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Cutaneous Manifestations of Cystic Fibrosis

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ABSTRACT

Cystic fibrosis (CF) is an autosomal recessive affliction triggered by genetic mutations in the cystic fibrosis transmembrane conductance regulator. The lung and pancreas are the most frequently affected organs in cystic fibrosis, cutaneous involvement is undervalued and underdiagnosed. Skin lesions observed in patients diagnosed with cystic fibrosis are not well known and can create confusions with other dermatological diseases. The diagnosis of cutaneous lesions as signs of cystic fibrosis by pediatricians or dermatologists, despite their overlapping with different nutritional deficiencies, would allow earlier diagnosis and proper treatment and could improve quality of life and outcomes.

Keywords: cystic fibrosis, manifestations, dermatology

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive affliction triggered by genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene situated on the long arm of chromosome 7, with over 1,500 different genetic variants being described to encrypt the synthesis of the CRT protein.[1,2] The CRT protein regulates the transportation of the chloride ion across epithelial cell membranes in the respiratory, digestive, reproductive tracts, as well as in the skin. Cutaneous lesions observed in patients diagnosed with cystic fibrosis are not well known and can create confusions with other dermatological diseases. The recognition of cutaneous manifestations of cystic fibrosis by pediatricians or dermatologists could represent the first step of an early diagnosis, a correct treatment, and follow-up, and may improve the quality of life and outcome.

Cutaneous lesions described in cystic fibrosis are:[1]

- nutrient deficiency dermatitis of cystic fibrosis (CFNDD);
- allergies: atopy, urticaria, drug hypersensitivity reactions, photosensitivity;

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TABLE 1. Differential clues between CFNDD and Kwashiorkor[3–6]

CFNDD	Kwashiorkor
Genetic defect: (7q31.2)	Severe malnutrition
Few cases reported in the literature	Frequently diagnosed in the Third World
• Multiple nutritional deficiencies • Abnormal production of prostaglandins • Free radical affecting cellular membranes	• Chronic severe protein malnutrition • Free radicals affecting mitochondrial and lipid membranes
Hepatomegaly rarely present	Hepatomegaly almost present
• No nail involvement • No hair abnormalities	The presence of "flag sign" (bands of light and dark pigmentation along hairs)
Peri-oral involvement	Oral mucosal involvement, mainly cheilitis
• Sweat test positive • Early presence of edema is associated with false negative sweat tests	Sweat test negative

- aquagenic palmoplantar keratoderma;
- cutaneous vasculitis;
- other dermatoses.

1. NUTRIENT DEFICIENCY DERMATITIS OF CYSTIC FIBROSIS (CFNDD)

CFNDD is rarely recognized and reported, being overlooked by dermatologists, especially in cases in which cutaneous signs are present before pulmonary and gastrointestinal involvement, in the absence of suspicion of cystic fibrosis. Sparse case reports of CFNDD are reported, although the entity is well documented.

The first skin lesions can be present at 2 weeks to 6 months after birth as small erythematous papules localized on the diaper area and face (periocular and perioral regions) that merge and form large plaques with annular configuration and desquamation localized to the extremities. Children with cystic fibrosis who are not breastfed are presumed to develop earlier lesions of CFNDD. Sometimes periorbital edema can be associated as an early sign.[3]

If the desquamation is excessive and dominates the clinical picture, CFNDD is named "peeling paint" rash or "peeling paint" dermatitis (Figure 1), and protein, zinc, and essential fatty acids deficiencies are significant due to malabsorption and malnutrition.[4,5] Desquamating erythema could be the first cutaneous sign, with periorificial, perineal, and acral distribution, associated with edema (induced by low albumin levels) and alopecia.[3]

Histopathologic examination of a skin punch biopsy can reveal non-specific features such as epidermal hyperplasia, parakeratosis, intradermic spongiosis, thin granular layer, and perivascular inflammatory infiltrate with mononuclear cells in the dermis.[3,4]

CFNDD is a multiple nutritional and metabolic deficiency resulting in a clinical kwashiorkor-like clinical picture, but differential diagnosis with kwashiorkor can be done due to clinical clues (Table 1).

