnesium in plasma, the degree of alkalosis, and the presence of local tissue injury [35].

Calciphylaxis

The pathophysiology of this entity is complex. It is believed that calciphylaxis is the result of an imbalance between inductors and inhibitors of calcification in the vascular wall [8]. The Braun model is practical and divides homeostasis of calcium and phosphorus metabolism into five systems: intestine, kidney, bone, intravascular compartment, and extraosseous calcifications. The only way of removing excess phosphorus in patients with CRF is bone deposition, osseous calcifications, or removal by dialysis. HD removal is insufficient to prevent phosphorus buildup, even with efficient treatment to reduce intestinal absorption. From the aforementioned, extraosseous calcification is a possible consequence [14].

There are increasing reports that support the relationship between bone and vascular calcification. Elevated levels of uremia and phosphatemia cause transdifferentiation of vascular muscle stem cells into osteoblast-like cells [9, 14].

It is concluded that calcium deposit in vascular walls is a dynamic process and not simply due to a passive mineral precipitation secondary to high levels of phosphorus/calcium. There are multiple case reports on patients with calciphylaxis who have normal levels of phosphorus/calcium and normal levels of parathyroid hormone [14, 25].

Calciphylaxis has been linked to acute coronary events. Although calcium deposits generate progressive narrowing of the lumen, the essential event is a thrombotic vascular occlusion [14].

Several risk factors have been linked to the development of calciphylaxis, such as renal failure, female gender, obesity, DM, liver disease, use of systemic corticosteroids, intake of coumarin anticoagulants, serum levels of aluminum higher than 25 ng/mL, hyperparathyroidism, vitamin D exposure, lymphomas, HIV, local trauma, use of calcitriol, salt intake, and production of calcium/phosphorus greater than 70 mg/dL^2 [7, 9, 13, 14, 19]. A series by Dauden Tello et al. (2002) based on 17 patients with cutaneous vascular calcification observed that a large number of patients had hypertension and/or DM and/or atheromatous disease [25].

Nephrogenic Systemic Fibrosis

It is considered that myofibroblasts are involved in this disease, suggesting that certain cytokines, such as TGF-β, could mediate fibroblast proliferation [9, 14, 27].

The etiology is not fully clarified, although exposure to gadolinium (contrast agent) is recognized as an inducing factor of NFS. The lesions appear after approximately 16 days from gadolinium injection [8, 9, 14]. The US Food and Drug Administration (FDA) has created a warning indicating that exposure to gadolinium in patients with renal GFR less than 30 ml/min/1.73 m^2 increases the risk of NSF [9, 14]. This also applies to patients with acute renal failure of any severity associated with hepatorenal syndrome or patients in the perioperative liver transplantation period [14].

Gadolinium is a metal that attracts magnetic forces, making it optimal as magnetic resonance imaging and angioresonance contrast [9, 14]. In its free form it is very toxic to tissues, and combines with chelating agents to create a relatively stable inert compound [14, 26]. After being formed this complex rapidly reaches equilibrium between interstitial and vascular spaces [14].

In patients with normal renal function, 95% of the gadolinium complex is excreted in the first 24 h post administration [9, 14]. In patients with impaired renal function, the removal declines. However, its small molecular weight allows it to be removed via HD up to 95% after three sessions of HD. Current theory suggests that the greater permanence of gadolinium in tissues of patients with CRF allows cytokine signals to activate fibrinogen [14]. The type of gadolinium also appears to be significant [14, 19].

Most cases were exposed to gadodiamide [14, 26]. The challenge is to understand why most patients exposed to gadolinium contrast agents are saved from this entity [14, 19].

Recent surgery, vascular procedures, hypercoagulable states, and thrombotic events have been cited as associated conditions in patients, suggesting that endothelial damage may be a cofactor. High doses of erythropoietin could be a cofactor but without consistent scientific basis [9, 14]. Kidney transplant failure and later onset of HD has also been described as a risk factor [9].

Lindsay Nails

The pathogenesis of this condition is attributed to an increased capillary density in the bed. On the other hand, Lindsay nails are thought to be due to a collapsed venous return in the nail bed [4, 8, 10, 19].

Uremic Frost

Uremic frost due to eccrine deposits of urea crystals on the skin surface in patients with severe

uremia [5, 13, 33]. Evaporation of sweat with high urea concentration causes urea to crystallize and deposit onto the skin [36].

Clinical Presentation

Nonspecific Cutaneous Entities with Higher Prevalence in Patients with Chronic Renal Failure

Xerosis

The term xerosis is often used to refer to the concept of dry skin [2]. It is a permanent symptom in CRF patients, with a clinical picture characterized by dry skin appearance, marked scaling and roughness, and poor skin smoothness (Fig. 44.1). Xerosis often affects the entire surface of the body, and may be more intense in some areas. Severe involvement of certain areas, such as the hands and feet, leads to possible functional impairment. As a consequence of an alteration in the cutaneous barrier function, the skin is more easily exposed to external attacks and aggression. As in some other severe xerotic conditions, a greater susceptibility to irritation caused by chemical factors (e.g., soaps and detergents) may be observed [37]. Severe xerosis can lead to fissured and cracked skin [1].

