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Skin Findings in Cystic Fibrosis Cases

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BACKGROUND/AIMS
Clinical trials investigating skin findings of cystic fibrosis are limited. The aim of the present study was to evaluate the dermatological findings of patients with cystic fibrosis.

MATERIAL and METHODS
Twenty-six patients diagnosed with cystic fibrosis by the Department of Pediatric Chest Diseases were included in the study. In the pediatric chest diseases outpatient clinic, full blood, vitamin D, vitamin E, albumin, and IgE tests were recorded. In addition to the routine dermatological examination required from the pediatric chest diseases polyclinic, a diagnosis of aquagenic wrinkling was made. The cases were contacted with water at at 39°-40° C in 27°C room temperature conditions, and the water-related wrinkle was assessed after 3 and 5 min of contact.

RESULTS
There were 12 male and 14 female cases. The average age of the patients was 78.80 (8-192) months, and the mean disease duration was 52.53 (2-180) months. In the dermatological examination of the cases, xerosis cutis (18 cases, 69.2%) was most frequently found. Aquagenic palmar wrinkles were observed in 20 (76.9%) cases, and palmar wrinkles were >30% at 5 min. In 5 (25%) cases, delta F508 mutation was present. In 7 (26.9%) cases, pili annulati was observed by light microcopy.

CONCLUSION
The most common skin finding in cystic fibrosis cases is xerosis. The percentage of aquagenic wrinkling is 76.9%. To our knowledge, the association of cystic fibrosis with pili annulation is a previously unreported finding and was reported for the first time in our study.

Keywords: Cystic fibrosis, dermatologic findings, pili annulati, aquagenic palmar wrinkle

INTRODUCTION

Cystic fibrosis is an autosomal recessive disorder. There is a defect in the gene region that encodes the chlorine ion transmembrane regulatory channel located in the long arm of chromosome 7. Globally, the delta F508 mutation has been identified to be responsible for the formation of 85% of defective genes (1). Abnormal ion transport is responsible for the clinical presentation. Chronic bacterial infection of airways and sinuses, fat malabsorption, infertility in men, increase chlorine in sweat, and exocrine pancreatic insufficiency are the clinical findings. Skin findings of cystic fibrosis are important findings of the disease. Increased incidence of atopy, increased drug hypersensitivity reactions, premature skin wrinkles caused by water, and vasculitis are the skin findings, especially in vitamin deficiencies (zinc, protein, and essential fatty acids). Early skin wrinkle that is formed with water is a rare condition, and its cause is unknown. Early skin wrinkle formed with water is also reported to be seen with atypical cystic fibrosis and classical cystic fibrosis. Skin findings can be associated with the disease as primary or secondary (2). Pili annulati is a rare hair shaft abnormality with a characteristic shiny appearance due to alternating light and dark bands of the hair shaft, and there is no study about the relationship between cystic fibrosis and pili annulati in the literature (3). Clinical trials investigating cystic fibrosis skin findings are limited. The skin findings are sometimes the first findings in this disease. The aim of the present study was to evaluate the dermatological findings of patients with cystic fibrosis.

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MATERIAL and METHODS

Ethical approval was obtained from the ethics committee of Necmettin Erbakan University Meram School of Medicine. Inclusion criteria were cystic fibrosis cases diagnosed by the department of pediatric pulmonary disease clinic and referred for dermatological evaluation and cases admitted to the dermatology department. The diagnosis was based on the current criteria, including symptoms consistent with cystic fibrosis and the presence of two disease-causing cystic fibrosis transmembrane conductance regulator (CFTR) mutations or sweat chloride levels >60 mm (4). The study was conducted from January to July 2016. The exclusion criteria for aquagenic wrinkling were used, and these are hyperhidrosis of the palms and soles and usage of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, and selective cyclooxygenase-2 inhibitors. Age, gender, disease duration, history of dermatological disease, which present at birth without a diagnosis in the early period, atopic predisposition, and history of previous or active dermatological disease were determined, and dermatological examination was performed. The hands of the cases were contacted with 39°-40° water; water-dependent wrinkle was assessed after 3 min of contact.

