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## **Acquired idiopathic partial anhidrosis successfully treated with adapalene gel**

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Running title: Treatment of AIPA with adapalene gel

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Dear Editor,

Acquired idiopathic anhidrosis (AIA) includes the partial form (acquired idiopathic partial anhidrosis; AIPA) and generalized form (acquired idiopathic generalized anhidrosis; AIGA).<sup>1, 2</sup> AIA is caused by unknown pathogenesis and leads to stinging pain or itch and heatstroke.<sup>1-3</sup> Although some AIA treatments, such as high-dose steroid therapy, immunosuppressants, and antihistamines have previously been reported, novel treatments for AIA are still desired.<sup>1-3</sup>

Here, we report a case of AIPA on the upper back of a patient who presented with severe tingling pain that was successfully treated with adapalene gel. A 27-year-old man reported a 4-month history of partial anhidrosis localized only on the upper back with heat intolerance accompanied by severe tingling pain in a warm environment. His physical examination at rest were normal, and laboratory findings were within the normal range. The thermoregulatory sweat test using the iodine-starch method (modified Minor test) with sweating provoked by heat stimulation showed anhidrosis of only the upper back (Fig. 1a,b). Neurological examination did not reveal any abnormality in the central or peripheral nervous system. Skin biopsies were taken from



the anhidrotic area and showed no morphological abnormalities of sweat glands, but the infiltration of lymphocytes around sweat glands and firm keratotic plugs were observed at the acrosyringium (Fig. 1c, d). Other diseases with hypohidrosis, such as Sjögren's syndrome, were excluded. Based on clinical (affected area is less than 25%) and histopathological findings, the patient was diagnosed with AIPA.

His symptoms were refractory to oral antihistamines, oral anti-anxiety drugs, keratolytic agents, and heparinoid ointment. Although steroid pulse therapy is reported to improve the symptoms of AIGA,<sup>2,3</sup> the affected area of our patient was limited. Therefore, the application of adapalene gel, which is reported to be effective for porokeratosis to reduce keratotic plugs, was administered twice a day as off-label.<sup>4</sup> Symptoms subsequently disappeared, and a thermoregulatory sweat test confirmed sweating improvement within 3 weeks (Fig. 1e, f).

To investigate sweat gland dysfunction and the production of sweat, we performed immunohistochemical staining of cholinergic receptor muscarinic 3 (CHRM3) and dermcidin.<sup>2</sup> We found decreased expression of CHRM3 in sweat glands and strong staining of dermcidin in the sweat ducts in the anhidrotic area before the administration

of adapalene gel treatment (Fig. 1g, h). One month after the administration of adapalene gel treatment, we observed the disappearance of lymphocyte infiltration around the sweat glands and firm keratotic plugs. Additionally, immunohistochemical analysis revealed the increased expression of CHRM3 in sweat glands and decreased staining of dermcidin in the sweat ducts after applying adapalene (Fig. 1k, l). Dermcidin is the major sweat antimicrobial peptide expressed in sweat ducts and is secreted into sweat.<sup>5</sup> In our case, immunohistochemical staining of dermcidin was strongly positive in the sweat ducts of the affected area and became weaker as symptoms improved, indicating the possibility of sweat excretion. Therefore, we hypothesized that adapalene gel might reduce the plug at the acrosyringium and prevent ductal blockage, thereby improving sweat delivery. Although further analysis is needed, our case may provide useful information for the treatment of refractory AIA.

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## FIGURE LEGENDS

### **Figure 1. Clinical and histopathological findings.**

**(a and b)** The thermoregulatory sweat test (modified Minor test) confirming no black dots (perspiration points) before the application of adapalene gel. **(a)**

The enlarged picture of (a). **(b)**

**(c and d)** The histopathological examination before the administration of adapalene gel treatment revealed the firm keratotic plug at the acrosyringium **(c)** and infiltration of lymphocytes around sweat glands (Hematoxylin-eosin [HE], original magnification  $\times 200$ ). **(d)**

**(e and f)** The thermoregulatory sweat test (modified Minor test) confirming many black dots (perspiration points) after application of adapalene gel. **(e)**

The enlarged picture of (e). **(f)**

**(g and h)** The immunohistochemical staining of anti-cholinergic receptor muscarinic 3 (CHRM3) before the administration of adapalene gel treatment revealed weak expression in the sweat glands (H-210; Santa Cruz Biotechnology, Dallas, TX;  $\times 200$ )

**(g)**, and dermcidin showed strong expression in the sweat ducts (G-81; Santa Cruz

Biotechnology, Dallas, TX;  $\times 200$ ). **(h)**

**(i and j)** The histopathological examination after application of adapalene gel revealed

the disappearance of keratotic plugs **(i)** and lymphocyte infiltration around the sweat

glands (HE,  $\times 200$ ). **(j)**

**(k and l)** The immunohistochemical staining of the skin specimen after application of

adapalene gel showed the increased expression levels of CHRM3 in sweat glands

( $\times 200$ ) **(k)**, and decreased expression levels of dermcidin in the sweat ducts ( $\times 200$ ). **(l)**



