

Review

Skin Changes of Patients on Dialysis Treatment

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Abstract

Background: Renal transplantation and dialysis (haemo or peritoneal dialysis) are the only therapeutic options of patients suffering from the end stage renal disease (ESRD). Unfortunately these treatment modalities are accompanied by considerable number of side effects some of which can affect the skin. Part of these unwanted reactions is due to immunosuppressive therapy administered by patients with renal transplantation. The main goal of this review is to describe the most common skin changes observed in people with ESRD, the evolution of these changes in the course of dialysis treatment and even appearance of new lesions in the period after the renal transplantation.

Introduction

According to World Health Organization (WHO) approximately 1,5 million people worldwide are suffering of ESRD and the number will double in the next ten years. The incidence of ESRD in the countries from Central and Eastern Europe is 130 – 180 / 1 mln population/yearly. In Bulgaria the incidence is 77 / 1 mln population / yearly. During the period 2001 – 2005 in Bulgaria are performed only 132 renal transplantations which are very insufficient. Approximately 500 people are enlisted in the waiting list for renal transplantation. The majority of Bulgarians with renal transplants are operated abroad [1]. Patients on dialysis in Bulgaria are approximately 2800 and another 450 receive immunosuppressive therapy after renal transplantation.

Deterioration of kidney function in majority of patients is slow and continuous process. Decreased clearance of metabolites such as urea, creatinine and uric acid can affect the

skin. Patients with chronic renal disease and ESRD are complaining of change in skin colour, dryness (xerosis), atrophy of skin appendages, subcutaneous haemorrhages (suffusions) etc [2]. Because of the suppressed immunity many of the patients with transplanted kidney are suffering from cutaneous malignancies [3].

Nanley et al. [4] stated that from 50% to 98% of patients on dialysis at least once have had dermatological complaints. Pico et al. [5] pointed out that the most common cutaneous change in patients on dialysis is alteration in skin colour. Other frequently observed changes are pruritus, xerosis, ichthyosiform lesion etc. [6] Abdelbaqi-Salhab et al. [7] classify the skin changes in dialysis patients as specific and non-specific (Table 1). Non-specific are itch, xerosis, colour alterations, acquired ichthyosis, half-and-half nails etc. As specific changes are described perforating dermatoses (morbus Kyrle), calciphylaxis, bullous dermatoses, nephrogenic fibrosing dermopathy (NFD) etc.

Table 1. Skin Changes in Patients on Dialysis

Specific	Non Specific
Perforating dermatoses Calciophylaxis Bullous Dermatoses Nephrogenic Fibrosing Dermopathy (NFD)	Pruritus (Itch) Xerosis Colour changes Acquired Ichthyosis Half-and-half nails

Uremic Itch (pruritus)

The incidence of uremic pruritus varies considerably from 22 to 90% [8]. The cause of uremic itch is not well known. There is a hypothesis saying that not well filtrated products of metabolism are responsible for the itch [9]. Other authors do not find correlation between duration and quality of dialysis procedures and pruritic complaints [10]. Thirty to forty percent of the patients confirm that they have had itch even before the beginning of dialysis. The condition is more severe in patients on peritoneal dialysis. An interesting fact is that in majority of cases pruritic complaints decrease rapidly after successful kidney transplantation. Some authors find correlation between the severity of itch and urea plasma levels [11]. Nowadays the two most plausible theories explaining uremic itch in dialysis patients are immunologic and opioid hypotheses [12,13]. According to the immunologic hypothesis in patients on haemodialysis there is constant stimulation of immune system. Key role in the pathogenesis of pruritus in those patients plays increased secretion of pro-inflammatory cytokine interleukin 2 (IL2) and activation of Th1 [14]. The opioid hypothesis points out that the cause for uremic pruritus is altered secretion of endogen opioids. There is decreased number of μ -opioid receptors and increased number of κ -opioid receptors in central nervous system (CNS) of patients on dialysis. Probably this imbalance of opioid receptors is the main cause for uremic pruritus in dialysis patients [15]. Treatment of uremic itch is considerable challenge. There is no single effective method of treatment. New promising options are topical immune modulators [16] or anticonvulsants such as gabapentine [17].

Skin Colour Changes

One of the reasons for changes in skin colour is accumulation of natural pigments in the

lower dermis and stimulation of melanin synthesis by substances like melanocyte stimulating hormone beta (Figure 1; Figure 2) [18]. There are rare cases of sudden skin darkening due to massive hemolysis at the start of dialysis (Figure 3) [19].

Xerosis

Skin dryness varies considerably in patients on dialysis [20]. There are evidences showing that the skin xerosis is connected with the disturbance in vitamin A metabolism. The dryness is generalized and there is no tendency for improvement with time. The atrophy of skin appendages is considerable. *Urbonas et al.* [21] found out correlation between the xerosis and the pH of epidermal stratum corneum. The increased pH stimulates some protease enzymes playing role in



Figure 1. 74-year old patient with diffuse skin darkening after 9 years on haemodialysis



Figure 2. Skin colour changes of 69-year old male patient after 7 years on haemodialysis

desquamation insensibilis. Decreased desquamation of corneocytes aggravates skin xerosis in patients on dialysis.

Nail Changes

Nail changes affect more than 70% of people on dialysis [22]. The clinical picture is very diverse – half-and-half nails (*Lindsay* nails), lack of lunula, subungual haemorrhages. There is a statistical correlation between the incidence of nail changes and the period on which the patients are on dialysis. Some scientists say that the severity of nail changes correlate with the effectiveness of dialysis [23]. In half-and-half nails there is a transversal separation of nail plate as the distal part is darker in colour. Lack of lunula is connected with the haemoglobine variations in dialyzed patients.