TABLE 2. Clues for differential diagnosis between CFNDD and acrodermatitis entheropathica[6–8]

CFNDD	Acrodermatitis enteropathica
Genetic diagnosis: mutations of the (CFTR) gene	Genetic diagnosis: mutations of the gene SLC39A4
Peri-orificial desquamating erythema	Peri-orificial desquamating erythema
Nail and mucosal involvement absent	• Nail dystrophy • Mucosal involvement: gingivitis, glossitis, anusitis, vulvitis, blepharitis • Alopecia of the scalp to varying degrees, loss of eyebrow and eyelash hairs
Intertriginous lesions absent	Intertriginous lesions present
• Variable serum zinc levels • No clinical improvement after zinc administration	• Reduced serum zinc levels • Low zinc levels in the hairs • Normal zinc elimination by urine, sweat and feces • Response to zinc treatment
Absence of necrolysis in the epidermis	Necrosis of keratinocytes in the upper layers of the epidermis

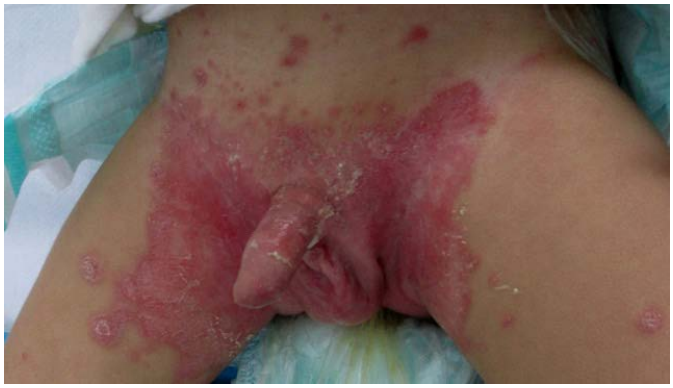

FIGURE 1. Nutrient deficiency dermatitis of cystic fibrosis in 5-year-old boy

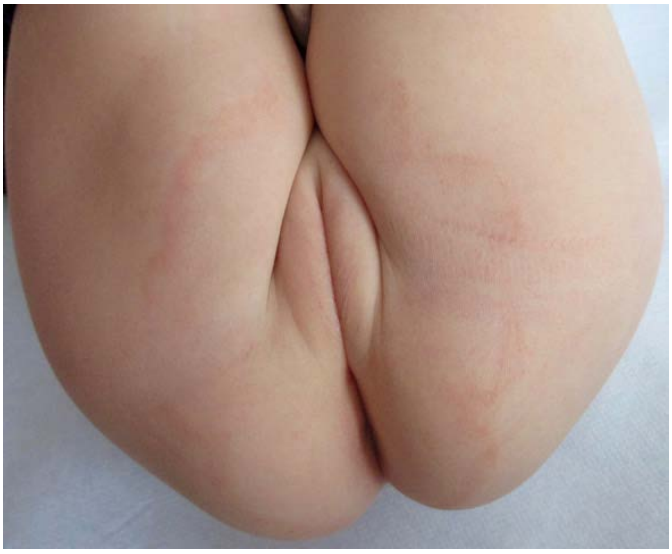

FIGURE 2. Urticaria

CFNDD is the consequence of primary essential fatty acid deficiency and pancreatic dysfunction with secondary deficiencies of vitamins, minerals, essential fatty acids, amino acids, and finally malnutrition.[1] The exact mechanism of CFNDD is not well understood and still raises questions and hypotheses.

Zinc deficiency may play a role in CFNDD, but clear distinctions must be made between CFNDD and acrodermatitis enteropathica (an autosomal recessive primary zinc deficiency disease) (Table 2).

Zinc deficiency is the result of variable mechanisms in CFNDD:

- a high percentage of infants diagnosed with CFNDD are premature, with multi-organ immaturity; liver dysfunction may interfere with the hepatic fetal storage of zinc;[3–10]
- zinc deficiency has been proved to be in direct correlation with birth order; multiparous women can give birth to children with high risk of CFNDD as the number of children grows;[1,10]
- low content of zinc in early fetal alimentation (zinc secretion in breast milk lowers after 3 months, with no improvement after zinc supplementation); moreover, cereals introduced in the diet may increase zinc deficiency due to iron and phytates that inhibit zinc absorption.[3,10]

Essential fatty acids deficiencies in CFNDD have been reported and expressed by reduced serum levels of linoleic acid, alpha linolenic acid (the precursor of docosahexanoic acid), and high serum levels of stearic and oleic acid.[3] Mutations of CFTR are involved in reducing the incorporation of linoleic acid in cell membranes, consequently allowing the increase of serum levels of arachidonic acid.[2] In cystic fibrosis, the abnormalities of chloride ion transport through pancreatic cells promote the retention of digestive enzymes in the pancreas and exocrine pancreatic dysfunction, resulting in important deficiencies of vitamins, aminoacids, minerals, and essential fatty acids.[11,12]

Protein deficiency in CFNDD is focused on serum taurine, which has been proved to be low in cystic fibrosis and be involved in fatty acids malabsorption, cell proliferation, collagen synthesis, and vitamin E absorbtion.[13]