FIGURE I. Palmar wrinkles >30% at 5 min

FIGURE 2. Pili annulati

In the palmar area, a wrinkle >30% was evaluated as positive (4). The hairs collected from the cases were evaluated by a light microscopy. Drugs used and laboratory findings were recorded. The pediatric chest diseases clinic performed routine complete blood count, zinc, vitamin D, vitamin E, and IgE tests in these cases. The hair, skin, and nail examinations of the cases were completed, and the appropriate dermatosis treatment was planned. Verbal informed consent was obtained from the patients and parents for the publication of the study.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA). The normal distribution suitability of the variables was tested by the one-sample Kolmogorov-Smirnov test. Variables with normal distribution were expressed as mean and standard error averages (mean±SHO). Chi-square and Student's t independent tests were used for statistical analysis. A $p<0.05$ was accepted as statistically significant.

RESULTS

Twenty-six patients diagnosed with cystic fibrosis by the Department of Pediatric Chest Diseases were included in the study. There were 12 male and 14 female cases diagnosed. The average age of the cases was 78.80 (8-192) months. The median disease duration of the cases was 52.53 (2-180) months. Owing to atopic dermatitis, diaper dermatitis, urticaria and dyshidrotic eczema, xerosis, and ichthyosis vulgaris, 5 (19.2%) cases were referred to the dermatology polyclinic. Two (7.69%) cases had a persistent diaper dermatitis story. The most common dermatological examination of the cases was xerosis cutis (18 cases, 69.2%) and other dermatoses (30.7%). Xerosis cutis was accompanied by cafe au lait macules (4 cases, 22.2%), nevus (4 cases, 22.2%), and seborrheic dermatitis (3 cases, 16.6%). Drumstick fingernails were observed in 7 (26.9%) cases. All of the cases had normal tooth development. Aquagenic wrinkling of the palms was observed in the cases. The hands of the cases were held in 39°-40° water. Twenty (76.9%) cases had palmar wrinkles >30% at 5 min (Figure 1). In 5 (25%) cases, delta F508 mutation was present. The hairs of the cases were evaluated by light microscopy, and 7 (26.9%) cases had pili annulati (Figure 2). The median scores of vitamin A, vitamin D, and vitamin E were 0.90 (0.40-12.20), 21.50 (7.00-38.0), and 14.55 (0.35-55.00), respectively. The median score of zinc in 20 cases was 13.75 (1.00-40.08). Of the cases, 69.2% vitamin A, 46.2% vitamin D, 42.3% vitamin E, and 19.2% zinc levels (23.1% in female and 15.4% in male) are decreased. Among them, 15.4% had anemia. The normal ranges of vitamin A (1.05-2.45 µmol/L), vitamin D (winter: 10-60 ng/mL and summer 20-120 ng/mL), vitamin E (11.6-46.4 µm/L), and zinc (men: 11.1-19.5 µmol/L and women: 10.7-17.5 µmol/L) were assessed in our laboratory.

DISCUSSION

Cystic fibrosis with dermatitis is known only in 24 cases (5), and presumably metabolic abnormalities and deficiencies of protein, zinc, and essential fatty acids are responsible for the formation of this dermatitis (1, 6-8). In the cases, widespread desquamative skin eruption starting from periorificial, perineum, and extremities and peeling paint rash accompanied by hypoproteinemia, anemia, increased liver enzyme, and malabsorption findings with widespread eruption can be seen. Generally,

the hair and nails are not affected (9). These rashes resemble acrodermatitis enteropathica (1). Pekcan et al. (10) reported a case of a 4-month-old boy who was admitted for having diffuse eruption in the perianal region, legs, trunk, hands, and face with failure to thrive, edema, hypoalbuminemia, and anemia. They thought he had acrodermatitis enteropathica-like eruption due to malabsorption. Cystic fibrosis associated with malabsorption and insufficient nutrition will lead to hypoproteinemia, zinc deficiency, and fatty acid deficiency, which may cause skin eruptions similar to acrodermatitis enteropathica. The eruption completely resolved with enzyme supplement, proper nutrition, and skin care (10). Vesicle, bullae, and pustule formation can also be seen. Eczematous skin can be infected secondary to *Candida albicans* and/or bacteria. Eruptions typically begin in the diaper area and may range in the perioral area, extremities, and entire body. A previous study reporting cheilitis was found (11). This rash is resistant to topical steroids, imidazoles, and antibiotics. Zinc replacement alone is not enough. The rash is stretching by intense nutritional support with pancreatic enzyme replacement within 2 weeks. A widespread rash with protein energy malnutrition in cystic fibrosis cases, an indication that prognosis is worse in these cases, was seen (1). Although antibiotics used for the treatment of lung infections in cystic fibrosis are thought to have an increased incidence of atopy as a secondary, in a study of 100 patients with cystic fibrosis, 16% (12) were found with urticaria, which is not different from the incidence of urticaria in the normal population (15%-25%) (12-13). In addition, atopic conditions do not cause urticaria development. It was found that urticaria was seen more frequently in atopic individuals, and that the cause was often food. It is also seen in non-atopic cases as chronic urticaria and often idiopathic (12). One of our cases had anamnesis of urticaria.

