Skin diseases in hemodialysis and kidney transplant patients

Alterações dermatológicas nos pacientes em hemodiálise e em transplantados

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Abstract

Recently, the world is facing an escalate in the incidence of chronic kidney disease (CKD). Databases containing information about patients in end stage renal disease (ESRD), especially in the United States, were the sources of initial information about it. Brazil has the third largest population on dialysis in the world, and there are about 680 dialysis centers, spread across all units of the federation in the present, providing treatment to an estimated population of almost 90,000 patients. Cutaneous involvement in the chronic renal failure is characterized by a number of manifestations, which may be related to three processes: the primary renal disease, the uremic state, or the therapeutic measures used in their handling. The skin changes in these two classes of patients, dialysis and transplant recipients, have been the subject of several studies. In recent years, however, great progress has been achieved in these two therapeutic modalities, which may have changed not only the type of the dermatologic disorders associated with these two conditions, but also their intensity or frequency. This article aims to yield an update as to the topic skin diseases in hemodialysis and kidney transplant patients.

Keywords: skin diseases, renal dialysis, kidney transplantation.

Resumo

Na atualidade, o mundo está enfrentando uma epidemia de doença renal crônica (DRC). Bases de dados contendo informações sobre os pacientes no estágio terminal da doença renal (DRCt), especialmente nos Estados Unidos, foram as fontes das primeiras informações a respeito deste assunto. O Brasil possui a terceira maior população em diálise no mundo, e atualmente existem cerca de 680 centros de diálise, distribuídos por todas as unidades da federação, atendendo uma população estimada em quase 90.000 pacientes. O envolvimento cutâneo na insuficiência renal crônica é caracterizado por uma diversidade de manifestações, as quais podem ser relacionadas a três processos: à doença renal primária; ao estado urêmico ou a medidas terapêuticas empregadas no seu manuseio. As alterações dermatológicas nessas duas classes de pacientes, dialisados e transplantados, já foram motivo de diversos estudos. Nos últimos anos, entretanto, grandes progressos foram alcançados nestas duas modalidades terapêuticas, os quais podem ter modificado tanto o tipo de alteração dermatológica associada a estas duas condições, quanto a sua intensidade ou frequência. Este artigo tem como objetivo oferecer uma atualização sobre o tema dermatoses em hemodialisados e transplantados.

Palavras-chave: dermatopatias, diálise renal, transplante de rim.

Introduction

Recently, the world has been facing an escalate in the incidence of chronic kidney disease (CKD). Databases containing information about end-stage renal disease (ESRD) patients, especially in the United States, were the sources of initial information about the subject.[1] Japan and Taiwan are the countries with the highest prevalence of ESRD. In 2003, there were approximately 1,800 and 1,600 patients per million citizens, respectively. Such prevalence is slightly lower in the United States and Spain, with numbers around

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1,500 and 1,000 ESRD patients per million people.[2] There is still no reliable information concerning this statistics in Brazil. However, the numbers in developing countries are lower than in developed countries, which might be the cause of the worst quality of public health systems. It is important to mention that the number of ESRD patients throughout the world is increasing, and the highest potential growth is in developing countries.[3] Diabetic nephropathy is the main cause of ESRD in developed countries, and it is close to the statistics about hypertension and chronic glomerulonephritis as the highest causes of ESRD in developing countries.[4]

In Brazil, which has the third largest population on dialysis in the world, there are currently nearly 680 dialysis centers. They are spread across the country, providing treatment to an estimated population of almost 90,000 patients.[5] When the prevalence is determined as to the population, the result is 390 patients on dialysis per million of population (pmp). It is noteworthy that Brazil is a heterogeneous country and that its prevalence rate is higher in the most developed areas, ranging from 159 to 493 pmp. If the number of kidney transplant patients with functioning graft is added, which is extra officially estimated by the Brazilian Association of Organ Transplantation (ABTO) in 27,500 (~150 pmp), the total adjusted prevalence of ESRD patients in Brazil in January 2007 is of about 540 pmp. This number still indicates the insufficient access to treatment by a portion of the population.