2. ALLERGIC REACTIONS IN CYSTIC FIBROSIS

A. Atopy

Data on atopic dermatitis in children and adults diagnosed with cystic fibrosis is limited, although a general consensus exists; the prevalence of atopic dermatitis is more reported in patients with cystic fibrosis than in the general population.[14,15]

B. Acute and chronic urticaria

Screening tests in patients with cystic fibrosis failed to demonstrate a higher prevalence of urticaria (Figure 2) compared to the general population.[16]

C. Drug hypersensitivity reactions

Hypersensitivity reactions are induced by drugs in patients with cystic fibrosis more frequently than in general population due to the increased use of drugs (especially antibiotics), to the atopic background, and to immune circulat-

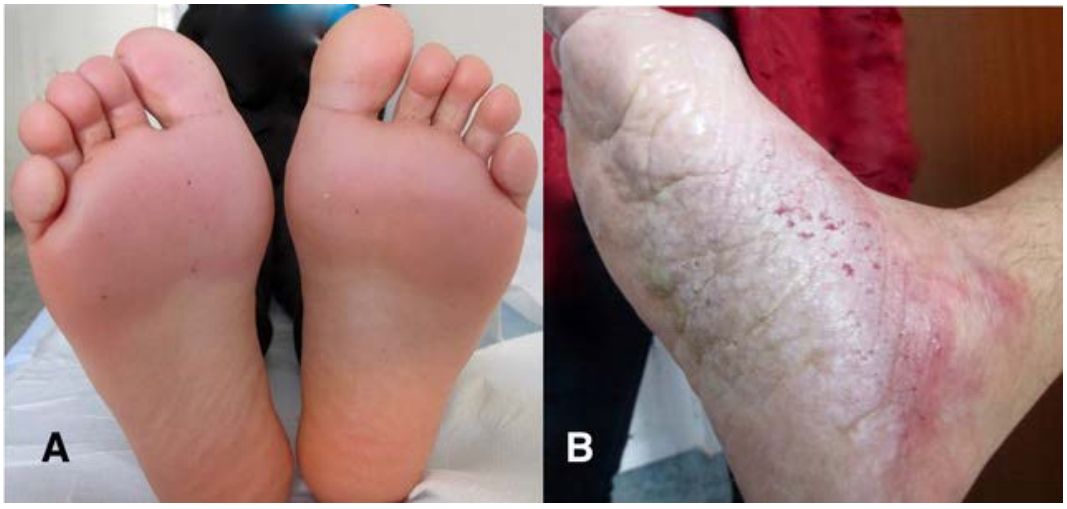

FIGURE 3. **A** – Excessive plantar sweating (hyperhidrosis) with discrete wrinkling at the toes in an adolescent diagnosed with cystic fibrosis; **B** – Aquagenic keratoderma in an adolescent male patient diagnosed with cystic fibrosis in early childhood

ing complexes.[17] The clinical expression of drug-induced hypersensitivity in cystic fibrosis varies from urticarial plaques with or without angioedema, to morbilliform rash, fixed drug reactions, Stevens-Johnson syndrome, and vasculitis.[1,17]

The most commonly involved drugs are antibiotics, especially beta-lactam antibiotics, cephalosporins, and rarely aminoglycosides and quinolones.[18,19]

D. Photosensitivity

Sensitivity to sunlight is present in patients diagnosed with cystic fibrosis after sunlight exposure or UVA phototherapy associated frequently with drug intake.[20]

3. AQUAGENIC PALMOPLANTAR WRINKLING (early skin wrinkling, aquagenic palmoplantar keratoderma, transient reactive papulotranslucent acrokeratoderma, aquagenic syringeal acrokeratoderma, aquagenic palmoplantar keratoderma, transient reactive papulotranslucent acrokeratoderma)

Excessive wrinkling of the palms and/or soles after short exposure to water and sweating, accompanied by edema, small papules, pruritus and/or pain characterize aquagenic palmoplantar keratoderma commonly observed in cystic fibrosis (Figure 3A). Aquagenic skin wrinkling is visualized within 2–4 minutes after contact with water or severe hyperhidrosis, and it is self-limited with spontaneous remission in the following hours after avoiding any contact with water.[22,23]

Aquagenic palmoplantar wrinkling can also be observed in healthy persons and can be overlooked in patients diagnosed with cystic fibrosis by its non-recognition or non-description; nevertheless, it is considered a specific clinical sign, and its frequency is around 42% of adult patients and even higher in children (approximately 78%) with cystic fibrosis.[22]

Genotype-phenotype correlations in patients with aquagenic palmoplantar keratoderma and associations with other comorbidities in cystic fibrosis are still under investigation (although an ancient correlation was established with homozygosity); no recent liaison has been estimated between the degree of malnutrition and the severity of aquagenic skin modifications (Figure 3B).[1]