Pruritus

Itching can be localized or generalized, with the back being the most commonly affected site. The intensity and distribution of pruritus may vary significantly over time [16]. It can occur without skin lesions, being a subjective symptom of the patient (better known as pruritus sine materiae), or become clinically present with lesions such as excoriations, lichen simplex, nodular prurigo (see below), or keratotic papules, all resulting from scratching [21]. Variations are described in frequency and severity and often are associated with severe paroxysms that disrupt sleep and impair the quality of life and daily activity [9, 13, 19]. It also contributes to the occurrence of the Koebner phenomenon of APD [13, 19].

As previously stated, prurigo could be a clinical presentation of pruritus. Nodular prurigo is chronic relatively frequent dermatoses among CRF patients. Hyperkeratotic pruritic papular nodules often develop in a symmetric distribution over extensor surfaces of extremities, and may affect the trunk and buttocks. Lesions become hyperpigmented over time and are often excoriated by scratching. The face and palmoplantar region are usually spared [38, 39]. It is the most intense form of lichenification. Itching is the key symptom, being intense and intolerable with nighttime exacerbations. Evolution is chronic and with no tendency to heal [39] (Fig. 44.2).

Dyschromia

Diffuse Hyperpigmentation

Most cases of diffuse hyperpigmentation are reported in sun-exposed areas and in fewer

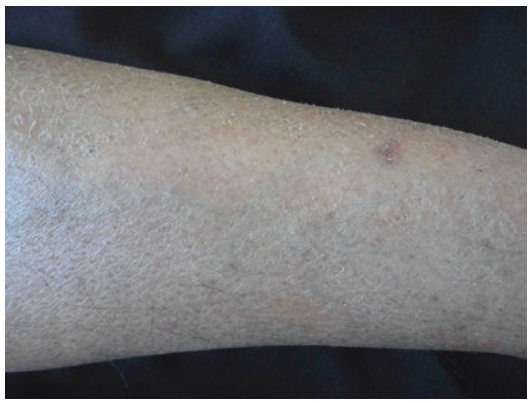

Fig. 44.1 Cracked skin and xerosis of the limb

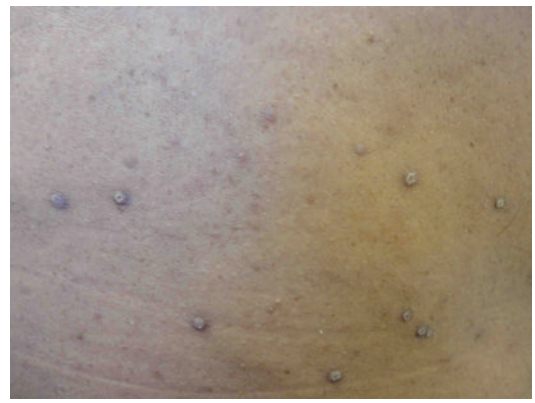

Fig. 44.2 Nodular prurigo

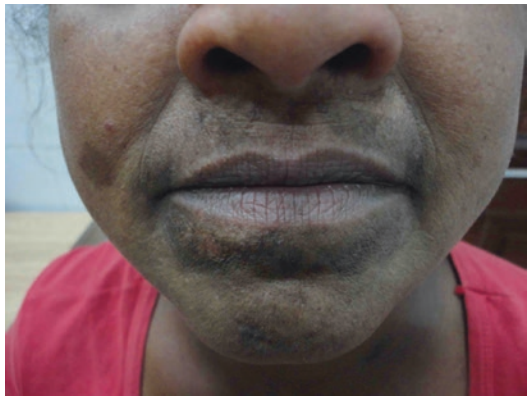

Fig. 44.3 Difuse hyperpigmentation in sun exposed areas

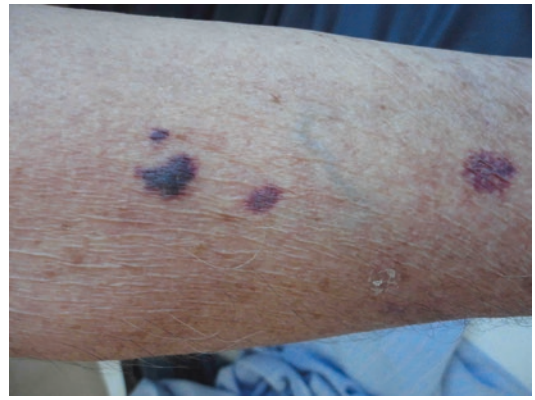

Fig. 44.4 Several ecchymosis of the arm

patients, with hyperpigmented macules on palms and soles [4, 5, 8, 10] (Fig. 44.3).

Sallow Skin

CRF patients may experience sallow complexion or citrine-colored skin, which may present an unhealthy and tired appearance. It occurs mainly as a result of urochrome accumulation in the skin because the impaired kidney cannot function well on its elimination [7, 19, 25].

Ecchymosis

Ecchymosis is characterized by a reddish or bluish macule. The onset of reddish or bluish discoloration of the skin is due to the escape of blood from ruptured blood vessels into the capillaries. It is a subcutaneous nonpalpable purpura. In CRF patients it appears more frequently in regions of trauma, such as arms or legs [13, 14]. It is easily recognized in puncture sites [14, 15] (Fig. 44.4).