Statistics regarding the types of dialysis show that 91% of the patients are treated by hemodialysis, and 9% with peritoneal dialysis. Out of the patients on dialysis, 26% were diabetic. Those at advanced ages (≥ 65 years) are more representative among dialysis patients (26%) in comparison to the Brazilian population above the age of 60 (10%),[6] which strengthens the idea that advanced age is a risk factor for CKD.

Both types of renal replacement therapy – dialysis and transplant – present some restrictions. For example, in regular dialysis, even patients considered to be well dialyzed are maintained with much higher serum urea and creatinine values than those found in people who do not have the condition. Therefore, this is a special population prone to develop dysfunctions in several organs and systems due to the state of incomplete correction of their biochemical and metabolic disorders. On the other hand, the kidney transplant patient also represents a special class. Firstly, because of the chronic use of immunosuppressant drugs that may cause specific diseases. Besides, the glomerular filtration rate after surgery is usually reduced. Therefore, according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, the patient who has undergone successful kidney transplant usually has CKD stage 2 or 3.

The skin changes in both dialysis and transplant patients have already been a topic of discussion in several studies.[7-10] However, in the past few years there has been some progress regarding both therapies, which might have changed the type of skin change associated with these two conditions and its intensity or frequency. Literature findings about dermatoses in hemodialysis and kidney transplant patients will be reviewed in this article.

Skin manifestations in hemodialysis and renal transplant patients

The skin involvement in kidney failure is defined by several manifestations, which can be related to the process that causes renal failure due to the uremic state or the therapeutic measures performed. A varied and complex multisystemic involvement frequently occurs, and the skin, mucosae, and phaneros can present important findings already at the first medical examination.

With the renal replacement therapy (dialysis and transplant), there were great advances in nephrology, as well as an increase in the survival rates of patients with ESRD and the change in the profile of skin manifestations of patients who underwent such treatments. Hence, some of the skin manifestations of patients on renal replacement therapy may also be a result of dialysis or post-transplant immunosuppressant treatment. In this study, only patients on hemodialysis or those who have had a kidney transplant will be analyzed.

Skin manifestations in hemodialysis patients

Pruritus is frequently described in patients with ESRD. Historically, the incidence of renal pruritus varies between 50 and 90% in patients on hemodialysis, which is the most important clinical symptom.[11,12] Some patients feel the relief of pruritus only during or right after hemodialysis, while others report symptomatic exacerbation during this period.[13]

In a study conducted with patients with pruritus that underwent hemodialysis, severe pruritus was found in 8% of the cases; moderate, in 24%; and mild, in 66%.[14] However, in this study conducted with 29 patients, the effects of the duration of hemodialysis on the severity of pruritus were not considered.

Another report showed significant improvement of the symptoms in patients who underwent dialysis for a longer period of time: out of 23 short-term dialysis patients (from two to three years), 78% complained of pruritus; whereas out of 28 long-term dialysis patients (more than eight years), only 43% carried on with the complaint.[7] On the other hand, in another report it was not possible to confirm the decrease of pruritus as the dialysis progressed.[15] Despite the little knowledge of their etiology, localized and generalized forms of uremic pruritus are mainly caused by the combination of several mechanisms: increased histamine, vitamin A and parathormone levels; mast cell hyperplasia; peripheral polyneuropathy, and xerosis.[11,16,17] Recent studies have shown that uremic pruritus may be a consequence of the inflammatory state associated with kidney failure, in which the increase of inflammatory cytokines, the low levels of serum albumin and the high ferritin levels in the plasma are seen.[18-20]

Clinically, in patients with pruritus, the skin may seem normal or demonstrate standards that differ as to lichenification or hyperkeratotic lesions.

