CASE REPORTS

Aquagenic palmoplantar keratoderma associated with cystic fibrosis gene mutation

Acroqueratodermia aquagénica associada a mutação do gene da fibrose quística

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Abstract

Introduction: Aquagenic palmoplantar keratoderma (APK) is a rare dermatologic condition characterized by excessive palmar wrinkling that occurs within minutes of exposure to water. Cystic fibrosis (CF) or CF carrier-associated forms, drug-induced cases, and idiopathic forms have been described. The exact pathophysiology remains unknown.

Clinical case: A 13-year-old female patient was observed for pruritus and palmar edema after brief contact with water with one month of evolution. Symptoms resolved spontaneously 20 minutes after drying the hands. Study of the cystic fibrosis transmembrane conductance regulator (CFTR) gene revealed an F508del mutation in one allele.

Discussion/Conclusion: Similar to what was described in this patient, the F508del mutation has been the most commonly associated with APK in patients with CF. In the present case, APK was the sole manifestation of the patient’s CF carrier status. This fact highlights the importance of considering and investigating this type of genetic alteration in these patients. Overall, CF should be considered in patients with APK, and patients with CF should be asked about symptoms of this condition.

Keywords: aquagenic palmoplantar keratoderma; cystic fibrosis; cystic fibrosis transmembrane conductance regulator gene; genetic screening; f508del mutation

Resumo

Introdução: A acroqueratodermia aquagénica palmoplantar (APK) é uma condição dermatológica rara caracterizada por enrugamento palmar excessivo poucos minutos após exposição a água. Têm sido descritos casos associados a fibrose quística (FC) ou formas associadas ao estado de portador de FC, bem como casos induzidos por fármacos e formas idiopáticas. A fisiopatologia da APK permanece desconhecida.

Caso clínico: É descrito o caso clínico de uma menina de 13 anos de idade com queixas de prurido e edema palmar após breve contacto com água com cerca de um mês de evolução. Os sintomas regrediam espontaneamente 20 minutos após a secagem das mãos. O estudo do gene regulador da condutância transmembranar da fibrose quística (CFTR) revelou a mutação F508del num dos alelos.

Discussão/Conclusão: À semelhança do presente caso, a mutação F508del é a mais frequentemente associada à APK em doentes com FC. A APK representou a única manifestação do estado portador de FC neste doente. Destaca-se assim a importância de considerar e pesquisa este tipo de alteração genética em doentes com APK.

Em conclusão, a FC deve ser considerada em doentes com APK, e os doentes com FC devem ser questionados sobre sintomas de APK.

Palavras-Chave: acroqueratodermia aquagénica palmoplantar; fibrose quística; gene regulador da condutância transmembranar da fibrose quística; mutação f508del; rastreio genético

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INTRODUCTION

Aquagenic palmoplantar keratoderma (APK) is a rare condition characterized by edematous, flat-topped papules on the palms or, less commonly, the soles, with wrinkling after brief exposure to water that persists for 20 to 30 minutes after exposure. Clinical findings are usually bilateral and symmetric. The diagnosis is relatively straightforward if one is aware of this entity. While the exact pathophysiology remains unclear, several mechanisms and associations have been proposed. One commonly described mechanism that may explain APK suggests that increased sodium retention in the stratum corneum results in increased water uptake capacity. Other hypotheses include stratum corneum barrier dysfunction, possible involvement of transient vanilloid receptor type 1, and increased skin aquaporin expression. Another hypothesis links APK to increased sympathetic activity and involvement of sympathetically innervated eccrine sweat glands. This theory is supported by the fact that several anticholinergic medications have been effective in the treatment of APK. APK can be idiopathic or induced by drugs. Drug-induced APK has been associated with rofecoxib, celecoxib, aspirin, and, less often, tobramycin. The proposed mechanism for the cases associated with rofecoxib, celecoxib, and aspirin involves cyclooxygenase-2 (COX-2) inhibition in epidermal cells, which may cause increased sodium reabsorption in a mechanism similar to the effect of COX-2 inhibitors on kidney cells. Histopathologic changes include orthohyperkeratosis with increased thickness and abnormal staining of the stratum corneum, dilated acrosyringia, and dermal eccrine ducts with hyperplasia of eccrine glands, clear cell changes and vacuolation, and increased capillaries around and adjacent to the eccrine glands.

APK is associated with cystic fibrosis (CF) and involves the same mutations found in CF (usually ΔF508 of the CFTR gene), either homozygous or heterozygous. It has been reported that 40-84% of patients with CF have concomitant APK. Although APK is more common in patients with CF, Gild et al. described the first case associated with an isolated mutation in the CFTR gene, suggesting that APK may be a sign of CF carrier status. However, APK is not specific to CF, as it is also found in other conditions such as marasmus, nephrotic syndrome, atopy, palmar hyperhidrosis, Raynaud’s phenomenon, malignant melanoma, Behçet’s disease, and nail psoriasis.