Skin-Specific Entities Characteristic of Patients with Chronic Renal Failure

Acquired Perforating Dermatosis

APD is clinically characterized by conical papules with keratotic plugs; the presence of keratotic pits on palms and soles is also described [5, 9, 14]. It predominates in areas of high surface friction or trauma, such as extensor surfaces (most commonly in lower limbs), areas with high density of pilosebaceous follicles, and the trunk [5, 13, 14, 19] (Fig. 44.5a, b). Etiopathogenically, the constant skin trauma due to pruritus could be the promoting factor [5]. The Koebner phenomenon can be seen [14]. In Caucasians, these papules acquire a pink color while in high phototypes they are brown or hyperpigmented [13, 14]. The most common symptom is severe itching [14]. A minority of patients report pain [13, 14]. The natural evolution is spontaneous resolution of individual lesions with the continuous appearance of new lesions [13].

Porphyria Cutanea Tarda

The clinical presentation does not differ from the one seen in sporadic PCT and is characterized by the development of vesicles and blisters in photoexposed areas, with a higher prevalence in back of hands and forearms. The presence of scabs and the erosions resulting from trauma are frequently seen, while hyperpigmented scars and milia formation are characteristics in the evolution. It is also common to see subtle face hypertrichosis and hyperpigmentation in sun-exposed areas. Bright, depressed, and slightly infiltrated plaques, known as sclerodermiform plaques, can be observed [8, 9, 13, 14].

Pseudoporphyria

Clinical features are identical to those of PCT but without hypertrichosis, hyperpigmentation, or sclerodermiform plaques [8, 13, 14] (Fig. 44.6).

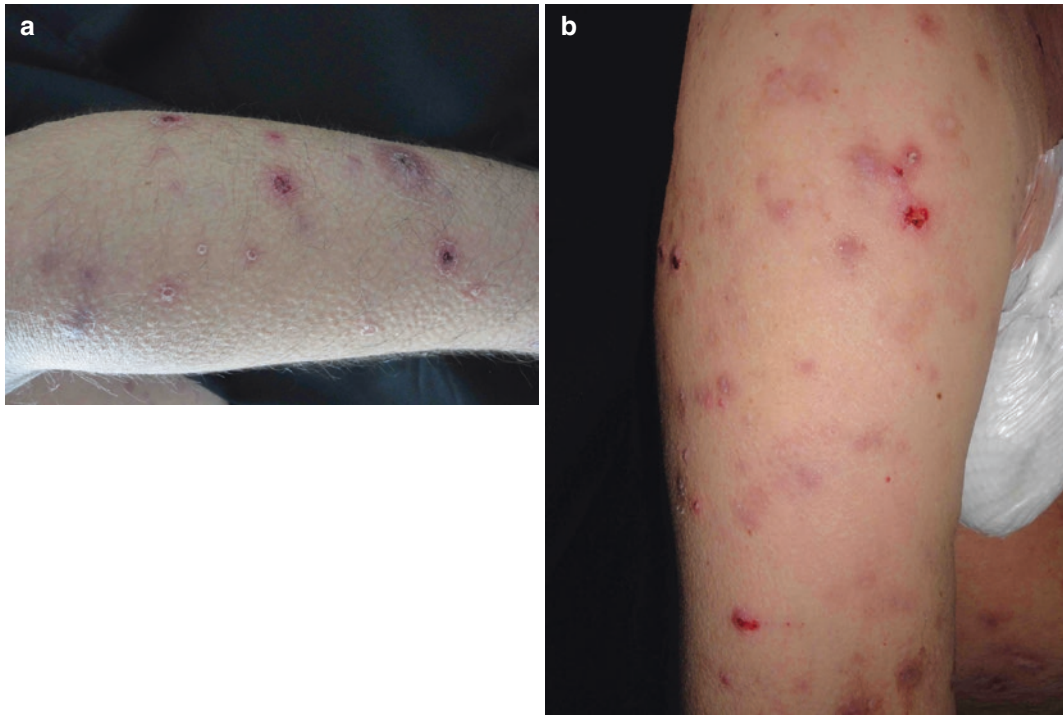

Fig. 44.5 (**a**, **b**) Acquired perforating dermatosis

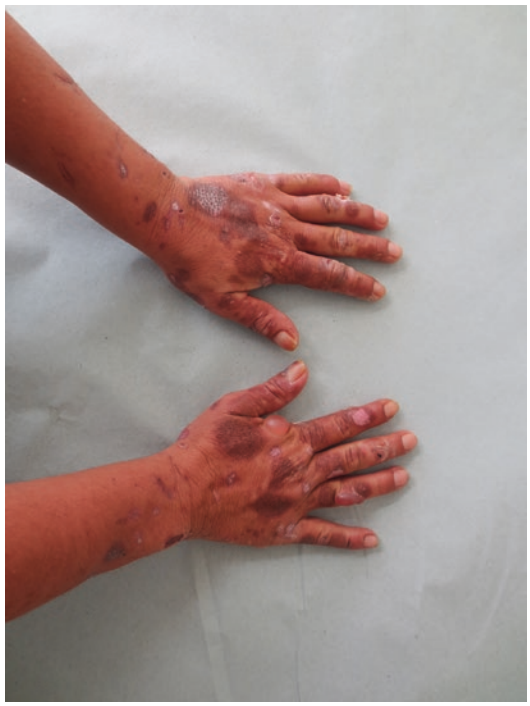

Fig. 44.6 Erosions due to blisters, pseudoporphyria

Benign Nodular Calcification

Also known as calcinosis cutis, this condition presents clinically as papules, plaques, or nodules near joints or fingertips firm to palpation. Most lesions are asymptomatic, although when located in the aforementioned topographies they can compromise joint function and be painful. In some lesions, the output of thick whitish substance can be seen through the skin [8, 14] (Fig. 44.7).