Perforating Dermatoses

Clinically there are firm, hyperkeratotic, umbilicated papules mainly on extremities. Koebner phenomenon is frequently observed. In the majority of cases the patients suffering from diabetic nephropathy develop perforating dermatoses after beginning of dialysis treatment [24]. In majority of ob-



Figure 3. Sudden skin darkening as a result of massive haemolysis at the start of dialysis of 64-year old male patient

served case there is a transepidermal elimination of keratin material with or without collagen and elastin fibres [25]. Based on histology the perforating dermatoses in dialysis patients are classified as 1) elastosis perforans serpiginosa (EPS); 2) reactive perforating collagenosis; 3) perforating folliculitis; 4) *Kyrle* disease [24].

Bullous Lesions

There is significant similarity between the bullous skin changes and lesions observed in porphyria cutanea tarda. Sun exposed areas are always affected. In all patients on dialysis with bullous lesions there is a complete failure of renal function [26]. Some authors suggest the term “pseudoporphyria” in such patients. As of today there is no porphyrine metabolite found in dialyzed patients with bullous lesions [27].

Calciphylaxis

The condition is characterized by accumulation of calcium deposits in tunica media of the wall of small arterial vessels [28]. Calcium deposits stimulate intima proliferation, thrombosis followed by skin necrosis and secondary infection. At the beginning skin changes resemble livedo reticularis but quickly superficial violet nodules are formed the latter rapidly necrotize to large not healing ulcers. The changes usually are symmetrical. There are two types of lesions proximal and distal (Figure 4 and Figure 5). Some authors point out the presence of internal organ involvement [29]. The survival rate of the patients with proximal lesion is considerably lower [30].



Figure 4. Distal type of calciphylaxis in 49-year old patient on dialysis treatment

Nephrogenic Fibrosing Dermopathy

In 2000 Cowper et al. [31] describe a group of 14 people on dialysis who develop fibrose skin changes resembling scleromixodema. Lesions are usually symmetrical and affect primarily trunk distal extremities more common distal 2/3 of lower limbs. At the beginning there is an oedema and tightening of the skin in distal extremities. Later, small skin coloured papules appear. As the time passes by the papules merge in big, reddish plaques with well defined border. The skin in affected areas is firm with atrophy of skin appendages and resembling orange peel so called peau d'orange [32]. Golden standard for the diagnosis is biopsy with histology. There is deep infiltration of elongated fibroblasts in lower dermis and subcutaneous fascia [33].

Lichen Ruber Planus (LRP) and Atopic Dermatitis (AD)

There is a deterioration of conditions such as LRP and AD when patients start dialysis treatment. LRP is closely associated with some viral diseases such as hepatitis B (HBV) and hepatitis C (HCV). [34]. The incidence of HCV infection in dialysis patients varies considerably from 8% to 51% [35]. Typical characteristics of LRP in dialysis patients are appearance of oral and genital lesions predominantly [36].

Psoriasis

Reports reveal the remission of psoriatic lesions of patients on dialysis [37]. This clinical course is observed only in patients on peritoneal dialysis [38]. The improvement is so significant that some authors even suggest



Figure 5. Distal type of calciphylaxis in 49-year old patient on dialysis treatment

peritoneal dialysis as alternative method of treatment of severe psoriasis [39]. According to some researchers the reason for this improvement is the interaction of some blood components and dialysis membranes and liberation of biologically active substances [40].

Pseudosarcoma Kaposi

The lesions are always formed in the areas of arteriovenous (AV) fistula [41]. Typical characteristic of the condition is the lack of lesion's ulceration. The evolution of changes is very unpredictable from spontaneous healing to fistula thrombosis. Histologic examination does not reveal in all cases typical for Kaposi sarcoma perivascular spindle shaped cells [42].

Malignancies

There is increased risk of malignant transformation in patients on dialysis [43]. Possible causes are chronic immune stimulation from dialysis, impaired DNA repair, nutritional deficiency etc. [44]. The type of dialysis peritoneal or haemodialysis does not influence the incidence of malignancies. The most common types of cancer in dialysis patients are renal carcinoma, cervix and outer genitals malignancies and multiple myeloma. There is no convincing evidence for the increased incidence of skin cancer in dialyzed patients [45].

Psychodermatoses

In dialysis patients there is an increased risk for psychodermatoses. The two most common complaints are *acne excoriée des jeunes filles* [46] and delusional parasitosis [47]. Characteristic feature of these conditions is that they

are not improved by the use of psychotropic medications [48].

Treatment

Therapeutic management of skin changes in dialysis is considerable medical challenge. There is no single established therapeutic approach. Generally the use of emollients and hydrating lotions is recommended. In severe cases of uremic pruritus phototherapy is found to be very effective [49]. Some life threatening conditions like calciphylaxis require intensive care. New treatment modalities for uremic pruritus are tacrolimus and gabapentine. Tacrolimus is an immune modulator. Probably the effect of this medication on patients with pruritus is due to its ability to suppress Th1 differentiation and IL-2 production. The standard mode of application is one percent tacrolimus ointment applied once daily for six weeks [16]. Considerable drawback of this method of treatment is its relatively high price in the non-developed countries. Gabapentine is generally used as anticonvulsant. Its mode of action is connected within metabolism of gamma-aminobutyric acid (GABA). The medicine blocks the voltage dependent calcium channels thus hinders the neurotransmission in CNS [17]. As a whole the dermatological changes in dialysis patients are neglected by the physicians. They cause considerable suffering in the patients so the therapeutic management is vital ingredient in the complex treatment of patients with ESRD on dialysis.

Conclusion

Skin changes in patients undergoing dialysis treatment are numerous and clinically diverse. They cause considerable impairment of quality of life of those patients. Good understanding of these skin complications can help the physicians in the diagnosis and treatment of those conditions.

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