CLINICAL CASE

A 13-year-old Caucasian female patient was observed for pruritus and palmar edema after brief contact with water with one month of evolution. Symptoms were more easily triggered by hot water and resolved spontaneously 20 minutes after drying the hands. The condition fluctuated between exacerbations and periods of complete resolution. The girl had no other dermatologic history except for occasional palmar hyperhidrosis. She reported no plantar symptoms or other associated complaints (e.g., respiratory or gastrointestinal). She had no relevant medical history, including no history of atopy or chronic cardiac or respiratory disease, and denied sinus, nasal, or gastrointestinal complaints. She was not taking any regular medication, only occasional paracetamol. There was no family history of cystic fibrosis or aquagenic wrinkling of the palms.

On physical examination, the patient’s skin was found to be dry with mild thickening of the palms and some subtle central white and flesh-colored papules. The remainder of the skin, scalp hair, and nails were normal. Nasal examination was normal with no nasal polyps, and lung auscultation was unremarkable. Within five minutes of immersion in water, the patient developed wrinkling of the palmar skin, web spaces, and digits with prominent dilated ostia, which were observed with a dermoscope.

CFTR gene study revealed an F508del mutation in one allele. Biopsy of palmar papule after water immersion showed hyperorthokeratosis, dermal edema, and dilatation of eccrine acrosin ostia. Sweat test was negative (< 60 mmol/L).

The patient was treated with topical aluminum chloride 20%, with satisfactory improvement of signs and symptoms. Considering the CF carrier status, the patient and family members were referred for genetic counseling.

DISCUSSION/CONCLUSIONS

Skin lesions typically appear after brief contact with hot or cold water, with complete resolution shortly after drying the hands. In the absence of water contact, the palmar and/or plantar skin does not show any of the described signs or in some cases continues to show the presence of hyperlinearity and multiple white millimeter papules. Lesions are usually asymptomatic but may occasionally be associated with complaints of pruritus and burning. This entity is more common in female patients (58%), especially in young age groups (onset between 9-42 years).

CF is usually diagnosed at an early age, with more than 75% of patients being diagnosed by the age of two. The diagnosis of non-classic CF in children and young adults is more challenging. To date, more than 2,000 CFTR mutations have been identified, which are classified according to their potential impact on CFTR function or according to their clinical implications.

The F508 mutation is the most commonly associated with APK in CF patients. Although this is the most common CFTR gene mutation, some authors speculate that it may be a predisposing factor for APK.

In the present case, APK was a unique manifestation of the patient’s CF carrier status. This fact highlights the importance of considering and investigating this type of genetic mutation in these patients. These diseases should be investigated not only in CF carriers, but also...
in CF patients to facilitate timely treatment. Therefore, identification of the genetic mutations underlying this disorder may help to elucidate the pathophysiological mechanisms involved. The authors believe that APK is an underdiagnosed entity that can be confused with the physiologic pallor and wrinkling of the palms and soles, usually caused by vasconstriction associated with prolonged water exposure.

Aquagenic urticaria (AU) is one of the conditions to consider in the differential diagnosis of APK. It is a rare form of chronic inducible urticaria that is triggered by water at any temperature. Pruritic wheals develop immediately or within minutes at sites of skin contact with water (but not on the palms and soles, which is the main clinical difference from APK), regardless of temperature or source, and clear within 30-60 minutes. Sweat, saliva, and even tears can cause a reaction. Symptoms often begin during puberty, but cases presenting in childhood have also been reported. A 20-minute water challenge test at body temperature is recommended for diagnosis of AU.15-18

Most treatment regimens for APK focus on reducing the hyperkeratosis associated with the condition or providing a water barrier to prevent exposure. Treatments involving the application of 12% ammonium lactate creams or petroleum jelly or the use of barrier to prevent exposure. Treatments involving the application of 12% ammonium lactate creams or petroleum jelly or the use of 20% aluminum chloride solution has been shown to result in rapid improvement of hyperkeratosis associated with the condition or providing a water barrier to prevent exposure. Treatments involving the application of 12% ammonium lactate creams or petroleum jelly or the use of 20% aluminum chloride solution has been shown to result in rapid improvement of symptoms in a series of three patients.19

Tap water iontophoresis, endoscopic thoracic sympathectomy, botulinum toxin injections, and oxybutynin are effective for refractory symptoms in a series of three patients.(19) Oral oxybutynin 5 mg/d is probably the best option for treating APK. The reported pathophysiologic effects of nonsteroidal anti-inflammatory drugs in this setting suggest that the use of prostaglandins may be warranted.20

The use of sweat chloride testing or genetic studies should be encouraged in these patients, as there is an association between APK and CF or CF carrier status, especially when APK occurs at young ages. In conclusion, the authors suggest that sporadic isolated APK should be included in the clinical spectrum of CFTR gene mutations as a CFTR-related disorder, especially in more dubious cases. Furthermore, screening for rare mutations in the CFTR gene should be recommended in patients with isolated APK in order to adapt genetic counseling as well as management and prevention of complications.

REFERENCES


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