Calciphylaxis

Calciphylaxis is a life-threatening affection that presents acutely by invalidating and severe cutaneous pain. The skin initially shows a small area of erythema or livedo reticularis (retiform purple) that rapidly progresses to shallow or deep stellate ulcerations, with central necrosis or sloughing. In peri-ulcer areas, skin becomes purple with a livedoid pattern on which patients experience exquisite pain [7, 8, 14]. It presents distinctive distribution features that could predict prognosis. Distal acral involvement has a better prognosis than proximal involvement. Peripheral pulses are

preserved distal to necrotic areas. When also involved with myopathy, hypotension, fever, dementia, and injury to the central nervous or intestinal system, it is known as systemic calciphylaxis [7, 8, 13]. Ocular ischemic neuropathy commitment has been described [7].

Nephrogenic Systemic Fibrosis

The clinical presentation of NSF is progressive, symmetric, and characterized by skin hardening of extremities and trunk, commonly being described as orange peel or woody induration and reminiscent, in some aspects, of scleromyxedema [5, 8, 14, 19, 26].It firstly shows a clear erythematous papule that may associate with edema of the affected region and then coalesces into brownish indurated plaques at distal areas, generally in the lower limbs, progressing in a cephalic fashion [7, 14, 26]. Sclerosis can generate joint contractures accompanied by numbness, itching, or pain [9, 14, 19, 26]. It tends to spare the head and neck [14]. Latterly, patients develop epidermal atrophy and loss of hair with orange cobblestone peel and hyperkeratosis with pruritus [9, 26]. Some extracutaneous manifestations include yellowish plaques in the sclera, muscle weakness, and deep rib or hip pain [8, 14, 26]. Although progress is slow, a minority of patients may suffer an acute course with immobility lasting several weeks [14].

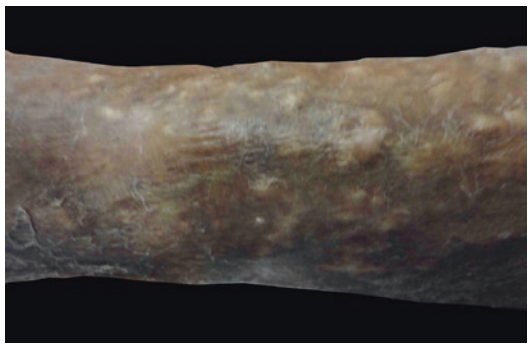

Fig. 44.7 Benign nodular calcification

Lindsay Nails

Lindsay nails are a change on the coloration of the nails characterized by red or chestnut coloration in its distal half (not disappearing with pressure) and white in its proximal half [5, 8, 15, 19]. Both fingernails and toenails are affected [19, 22] (Fig. 44.8a, b).

Uremic Frost

Uremic frost consists of a white-yellowish crystal-like cover, formed by urea in the beard area and other parts of the face, neck, and trunk. In 2 weeks peeling occurs and fissures appear [5].

Complementary Examinations

Most of the aforementioned dermatoses do not require complementary examinations to reach diagnosis. Dermatoses that do require complementary examinations are cited here.

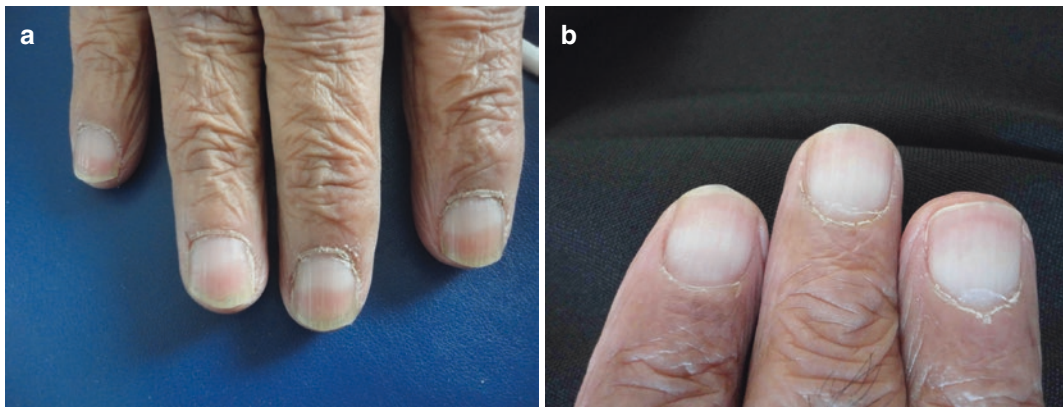

Fig. 44.8 (**a**, **b**) Lindsay nails

Acquired Perforating Dermatoses

Skin biopsy can help to diagnose this entity in most cases [14]. Differential clinical diagnoses include primary perforating disorders, nodular prurigo, eruptive keratoacanthomas, phrynoderma (vitamin A deficiency), hyperkeratotic lichen, and warts [8, 13, 14].

Histopathology is similar to that of other perforating dermatoses, and overlapping characteristics can be observed in the same skin biopsy sample [8, 13, 14]. An accumulation of keratin is typically observed to fill an epidermal invagination or a dilated hair follicle [8, 14, 19]. The adjacent dermis is characterized by altered and thickened collagen fibers and/or elastic fibers [9, 14]. In evolved lesions, giant foreign body cells due to degenerating inflammatory cells can be seen [8, 13].