The atopy rates are higher in cystic fibrosis cases than in normal populations. The rates of atopy vary from 46% to 76% (14-15), but this ratio is found to be 40% in the normal population (16). In our case, 5 (19.2%) patients were referred to the dermatology polyclinics due to atopic dermatitis, diaper dermatitis, urticaria and dyshidrotic eczema, xerosis, and ichthyosis vulgaris. There were stubborn diaper dermatitis stories in 2 (7.69%) cases. The most common dermatological examination of the cases was xerosis cutis (18 cases, 69.2%) and other dermatoses (30.7%). Xerosis cutis was associated with cafe au lait macules (22.2% in 4 cases), nevus (22.2% in 4 cases), and seborrheic dermatitis (16.6% in 3 cases). None of the cases described a common skin eruption at the time of diagnosis. None of the case has acrodermatitis enteropathica-like eruption or its history. One of our cases had atopic dermatitis story in the past. The most common skin lesion detected is xerosis cutis (69.2%). Of the cases, 18 can be interpreted as favoring atopy because it is in the minor criteria of atopic dermatitis, but it may not be directly related to atopic dermatitis. In addition, vitamin A deficiency causes skin dryness (17). Vitamins A and D were decreased in our study. In our cases, the mean zinc level was found within the normal range. Therefore, the presence of both cystic fibrosis and vitamin deficiency in our cases can be seen as atopic predisposition used to describe skin dryness.

In cases with cystic fibrosis, premature skin rupture on the hands and feet is seen after exposure to water (9, 18). The skin crust typically begins to form in the second minute of exposure to the water (19) and describes that when they have jobs associated with water, they have wrinkled hands (20-21). This finding is usually transient and remains within a few hours of contact with water (20). Findings, such as itching, tingling, and hyperhidrosis, may be accompanied (20-21). This condition is not related to the degree of malnutrition. The aquagenic palmar wrinkle is called transient reactive papulotranslucent acrokeratoderma. When seen without cystic fibrosis, it is called aquagenic keratoderma, aquagenic syringeal acrokeratoderma, aquagenic palmoplantar acrokeratoderma, and transient reactive papulotranslucent acrokeratoderma. The mechanism of formation, increased sweat chloride content, increases the binding of keratin to water, the mutated CFTR gene changes the regulation of the water membrane channels, aquaporins, resulting in abnormal fluid regulation throughout the epidermis. Eccrine channel dysfunction is also responsible for aquagenic palmar wrinkling (9). Early palmar wrinkles associated with water were found to be related to the homozygous gene delta F508, which is frequently detected for cystic fibrosis (20). In a study in which 44 cases and 26 healthy cases were included, the cases were evaluated for aquagenic palmar wrinkles by standing in water at 39°-40° C in 27°C room temperature conditions for 3 min. The aquagenic palmar wrinkle score was statistically significantly higher in cases with cystic fibrosis than in the control group. These cases were found to be homozygous positive for delta F508 (18). In another study, 21 patients with cystic fibrosis, 13 carriers, and 15 control patients were found to be positive in 25% and 80% of patients with aquagenic wrinkling, respectively, but not in the control group and statistically significant (2). In the study by Tolland et al. (22), 105 cases of cystic fibrosis questioned for aquagenic palmar wrinkling and 41% were positive. Since these cases are preliminary about the gastrointestinal system and chest diseases, they suggest that they do not care about it as much as they should, and they do not report to the doctor. Again in a study of 37 cases, this rare condition was found to be positive in 19 cases (18). In the study by Arkin et al. (4) involving 51 cystic fibrosis cases and 25 controls, the hand was immersed for 5 min in 39°-40° water. The detection of an aquagenic wrinkling at ≥30% of the hand surface was considered positive. Transepidermal water loss of the palms was also seen. Aquagenic palmar wrinkles were detected in 43 (84%) cases, but not in the control group. In addition, it has been found that transepidermal water loss is higher in cases with cystic fibrosis, which is an aquagenic palmar wrinkling, than in cases without aquagenic palmar wrinkling with cystic fibrosis (4). In our study, 20 (76.9%) cases had palmar wrinkles in >30% at 5 min. In 5 (25%) cases, delta F508 mutation was present.