The treatment for renal pruritus is usually empirical. Topical moisturizers relief the pruritus associated with xerosis. Topical corticoids and ultraviolet phototherapy are frequently used to suppress inflammation on the treated areas. Topical capsaicin depletes the substance P from nerve endings, suppressing the itching sensation.[21] Improving the efficacy of the dialysis and/or changing the calcium concentration in the dialysate might help relieve the pruritus.[22,16] Some patients were responsive to the treatment with intravenous lidocaine, heparin, and cholestyramine.[16] Surgical options include subtotal parathyroidectomy, electrical stimulation with needles, and kidney transplant.[16,17,12] Erythropoietin can be effective to reduce the plasmatic histamine concentration with further improvement of pruritus, according to a report.[23] Preliminary studies indicate that the use of primrose oil and tacrolimus ointment may have a therapeutic effect. [24,25] Another option is thalidomide, which caused relief or disappearance of the symptom in about 70% of patients, in a study conducted with 14 patients with uremic pruritus.[26]

The skin of the ESRD patient is usually dry and has a desquamation with ichthyosiform aspect. Out of the patients on dialysis, 96% present xeroderma with decrease of sebaceous and sweat glands. This condition might partly result from the metabolic alteration of the vitamin A in ESRD, together with changes of the hydration state due to hemodialysis.[27]

The skin color also changes in ESRD. Generally, there is paleness due to chronic anemia and the skin has a yellow-gray tone, probably due to the accumulation of carotenoids and nitrogenous pigments (urochromes) in the dermis.[27] The skin aging becomes aggravated.

In patients on long-term hemodialysis, peculiar forms of hyperpigmentation appear in more than 50% of the cases.[23] Hyperpigmentation in photoexposed areas has been described in many patients. In a prevalence study conducted with 102 patients undergoing dialysis, the most frequent finding was the alteration in the skin pigmentation, noticed in 70% of the cases. The diffuse hyperpigmentation was present in 22% of the patients.[28,10]

Hyperpigmentation could be a result of the increased melanin concentration on the basal and superficial layers of the dermis. Such phenomenon would occur due to the accumulation of beta-melanocyte-stimulating hormone (B-MSH) secondary to reduction of renal function.[29]

Infection by hepatitis C virus (HCV) may also be related to the hyperpigmentation in patients undergoing hemodialysis. The virus triggers a disorder of the porphyrin metabolism, which can be clinically expressed by this symptom.[30]

Actinic elastosis is frequently observed, as well as lentigo and purpura senilis. The early occurrence of actinic elastosis leads to facial wrinkling and formation of comedones, bringing Favre-Racouchot[31] to mind. It also leads to the formation of extended nape wrinkles (*cutis rhomboidalis nuchae*) and vascular dilatations (telangiectasias). Based on multiple analyses, a study concluded that the acceleration of skin aging occurs due to dialysis time.[32]

The nails also present a change in color. Lindsay's nails, or half and half nails, have a usual tone in their distal half, but the proximal half is white. The term 'Terry's nails' has been used for nails in which only 20% distal have the usual color. These alterations are strongly associated with ESRD, but they can also be found in patients with chronic liver disease and in healthy subjects.[27] In a study conducted with 182 patients that had been on hemodialysis, 127 (69.8%) presented at least one type of ungueal alteration. Absence of lunula, subungueal hemorrhage, and half and half nail were the predominant changes in comparison with 143 healthy subjects.[21]

The frequency of malignant skin tumors also is higher in the patients on hemodialysis. A report described carcinomatosis skin lesions in 2.6% out of the 114 examined patients on hemodialysis.[32]

Due to abnormal coagulation and platelets, skin bruises are common. The skin blood flow is significantly reduced in hemodialysis patients when compared to healthy control subjects. A correlation between the levels of vascular change and the dialysis time was described in a study on dermal angiopathy in patients on hemodialysis.[33] Reduced blood flow explains not only the increase in vulnerability, but also the difficulty in wound healing in dialysis patients.[33,34] A study compared patients with ESRD not on dialysis and the ones on dialysis, and there were no differences between both groups concerning the dermal microangiography changes.[35]