Porphyria Cutanea Tarda

Patients with PCT have a large iron reservoir, so high levels of iron and ferritin support this diagnosis. The presence of high levels of urine uroporphyrin I and low urine levels of uroporphyrin III, 8-carboxyl uroporphyrin, and 7-carboxyl uroporphyrin are sufficient for diagnosis. In anuric patients, assessing the stool for high levels of isocoproporphyrin III and plasma for high levels of uroporphyrin may be used to reach diagnosis [14].

Skin biopsy for histopathology and direct immunofluorescence helps to distinguish PCT and pseudoporphyria from other subepidermal bullous dermatoses [14].

Histopathologic findings are subepidermal separation with minimal or no swelling. It is typical to find collections of intraepidermal eosinophilic collagen type IV, called caterpillar bodies, in the basement membrane. Direct immunofluorescence of perilesional skin reveals linear deposits of IgG, complement 3, and fibrinogen along the dermal–epidermal junction and around blood vessels [8, 13, 14].

Serology for HIV, HBV, and HCV should be considered, as well as genetic testing for hemochromatosis in all patients with PCT as they are frequent comorbidities and triggers of this disease [14].

Pseudoporphyria

As already described, porphyrin assays show normal plasma and fecal levels. Biopsy of affected skin reveals subepidermal blisters, lymphocytic perivascular infiltrate, and sclerosis of collagen. In other words, histopathologic features are similar to those of PCT although less thickening of the vessel wall is observed [8, 13, 24]. Direct immunofluorescence may be positive, showing linear IgG deposits in vessel walls and at the basement membrane zone. These results are consistent with a diagnosis of HD-associated pseudoporphyria [24].

Difficulty often arises in establishing a diagnosis of pseudoporphyria in patients undergoing HD because PCT concurrent with CRF may occur. Patients without symptoms undergoing long-term HD have been shown to exhibit higher plasma uroporphyrin levels than normal controls, further complicating the distinction between pseudoporphyria and true PCT. These levels have reached those measured in the plasma of patients with symptomatic PCT. Interestingly, uroporphyrin concentrations are significantly higher in patients undergoing HD in comparison with patients undergoing continuous ambulatory peritoneal dialysis, possibly because of better clearance of larger molecular weight "middle molecules" such as uroporphyrin by continuous ambulatory peritoneal dialysis [34].

Investigation of the dialysis patient poses practical diagnostic difficulties because urinary porphyrin profiles are not available. It is important to investigate anuric patients with fractionation of both fecal and plasma porphyrins [40].

Benign Nodular Calcification

A skin biopsy should be performed to confirm the diagnosis of BNC. Histopathologic calcium reservoir is shown in dermis and subcutaneous

tissue. Foreign body giant cells and inflammation can be seen around calcium deposits. Although calcium is clearly distinguishable with hematoxylin and eosin staining, Von Kossa staining (calcium stains black) can highlight deposits [8, 14].

The degree of severity is related to calcium and phosphorus levels in plasma. Normalization of the aforementioned minerals can lead to regression of lesions [8].

Calciphylaxis

Skin biopsy may confirm this entity, although histologic findings are not pathognomonic [8, 13, 14]. Diagnostic features are located in the deeper dermis and subcutaneous tissue, so biopsy should be deep. The distinctive features of intimal hyperplasia and medial calcification are located in dermal small arterioles or subcutaneous arteries and arterioles. Fibrin thrombi in the vascular lumen of dermis and subcutaneous tissue are frequently observed. Overlying dermis and epidermis are necrotic and ulcerated [8, 9, 13, 14]. A few calcium deposits around lipocytes or global calcification of subcutaneous tissue capillaries may be observed [13].

X-ray of the affected area shows the medial calcification as a double reticular fine line in the vessel topography. The commitment of small vessels is radiologically defined as involvement of smaller vessels than 0.5 mm in diameter and is probably the most specific radiologic finding of calciphylaxis. Mammography is more sensitive in many cases, though not routinely performed [13].

The differential diagnosis can be divided into processes of connective tissue such as vasculitides, hypercoagulable states (cryoglobulinemia), deep fungal infection and, on the other hand, embolic events [13, 14]. The crucial point in diagnosis is an adequate sample of tissue for biopsy [14].

Laboratory analysis includes renal function, phosphorus, calcium, parathyroid hormone levels, and urine sediment. Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody tests may also be necessary. Cryoglobulins and serology for hepatitis are usually requested [13, 14].

Nephrogenic Systemic Fibrosis

Differential diagnosis in these patients includes other fibrosing disorders such as scleromyxedema, sclerederma diabeticorum, and diffuse or limited cutaneous sclerosis [19, 26]. One of the features that differentiate these entities from NSF is the absence of facial involvement in the latter [9, 26]. The absence of Raynaud's phenomenon, periungual capillary dilation, and telangiectasia also excludes other sclerotic disorders [26].

Negativity of antibodies in plasma helps to rule out autoimmune sclerosis, and the absence of circulating paraprotein helps differentiate the NSF from scleromyxedema [26–28].

Gadolinium has been quantified in skin biopsies from patients with NSF. It has been described as 35–100 times higher bone deposits compared with healthy volunteers [14].