The histopathological hallmarks of skin wrinkling are hyperkeratosis and dilation of the eccrine ostia, and for these reasons the accepted terminology is "aquagenic wrinkling of the palms" to distinguish it from other types of keratoderma.[24]

Several pathogenic mechanisms for aquagenic wrinkling of the palms have been proposed:

- the high concentration of sweat chloride accelerates the binding of water to keratinocytes;[1,22]
- abnormal CFTR affects transmembrane water loss via dysregulation of water membrane channels, especially aquaporin 3;
- the primary anomalies of eccrine ducts (such as dilated walls) can be a trigger factor for eccrine dysfunction.[12]

4. CUTANEOUS VASCULITIS

Vasculitis in cystic fibrosis is of cutaneous type, affects 2–3% of patients, mostly adults, and it is associated with a severe form of the disease.[1]

Cutaneous vasculitis in cystic fibrosis is an immune-mediated vasculitis, with circulating immune complexes and accumulation in the vascular wall, as a response to antigens such as: bacteria (*Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, group A streptococci, and *Mycobacterium leprae*, causative agents of chronic respiratory infections), and drugs that are intensively used in cystic fibrosis (antibiotics, sulfasalazine, pancreatic enzymes, and other supplements).[26] Recently, the correlation between sputum microbiology (during an exacerbation of an infection of the respiratory tract) and vasculitis has been demonstrated, so it was highlighted that BPI (bactericidal/permeability-increasing protein) antibodies play a key role in vasculitic inflammation. BPI is a protein hosted in the granules of neutrophils and represents a powerful weapon against bacteria and lipopolysaccharide.

Cutaneous vasculitis in cystic fibrosis can clinically express as purpuric vasculitis, localized on the inferior limbs, rarely associated with arthralgias and observed during an exacerbation of a respiratory episode. The typical picture is of a young adult, diagnosed during childhood with cystic fibrosis, who presents a palpable purpuric vasculitis rash on the dorsa of the feet, ankles, and tibial surfaces (Figure 4). The evolution of cutaneous vasculitis can be to spontaneously resolve within 2 weeks, it can respond to steroid therapy, or it can evolve with several recurrences.[25–27]

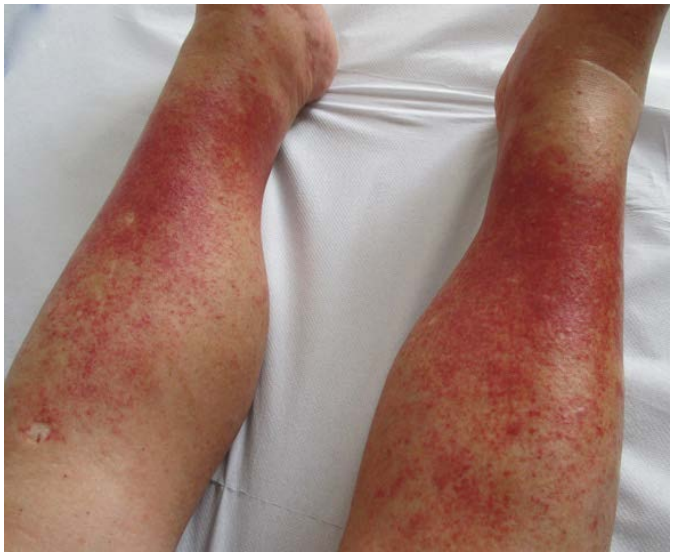

FIGURE 4. Purpuric rash in a patient with cystic fibrosis

Cutaneous biopsy may reveal leukocytoclastic vasculitis, characterized by the deposition of neutrophils in a perivascular manner and within the small vessels ("dust"), the presence of fibrin around the vessels, and endothelial cell damage.[27] Direct immunofluorescence is positive due to the presence of C3 and/or without immunoglobulin in the vascular walls in the papillary dermis.[25–27]

5. RARE SKIN LESIONS IN CYSTIC FIBROSIS

Other skin lesions associated with cystic fibrosis that have been cited in case presentations include basal cell carcinomas,[28] congenital generalized follicular hamartoma,[29] neurofibromatosis,[30] and premature reversible graying hair.[1]

CONCLUSIONS

The pulmonary and pancreatic sites are the most commonly affected organs by cystic fibrosis, while subsequent cutaneous lesions are frequently dismissed and underdiagnosed. The identification of cutaneous lesions as clinical signs of cystic fibrosis involvement, despite the overlapping with different nutritional deficiencies, may promote early diagnosis, proper therapeutic management and follow-up, by a multidisciplinary team that includes geneticists, pediatricians, dermatologists, and nutritionists, and could improve the health related quality of life and patient outcomes.

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CONFLICT OF INTEREST

None for all authors.

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