The porphyria cutaneous tarda (PCT) has been described in patients with ESRD on hemodialysis, with the development of blisters in photoexposed areas, especially hands and face.[36,37] These blisters vary in size, and they appear even after a minimum exposure to the sun, mainly on the back of hands and fingers.[38] Subsequently, there are erosions with hemorrhagic crusts and atrophic scars. Porphyria can also lead to hyper or hypopigmentations. After the wound healing, milium formation is not uncommon. Although the etiology of this phenomenon is not clear, the improper clearance of porphyrin precursors, bound to plasma by urinary excretion or hemodialysis, can lead to porphyrin deposit on the skin, which is clinically manifested as photosensibility and subepidermal bullous disease.[39-41]

Bullous dermatoses of dialysis or pseudoporphyria may affect 8 to 18% of the patients on hemodialysis.[30,39-41] Usually, this condition is equivalent to PCT, showing the skin fragility and the formation of blisters in the photoexposed areas. Therefore, hypertrichosis is less common and plasma porphyrin levels are usually normal.[39,30]

The treatment of PCT or pseudoporphyria is difficult in most patients with ESRD. Phlebotomy may reduce the liver iron content so that a new hepatic uroporphyrinogen decarboxylase can be formed.[42] However, patients with ESRD may frequently have anemia and have a low tolerance of phlebotomy. While the intravenous erythropoietin incites erythropoiesis, it can also reduce the body's total iron stores and improve the tolerance of phlebotomy.[42,43] Deferoxamine may also decrease serum porphyrin levels.[43] Some patients may need a kidney transplant in order to completely resolve the symptoms.

Patients who depend on dialysis have intolerance of low temperatures and of Raynaud's phenomenon.[9,42] The less frequent diseases are: Dupuytren's contracture[7,38,44] and prurigo nodularis.[9,14] Hair changes are also less often described, and are usually related to non-cicatricial diffuse alopecia. The likely causes are the use of heparin, endocrine changes associated with oligo or amenorrhea, or the increase in vitamin A in uremic patients.[9,45]

The metastatic calcification of the skin in ESRD results from the secondary or tertiary hyperparathyroidism, or may be associated with adynamic bone disease. Abnormally high levels of parathormone (PTH) may provoke the calcium pyrophosphate crystal deposition on the dermis, subcutaneous tissue, and arterial walls.[46] Vascular calcification is actually very common in patients with ESRD; however, it is rarely symptomatic. However, the calcified vessels may have an acute thrombosis with the appearance of livedo reticularis, which is known as calciphylaxis. The livedoid areas are extremely painful due to ischemia, and they quickly become hemorrhagic and ulcerated. Calciphylaxis is associated with a high mortality rate, especially when the trunk is involved, as opposed to the expectation of a better prognosis when the involvement is limited to the extremities.[46] The mechanisms potentially involved are many,[47] and the risk factors already described are: female gender, deficit of antithrombin III and/or protein C or S,[48] use of corticosteroids,[49] immunosuppressors,[50] oral anticoagulant,[51] estrogens,[52] intravenous iron overload,[53] smoking, diabetes mellitus, heart failure, morbid obesity, malnutrition,[54] dyslipidemia, losing weight, local traumas, and severe clinical settings such as sepsis, endocarditis, hepatic cirrhosis, and processes with a subjacent immunologic basis.[55]

The laboratory evaluation generally demonstrates an increase in PTH. Calcium and phosphorus serum levels and the calcium-phosphorus product are usually just a bit increased, or they may be normal.

Besides, the vascular calcification and the calciphylaxis, calcified nodules, may occur on the dermis or in the fat tissue of patients with ESRD. Calcium deposits are identical to those found in calcinosis cutis due to other causes. The tissue involved may suffer ulceration, but of subacute evolution, without livedo or ischemic pain. Prognosis of patients with this non-vascular calcification is excellent.