The histopathologic features mimic scleromyxedema and depend on the evolutionary stage of the lesion biopsied [5, 14]. The older lesions show CD34, procollagen 1, and CD45Ro in fusiform dermal cells with varied amount of mucin [7, 14]. The expression of CD34 and procollagen 1 suggest that the fusiform dermal cells are circulating fibrocyte infiltrates [14, 19]. The presence of dense fibrous bands that extend into the subcutaneous tissue is related to the clinical presentation of cutaneous induration [14]. Inflammation is absent [9, 14].

Therapeutic Approach

Some of the mentioned dermatoses tend to disappear when the patient is subjected to renal transplant, confirming the role of renal dysfunction in the onset and perpetuation of these disorders [2].

Xerosis

Dry skin affects patients' quality of life, especially when the hands are involved [2]. Treatment is based on skin hydration and treatment of pruritus, if present. Repetitive bathing must be avoided should be short, with warm water avoiding

friction with sponges [2, 21]. Once bathing is over, immediate application of emollients preventing transcutaneous water evaporation is mandatory. The application of creams, ointments, or scented lotions is not recommended (especially if they contain alcohol) [2].

The most widely used and effective humectant is glycerol, owing to its excellent hygroscopicity, lipid-modulating, and corneodesmolytic activity. Other humectants include urea and NMF (normal moisturizing factor) components, whereas other corneodesmolytic agents include the hydroxyacids. Topically applied ceramides and other bilayer-forming lipids are, therefore, an option. An equimolar mixture of the three dominant stratum corneum lipids (ceramide, cholesterol, and fatty acids) has been shown to allow normal rates of barrier recovery, whereas adjustment to a 3:1:1 molar ratio accelerates barrier recovery [41].

Pruritus

Despite the almost constant presence of xerosis, classic emollients and keratolytic and antihistamine therapies produce modest benefit in the treatment of pruritus [7, 13]. Antihistamines have limited benefit in uremic pruritus and relies on its side effect to induce drowsiness [9]. Renal transplantation is seen as curative treatment by some authors [13, 19].

In patients undergoing HD, the type of membrane used does not seem to influence the incidence of pruritus, although an uncontrolled study showed a significant reduction when HD was performed with high-flux membrane polymethylmethacrylate [9]. Some authors believe that general measures in the management of pruritus include optimizing the efficiency of HD using biocompatible membranes and improving the nutritional status of the patient [9, 11, 19].

Topical treatments, besides emollients, include capsaicin cream and tacrolimus. Capsaicin is a natural alkaloid found in the hot pepper plant. It acts by reducing levels of substance P in type C sensory cutaneous nerves. The studies carried out show that applications of 0.025% cream significantly relieves itching in HD patients, with no observed adverse effects. While this is a good choice in localized pruritus, it is impracticable in generalized pruritus [9, 42].

Topical tacrolimus is a calcineurin inhibitor that works by blocking the differentiation of Th1 cells, thereby inhibiting the production of IL-2. There is a single pilot study of 25 patients with uremic pruritus receiving tacrolimus ointment 0.03% for 3 weeks and 0.1% for the next 3 weeks, describing a significant reduction of pruritus without detection of serious toxicity [9]. Since 2006, the FDA has included a warning sign on tacrolimus boxes informing about the risk of cutaneous malignancy after using this agent for long periods. However, to date they have not observed an excessive amount of cutaneous malignancy in 9,800 patients with atopic dermatitis using tacrolimus 0.03% [19].

UVB (280–315 nm) radiation is the most effective treatment for uremic pruritus [8, 13, 19]. The mechanism of action is speculative and is thought to be due to a "photoinactivation" of pruritogenic substances and histamine-releasing factors. UVB also reduces vitamin A levels in the epidermis, which is suggested to contribute to pruritus [5, 13]. Three weekly sessions should be held for several months to obtain benefits. The potential carcinogenic effect of UV radiation requires serious consideration, particularly in patients with Fitzpatrick skin type II or I [9, 19]. Benefits of UVA phototherapy are controversial [7, 13, 19].

Other treatment options include oral cholestyramine, coal, and opioid agonists such as naltrexone or nalfurafine [5, 8]. The latter is successfully used in intractable pruritus in patients receiving HD, based on the hypothesis that endogenous opioids contribute to the development of pruritus. Among various trials the results are controversial [5, 9, 13]. Coal is widely used in England (where phototherapy is a less common treatment modality) as first-line treatment. Six grams daily of activated carbon is used orally and is believed to act by binding pruritogenous substances in the intestinal lumen with absorption preventing action [7, 13]. A limitation of coal is its low tolerance [7]. Cholestyramine, used in other pathologies with high effectiveness,

seems not to show similar efficacy in uremic pruritus. The administration of 5 g every 12 h orally is not well tolerated because of gastrointestinal side effects. The risk of acidosis should be considered [19].

Erythropoietin treatment relieves itching in some HD patients by reversibly decreasing plasma histamine levels, according to a small crossover placebo-controlled study that was carried out for 10 weeks in patients receiving HD [5, 9, 19]. Other drugs that have been tested in uremic pruritus are ondansetron orally (a serotonin antagonist receptor and a selective 5-HT_3 antagonist) and gabapentin orally, both with good results [5, 7, 19]. Gabapentin at a dose of 100–300 mg is administered after each HD, reducing significantly the severity of pruritus [9, 19]. Neurotoxic side effects such as dizziness, drowsiness, and coma should be considered. In a small uncontrolled study the efficacy of granisetron (another 5-HT_3 antagonist) was shown in uremic pruritus [9].