The nail and hair are not affected in cystic fibrosis (9). In our study, fingernails were clubbed in 7 (26.9%) cases. It was thought that the appearance of this drumstick finger, which had no significant nail finding, developed due to pulmonary involvement of the present disease. All of the cases had normal tooth development. In contrast to acrodermatitis enteropathica, the mucous membranes and nails are not retained (2). In our study, there were no description of mucosal involvement and no mucosal involvement at the time of examination.

Alopecia has been reported at various grades, and hypoalbuminemia and hypoproteinemia are usually present in these

cases (23). Congenital generalized follicular hamartoma associated with hair loss was reported in three relatives with cystic fibrosis (24). Case reports with hair depigmentation and dermatitis were present (25). Dalgıç et al. (26) reported an acrodermatitis-like rash on an 11-month-old cystic fibrosis and a gray hair onset at 3 months. With enzyme replacement, the complaints at the case have declined, and gray hair is defined as associated with cystic fibrosis. Pili annulati is a rare hair shaft abnormality with a characteristic shiny appearance due to alternating light and dark bands of the hair shaft. The light bands seen by the unaided eye correspond to the dark bands seen by light microscopy. They are due to air-filled cavities within the cortex of the hair shaft, which has been confirmed by scanning and transmission electron microscopy (27). Pili annulati is considered to be an autosomal dominant disorder, but sporadic cases have also been described (3). Pili annulati diagnosis and clinical manifestations, as well as in light microscopy, are made based on the presence of dark bands (28). On differential diagnosis, the pseudo-pili annulati that shows similar banding in the main body of the hair is located. The banded appearance of the pseudo-pili annulati is due to the superficial optical effect caused by the characteristic bending and elliptical shape of the hair. Although the pseudo-pili annulati shows similar microscopic findings, this condition is not inherited and is not associated with any hair cortex anomaly. Both hair diseases are mainly seen in light hair, and there is no coexistence with hair fragility. With transverse illumination, the pili annulati light is banded whichever way it comes from, whereas the pseudo-pili annulati is seen only when the hair is turned to certain positions. In addition, the pseudo-pili annulati has no abnormality in the scanner and transparent electron microscope examination of the hair cortex and cuticle (29). In the literature, there were no studies about the relationship between cystic fibrosis and pili annulati. Pili annulati is found to be a locus of chromosome 12q24.32-24.33 (28, 30). Cystic fibrosis chromosome is 7. Although there is a connection for the F508 mutation in the chromosome, inheritance patterns are not similar. Pili annulati is an autosomal dominant disorder, and cystic fibrosis is an inherited autosomal recessive disorder. The hairs of the cases were analyzed under light microscopy, and 7 (26.9%) cases had pili annulati. In our case with cystic fibrosis, this finding is striking considering the frequency of occurrence in both diseases. The main limitation of this study were the limited number of cases.

The most common skin lesion is xerosis cutis. Transient aquagenic palmar wrinkling is a rare condition associated with the occurrence of cystic fibrosis and may be a clue to early diagnosis. In our study, the percentage of this symptom is 76.9%. When there are skin drying and transient aquagenic wrinkling of the palms in the cases, cystic fibrosis should also be considered and investigated by the pediatricians. Pili annulati was an interesting finding, and we thought that these two conditions can be often seen together. Previously, children with cystic fibrosis have not been reported in the literature. Therefore, this finding is needed to assess cystic fibrosis in children for pili annulati more carefully. In the cystic fibrosis investigated cases, in addition to other findings, aquagenic skin wrinkling should also be questioned, which sometimes makes it easier to make the diagnosis and maybe look for hair for pili annulati.

Ethics Committee Approval: Ethics committee approval was received for this study from Necmettin Erbakan University Meram School of Medicine (Approval Date: 01.06.2018, Approval Number: 2018/1392).

Informed Consent: Verbal informed consent was obtained from the patients and parents of the patients for publication.

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