The treatment for calciphylaxis is extremely difficult. Pain management, debridement of gangrenous tissue, and mainly parathyroidectomy, have had some success;[56,46] however, convincing evidence of prognostic improvement is still fragile. Studies to assess the role of antiplatelets and thrombolytics still need to be conducted. The nonvascular calcinosis associated with ESRD may be managed by surgical excision of calcified nodules.

Acquired perforating dermatoses, such as perforating folliculitis or other perforating dermatoses, like reactive perforating collagenosis[57], may be associated with ESRD.[40,58] This condition affects more than 10% of the patients on hemodialysis, and it seems to be more common in black people.[59,57,40]

Clinically, patients present hyperkeratotic papules with a certain central crater filled with crust, in the trunk and extensor surfaces, usually with linear distribution.[59] The simultaneous transepidermal elimination of collagen and elastin has been detected.[57] The etiology of this process is not clear. However, the proposed mechanisms include: diabetic microangiopathy, microtrauma caused by chronic pruritus, deregulation of vitamins A and D, abnormality of collagen fibers and/or elastin or local inflammation and conjunctive tissue degradation, caused by dermal microdeposit of substances, such as uric acid and calcium pyrophosphate.[56,57] Topical and intralesional steroids, topical and systemic retinoids, cryotherapy and ultraviolet radiation have been some of the described treatments.[59,57]

The nephrogenic systemic fibrosis (NSF) affects mainly the subjects on hemodialysis and most of those who returned to hemodialysis after kidney transplant failure. It has also been described in some patients with acute renal failure.[60,61] In the first half of 2006, the initial evidence of a relationship between gadolinium-based contrast agents, especially gadodiamide, and NSF development, increased.[62,63] Clinically, patients develop sclerotic and erythematosus dermal plates on legs and arms in a progressive manner, sparing head and neck.[60,61] Pruritus is a common feature and all described patients have a persistent disease, and even if renal function could recover in some cases, there is no effective treatment.[60,61] North-American and European guidelines agree that patients with severely reduced renal function have a higher risk of developing NSF, and the use of gadolinium-based contrast agents should be avoided.[64]

Skin infections happen more frequently in hemodialysis patients than in healthy controls. Infections by less common agents, like pseudomonas or even mycobacteria (tuberculosis), may occur.[65,66] These infections may be the result of compromised immunity, which can be observed even before the hemodialysis starts. The nature of the immunity deficiency is unknown, but lymphopenia and the decrease in activity of B and T cells may be present.[59,66]

An article has reviewed the mechanisms of development and possible causes for the immune dysfunction in patients with ESRD, mainly those related to the mononuclear phagocyte system, which has an important role against bacterial infections. These findings were related to changes in the receptors expression. However, evidence points to metabolic functional disorders, especially in the production of NADPH-oxidase-derived free radicals. The most important causal factors are: uremic toxicity, iron overload, anemia, bio-incompatibility of the patient on dialysis, and the type of renal replacement therapy. The conclusion was that the phagocyte defect is multifactorial and each factor should have its own therapeutic measures.[67]

Skin manifestations in kidney transplant patients

Kidney transplant is certainly a treatment modality that is capable of assuring the homeostatic balance of the ESRD patient, improving uremic state. On the other hand, ensuring longer recipient and graft survivals at the cost of chronic immunosuppression makes the body prone to a chronically altered immune response and to adverse effects of the immunosuppressant drugs. The skin becomes a mirror for the multi-systemic changes, as it reflects the improvement of the uremic state and the arise of changes due to the immunosuppressants.

Nowadays, an immunosuppressor that is capable of providing good graft outcome with minimum side effects is being searched. Steroids, anti-proliferative agents, calcineurin inhibitors, monoclonal antibodies and mammalian target of rapamycin (mTOR) inhibitors are some of the immunosuppressant drugs.

Several skin changes have been described in kidney transplant patients, mostly the ones related to direct immunosuppressive effects or to the side effects of drugs. They can be categorized as viral, bacterial and fungal infections, preneoplastic and neoplastic, iatrogenic and miscellaneous lesions.