Thalidomide is a suitable drug for uremic pruritus. It is contraindicated in women of reproductive age because of its teratogenic effect, and must be borne in mind as a possible cause of severe polyneuropathy [7, 9].

A controlled double-blind placebo study showed that nitroglycerin, a dopamine receptor and partial α-adrenergic blocker, at doses of 30 mg per day orally plus 5 mg intravenously in HD relieved pruritus in most patients with an effect lasting 24–48 h [19].

Alternative medicine, principally acupuncture, was reported to be useful in several case reports [7].

Pruritus has a substantial effect on the quality of life of this population, causing discomfort, anxiety, depression, and sleep disorders. The latter is associated with chronic fatigue with impaired physical and mental capacity [9, 19].

Dyschromia

Diffuse Hyperpigmentation

Hyperpigmentation, which commonly affects dark-skinned individuals, is often challenging to treat. It has been demonstrated to have a negative impact on quality of life [43].

To date, specific studies on the treatment of diffuse hyperpigmentation in patients with CRF have been lacking. In any event it appears that treatments tend to be ineffective and disappointing. One possible option is tyrosine inhibitors such as hydroquinone, arbutin, aloesin, azelaic acid, kojic acid, licorice extract, proprietary oligopeptide products, phenylethyl resorcinol, mequinol, and free radical scavengers (α-lipoic acid and ascorbic acid) [43, 44].

Hydroquinone is available in strengths up to 4%, with higher concentrations available as a compounded product. Even with diligent application, hydroquinone takes 3 months or more to produce clinical results, and contact dermatitis is often reported. Combining hydroquinone with another product, such as glycolic acid, vitamin C, or vitamin E, may improve efficacy and shorten the time necessary to achieve visible results. A well-known formula is to compound it with a topical retinoid and corticosteroid. Arbutin is a naturally occurring derivative of hydroquinone that also exerts its antimelanogenic activity via tyrosinase inhibition [43].

On the other hand, melanosome transfer inhibitors such as soy-based products, niacinamide, glycolic acid, and cell-turnover inducers are described. The latter are retinoids, commonly used as monotherapy or in combination with other topical medications. Retinoids have a dual mechanism of action; apart from melanosome transfer they stimulate cell turnover, discarding melanized keratinocytes [43, 44].

Currently laser treatment is a reasonable option for the treatment of hyperpigmentation. Among these, good results are described with Q-switched alexandrite laser, Q-switched Nd:YAG 1064/532 nm, and Q-switched ruby laser [45, 46].

Medical makeup, transitory or definite, is an interesting option for the management of hyperpigmentation. Last but not least, external photoprotection is fundamental to the hope of improving hyperpigmentation, whatever its etiology. Sun exposure always plays an aggravating role, considerably reinforcing hyperpigmentation

already present and facilitating the appearance of new brown areas [47].

Sallow Skin

To the best of our knowledge there are no published reports to date of cosmetic treatments performed for this type of dyschromia.

Acquired Perforating Disorder

There have been no randomized controlled trials comparing different treatment modalities [13, 14]. There are reported cases of spontaneous resolution [19, 48]. High-potency topical corticosteroids under occlusion and intralesional corticosteroids could collaborate to reduce swelling and itching but do not prevent the appearance of new lesions [7, 8, 14]. Topical and oral retinoids, and oral vitamin A (100,000 U/day) have also been reported as having some therapeutic success, in addition to cryotherapy and topical keratolytic drugs [7, 8, 10, 13, 14, 49]. Kidney transplantation has shown benefits in some cases, although cases of APD after transplantation have been described [9, 14, 19]. A recent report has documented therapeutic success with five patients who were treated with narrowband UVB two or three times per week. Pruritus improved after three to five sessions and smaller lesions began to return after five to seven sessions. A maintenance dose of one or two times per week slowed the development of new lesions for at least 7 months in two of the five patients reported. There are isolated cases mentioning improvement with allopurinol (100 mg/day) and allopurinol combined with psoralen and UVA [3, 28, 48, 49].

Porphyria Cutanea Tarda

As mentioned earlier, standard HD does not remove porphyrins; however, high-flux membranes have led to their reduction, though generally not sufficient to generate clinical remission [8, 9, 13, 14].

Avoidance of sun exposure is a crucial factor in treatment [9]. The mainstay of treatment in patients with normal renal function is based on phlebotomy of 500 mL every 2 weeks, a procedure not feasible in patients with CRF [8, 13, 14]. Chronic kidney disease patients with iron overload and currently not requiring blood transfusion can be treated with small-volume phlebotomy (50–100 mL) once or twice a week. This regime has been reported to induce remission after 8 months of treatment. The normalization of iron and ferritin levels is the ultimate goal of treatment [14].

Chloroquine acts by binding to porphyrins, chelating them and facilitating their excretion. Attempts to remove this complex via HD have been unsatisfactory and may result in an exacerbation of the disease, and for this reason chloroquine is not fully recommended [14, 19].

Deferoxamine has been used as an iron and aluminum chelator in toxicity cases. Several researchers have used this drug in HD patients with PCT, obtaining discordant results depending on the administered dose [8, 14]. More recently another oral-administration iron chelator, deferasirox, is available, with no reported use in patients with PCT [14].

IFN-α treatment has shown to induce remission, suggesting that HCV could play a role in PCT [19].

Benefits of plasma exchange have also been shown, by removing 4 L of plasma twice and separated for 48 h, and reconstruction of erythrocytes with fresh frozen plasma [19].

