Aquagenic Wrinkling of the Palms: A Potential Sign of Systemic Treatment Response to Elexacaftor-Tezacaftor-Ivacaftor

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Abstract
Cystic Fibrosis is a life altering disease resulting from a mutated gene and ion channel. It is a systemic condition that affects multiple body systems including the skin. Aquagenic wrinkling of the palms (AWP) is the rapid formation of white plaques on the palms after exposure to water and is commonly seen in patients with cystic fibrosis. Numerous theories exist to explain this pathophysiology however no one explanation has been able to characterize it completely. Our patient is a 25-year-old with a past medical history of cystic fibrosis and AWP who was started on Trikafta® (elexacaftor-tezacaftor-ivacaftor). Shortly after she started treatment she observed near total resolution of her AWP. This is the second documented case of this phenomenon and may be a marker for systemic improvement and response to this drug.

Keywords
Cystic fibrosis, AWP, Trikafta

Introduction
Cystic fibrosis (CF) occurs due to an inherited mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which diminishes the body’s ability to regulate electrolyte concentrations across membranes. Consequently, bodily secretions become thickened, leading to pathologic abnormalities of the pulmonary, gastrointestinal, and endocrine systems. Aquagenic wrinkling of the palms (AWP), or rapid formation of white plaques on the palms and occasionally soles after exposure to water, is a common cutaneous manifestation of CF; occurring in up to 80% of affected individuals and 25% of carriers [1,2].

There is no known cure for cystic fibrosis, but there have been promising pharmacological treatment options. Trikafta® (elexacaftor-tezacaftor-ivacaftor) is a novel combination therapeutic that has shown promise in treating patients with severe pulmonary disease. Little is known about its effects in extrapulmonary tissue as these were not evaluated in clinical trials. Only one prior report has detailed improvement of AWP in a patient treated with Elexacaftor-tezacaftor-ivacaftor to date; however, a review of Internet forums reveals numerous patient anecdotes of similar improvement [3]. Here we report a patient with a homozygous F508 deletion, who after 4 months of treatment with Elexacaftor-tezacaftor-ivacaftor noticed complete resolution of her AWP.

Case
A 25-year-old female with a past medical history of cystic fibrosis (homozygous F508 deletion), Mycobacterium abscessus pneumonia, and chronic peripheral eosinophilia presented to dermatology clinic due to concern for acute onset guttate psoriasis. She noted a long-standing history of AWP with wrinkling of her palms within 2-3 minutes of water exposure, worse with warmer water. She reported that her AWP was mostly asymptomatic, with rare complaints of pruritus.
She was started on Elexacaftor-tezacaftor-ivacaftor for her CF and noted complete resolution of her AWP within 4 months.

Discussion

The association between AWP and CF is well-documented. It tends to occur in those with severe disease but has also been seen in otherwise asymptomatic carriers of a CFTR-mutation [2,4]. The time to wrinkle also differs between diseased patients and carriers with the former wrinkling within 2-3 minutes and the latter within 7 minutes. Healthy controls, in comparison, typically develop wrinkling within 11 minutes [5]. Interestingly, the severity of AWP does not appear to correlate with the sweat chloride levels of those with CF, which suggests that the osmotic gradient caused by faulty CFTR channels is not solely responsible for the development of AWP [6-8]. Other hypotheses have been proposed to explain this paradox, such as nerve or eccrine duct dysfunction, however these have yet to be validated [2]. While AWP is a relatively benign condition; aluminum chloride, antihistamines or iontophoresis can be used for symptomatic management with varying efficacy [1].

Elexacaftor-tezacaftor-ivacaftor is a combination therapy that modulates the affected CFTR channel in patients with at least one F508 mutation. Ivacaftor facilitates chloride ion flow through the channel, while both tezacaftor and elexacaftor correct the misfolding of the protein, enhancing its transfer to the cell surface [9]. These drugs not only correct the mutated chloride channels present in the lungs, but also those in other organs including possibly the skin [10]. Interestingly, AWP resolution has not been documented in patients treated with dual CF-modulating therapy.

Here we report the second documented case of AWP improving quickly with elexacaftor-tezacaftor-ivacaftor therapy in a patient harboring a homozygous F508 mutation. This anecdotal case suggests the pathophysiology of AWP may be related to electrolyte imbalance. Theoretically, if AWP is due to the skin’s inability to regulate the flow of water and electrolytes because of a faulty CFTR channel, then restoring function to this channel should result in resolution of AWP.

Aside from providing evidence of a pathophysiologic mechanism of AWP, the significance of the improvement is unclear. Our patient was not particularly bothered by AWP, so any improvement in quality of life would be fairly minimal. Improvement in AWP may serve as a surrogate marker for improvement in other organ functioning (i.e. as suggestion that a patient may have robust pulmonary function improvement) and help set expectations of improvement for CF patients. Or it may be simply an interesting but incidental finding in these patients.

In summary, we present the second published case of elexacaftor-tezacaftor-ivacaftor resulting in complete resolution of AWP in a CF patient. The full implications of this improvement remain to be seen.

Conflicts of Interest Statement

The author R. Hal Flowers has a non-relevant conflict of interest as he is a researcher for Venthera and Concert. The subject material of this manuscript however is not related to his work for them, nor is there any financial conflict of interest. The other two authors, Ariel Finberg and Merrick Kozak, have no financial or professional conflicts of interest with any of the materials discussed in the manuscript.

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