Iatrogenic injuries, which are a result of corticotherapy, are described in most studies. Generally, they are more evident in the first year of treatment, and show a progressive improvement as the dose decreases. [31]

A study with 14 kidney transplant patients on immunossupressants revealed the presence of fungal infections in 87.7% of the patients; viral infections in 28.6%; and bacterial infections in 21.4%. Allergic manifestations had a prevalence of 7.1%; pre-tumor, of 7.1%; vascular, of 14.3%; and tumor, of 14.3%. Iatrogenic injuries did not differ from those described in literature, and they are mainly related to steroids. Skin lesions tended to be more atypical and unresponsive to therapy when patients presented

renal functional deficit, regardless of the dosage of immunodepressants.[68]

Another study conducted with 120 patients had 100% cases of renal post-transplant dermatologic manifestations. The most frequent viral dermatosis was the common wart, and the most frequent fungal dermatosis was pityriasis versicolor. There was not prevalent bacterial infection. Actinic keratosis is distinguished among pre-neoplastic lesions. As to the neoplastic lesions, basal cell carcinoma, spinocellular carcinoma, Bowen's disease, bowen-like malignant seborrheic keratosis, and Kaposi's sarcoma were found. Out of the iatrogenic injuries, the main manifestations were: hypertrichosis, Cushing, and acne.[52] In miscellaneous lesions, seborrhoeic dermatitis can be pointed out. The post-transplant time significantly interfered in the development of pre-neoplastic and neoplastic lesions, but not in other dermatoses. The variables 'type of donor', 'type of dialysis' and 'time of dialysis', 'number of transfusions' and 'type of immunosuppressant' did not significantly interfere in the arising of dermatologic lesions.[52]

Regarding ungual changes, kidney transplant has proved to be capable of reducing the frequency of subungual hemorrhage and half and half nails. However, in a study conducted with 116 patients, leukonychia was more frequent in kidney transplant patients.[21]

A few studies in literature simultaneously compare the dermatologic manifestations of hemodialysis patients and kidney transplant patients. A Master's degree thesis concluded in 1995 compared both populations in a sample from the cities of Niterói and Rio de Janeiro, Brazil.[22] One hundred and forty-one patients in a regular program of hemodialysis and 60 kidney transplant patients were examined. Xerosis was observed in 90.1% of the hemodialys patients, which was the most common characteristic of this group. Affected patients had been on hemodialysis for longer. Pruritus was seen in 58.2% of the hemodialysis patients, and this was the most frequent symptom of this group. Affected patients were older. Diffuse hyperpigmentation and half and half nails have also been frequent in patients on hemodialysis. Regarding hair changes, the most common ones were alopecia in the hemodialysis group and hypertrichosis in the transplanted one. Purpuric lesions were similarly prevalent in both groups, despite having different etiologies. Infectious dermatoses were the most common in transplant recipients. However, in both groups, fungal etiology was the most prevalent. Time of transplant was longer in patients with viral dermatoses, which confirms the idea that the immunosuppressant period determines such infections. Malignant and pre-malignant lesions had a relatively low and similar frequency in both groups.[22] The study has confirmed many reports that showed the high incidence of skin manifestations in CKD patients, as well as a series of unusual findings associated with the type of treatment for each population.

Conclusion

The literature review shows that skin alterations are frequent, which causes many dysfunctions and a decrease of quality of life in hemodialysis and transplant patients.

As to the hemodialysis patient, xerosis is the most common sign, while pruritus is the most frequent symptom; time and length of treatment directly influence dermatologic findings. Regarding transplant patients, time of transplant may also have a negative influence on the skin lesions, especially the infectious, neoplastic and pre-neoplastic ones, since the cumulative immunosuppressive load is much higher for those patients. Periodic dermatologic evaluations enable the reduction of exposure to risk factors and are essential for prevention, diagnosis and treatment of those affections.

It is noteworthy that the techniques of renal replacement therapy have significantly progressed in the past decades. It would be interesting to analyze if such innovations could be transformed into the reduction of frequency and severity of dermatoses in that population.

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