Complete remission has been reported in patients after receiving a kidney transplant [14].

In every case the withdrawal of precipitating factors such as alcohol, exposure to sunlight, and estrogens is essential [13, 14]. Suspension of iron supplements and vitamin B is highly recommended [9].

Pseudoporphyria

The cornerstone of treatment is based on discontinuation of the suspected photosensitive drug and UVA strict protection [8, 14, 19]. There are increasing numbers of reported cases of pseudoporphyria associated with HD, with complete remission following

treatment with *N*-acetylcysteine. The dose ranges from 800 to 1,200 mg per day divided into two doses. It is believed that *N*-acetylcysteine increases production of glutathione, a powerful antioxidant. The improvement mechanism is not clear. However, double-blind controlled studies should be performed to confirm its effectiveness. Even with proper treatment, the symptoms take months to subside [14, 19].

Benign Nodular Calcification

The therapeutic goal is to normalize calcium/phosphorus levels, thereby achieving cure by spontaneous disappearance of lesions [14]. An antacid recently approved (sevelamer), an organic phosphate binder, is recommended as the one of choice [13]. In refractory cases surgery may be considered [13, 14].

Calciphylaxis

Treatment of patients with calciphylaxis is frustrating, with mortality rates of between 60% and 80%. Sepsis remains the leading cause of death [8, 13, 14].

Calciphylaxis prevention is achieved by minimizing risk factors such as obesity, local trauma, calcium/phosphorus intake control, avoidance of excessive vitamin D administration, and secondary hyperparathyroidism [13, 14, 19]. Relieving pain is essential in the therapeutic management of these patients [19]. Most current therapeutic options aim at calcium/phosphorus metabolism disturbances, a diet low in phosphorus (<43 mg/day) being a main therapeutic [7, 9, 13, 14]. Bisphosphonates such as sevelamer have been reported anecdotally as effective, but the overall prognosis is poor. Parathyroidectomy in patients presenting with hyperparathyroidism has shown controversial results, although it has shown some efficacy when autologous transplant of a portion of the parathyroid is made in the forearm [13, 14]. Although all treatments proposed can help in preventing progressive calcification, the ability to restore ischemic tissue perfusion is questionable, which would explain the low rates of treatment success [14].

Vitamin K is recommended when calciphylaxis is associated with the intake of coumarin [9].

Sodium thiosulfate is gaining support as the agent of choice for calciphylaxis treatment [14]. It likely acts as a chelator by dissolving calcium salts and to inducing an antioxidant effect and, eventually, synthesis of endothelial nitric oxide levels, which improves blood flow and tissue oxygenation [9, 14]. It is well tolerated and considered a safe drug. Adverse effects, especially acidosis and bone resorption by osteoclasts and the activation of intravascular volume overload, are expected [14]. The dose commonly used to treat calciphylaxis is 25 mg administered intravenously three times a week, which can be used for many months to maintain the initial positive response [9, 14]. The biggest limitation is its common side effect, nausea [9].

The use of corticosteroids is controversial, although there is a case report that encourages its use [13].

Meticulous management of ulcers, the generous use of antibiotics, and prevention by debridement are measures universally accepted to increase the survival of these patients. There are studies supporting debridement as part of the treatment and additional use of hydrocolloid patches to guide healing [7, 9, 13, 14, 19]. The hyperbaric chamber has been reported as effective in aggressive debridement of ulcers with consequent greater healing by raising the partial pressure of oxygen in the affected tissues, which improves angiogenesis and phagocytosis, inhibiting bacterial growth and decreasing local tissue edema [7, 13]. The long-term benefit of this therapeutic modality should be validated in larger studies [13, 19].

Sepsis is the leading cause of death [13].

Nephrogenic Systemic Fibrosis

No specific treatment for NSF has universal approval. It seems that the improvement in renal function may be the most beneficial treatment and that transplantation could be the solution, although it does not guarantee symptomatic relief

[5, 7, 9, 14]. There are anecdotal reports of successful trials with thalidomide, pentoxifylline, high doses of intravenous Ig, prednisone, UVA phototherapy, cyclophosphamide, extracorporeal photopheresis, plasmapheresis, sodium thiosulfate, and topical calcipotriol under occlusion [9, 14, 19, 26]. Imatinib mesylate was recently reported to effect a significant improvement in three patients [14, 26]. Enrolling patients into physical treatment sessions such as deep tissue massages seem to be beneficial and do not involve additional risk [7, 14]. There also have been reports of spontaneous remission [19].

While gadolinium plays a major role in the development of NSF, exposure to this agent in patients who present with CRF does not always lead to this condition; it would therefore seem to be a multifactorial process [14].

Glossary

Dyschromia Alteration of the color of the skin.
Gynecomastia Enlargement of the breast in the males, caused by an excess of estrogens.
Macroglossia Excessively large tongue.
Microangiopathy Pathologic processes of the microvessels.
Pruritogenic substances Substances capable of causing pruritus (itching).
Raynaud's phenomenon Abrupt onset of digital paleness followed by cyanosis and erythema in response to cold.
Teratogenic effect Capacity of some substances of generate physical defects in the developing embryo.
Uroporphyrins Porphyrins produced by oxidation of uroporphyrinogen, which can be excreted in excess in the urine in the context of porphyrias.
Xerostomia Decreased salivary flow (dry mouth).

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