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Generalized hyperhidrosis secondary to presumed eccrine gland dysfunction with possible apocrine metaplasia.

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Abstract

We present a 57 year-old man presented with generalized hyperhidrosis and widespread, smooth, flesh colored papules on the torso and extremities. Histological examination from multiple biopsies demonstrated morphologic alteration of the eccrine glands with an apocrine phenotype, suggesting either apocrine metaplasia or the presence of "apoeccrine glands." The morphologic similarities between eccrine, apocrine, and apoeccrine as they relate to our patient's histologic findings are discussed. We consider secondary causes of generalized hyperhidrosis, which may also play a role in this patient's presentation. Treatment and further workup are discussed, while management of this patient remains in progress.

Keywords: hyperhidrosis, apoeccrine glands, apocrine metaplasia

Introduction

HISTORY: A 57-year-old Hispanic man with a history of type II diabetes mellitus presented to the Skin and Cancer Unit for evaluation of generalized hyperhidrosis causing emotional and physical discomfort for the past 15 years. The sweating was neither associated with physical activity nor psychological stress. The patient noted arising in the morning with moist clothing and awakening from sleep to change his clothing due to excessive moisture. In addition to hyperhidrosis, the patient noted textural skin changes, described as "chicken skin", on his arms, back, chest, and legs. There was no family history of similar symptoms. Prior treatments included axillary injections of botulinum toxin as well as roll-on 20% aluminum chloride, both of which yielded only mild symptomatic relief.

Pertinent past medical history includes type II diabetes mellitus, hypertension, chronic back pain, and depression. Medications included metformin and daily insulin injections, anti-hypertensive medications, NSAIDs, and bupropion. He denied recent travel, sick contacts, or identifiable environmental exposures.

PHYSICAL EXAMINATION: On physical examination, the patient was an overweight, well-appearing man with Fitzpatrick skin type III. Distributed over his arms, thighs, chest, back, and abdomen were widespread, smooth, skin-colored, 5-mm, thin papules. His skin and clothing were both damp to touch. No malodor was detected.

LABORATORY DATA: Prior routine screening studies including a complete blood count with differential,

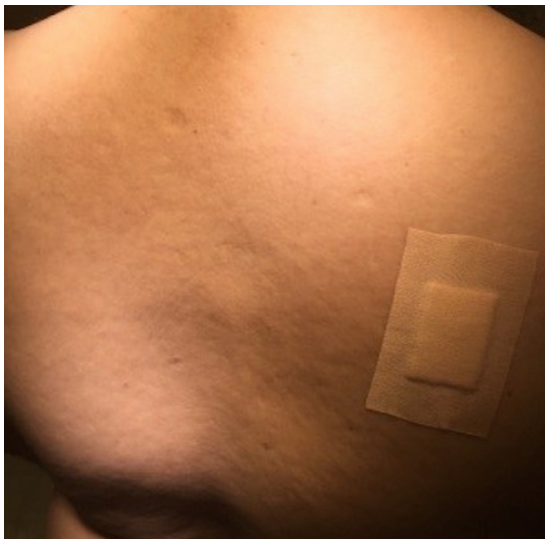

Figure 1. *Upper back and shoulders showing innumerable thin, smooth, skin-colored papules seen best with tangential lighting. Bandage covering biopsy site.*

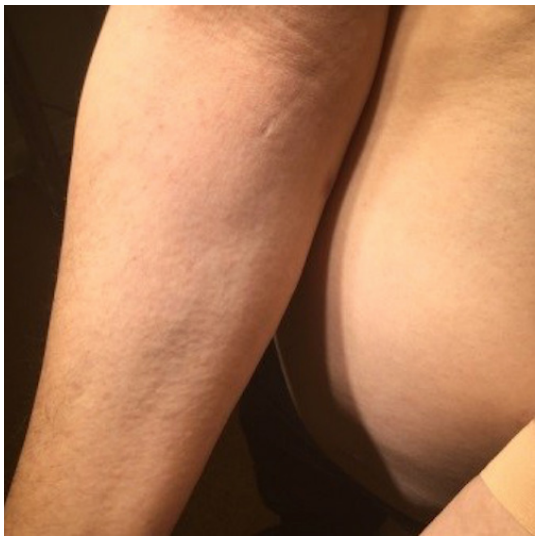

Figure 2. *Numerous thin, smooth, skin-colored papules on the forearms and abdomen.*

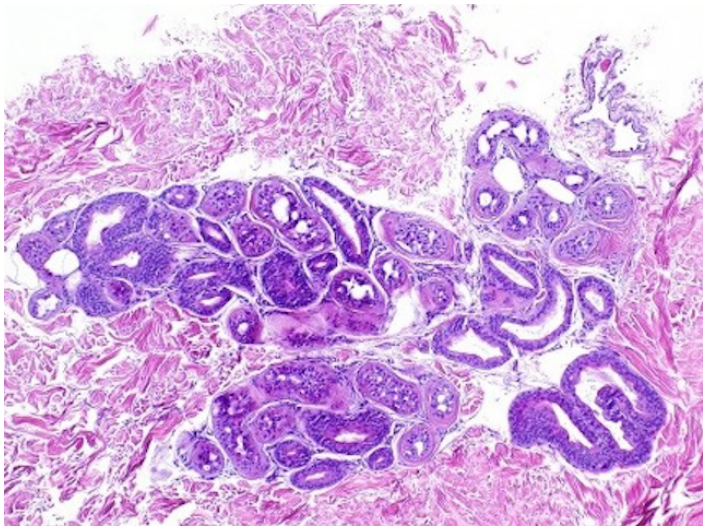

Figure 3. *Hematoxyiln and eosin stained punch biopsy taken from right upper back showing two populations of glandular formations some of which were lined by columnar cells with hints of decapitation secretion while others were lined by cuboidal cells with more clear cytoplasm. The ducts opened directly to the epidermal surface.*

liver function tests, thyroid stimulating hormone level, and lipid panel were within normal limits. Basic metabolic panel had elevated serum glucose and a hemoglobin A1c level of 10.4%. Testosterone levels were also normal.

HISTOPATHOLOGY: The patient underwent 4-mm punch biopsies from the right ventral forearm, left upper arm, and right upper back (site covered with bandage in clinical image above). All biopsies showed similar histological changes. Within the deep dermis, there were two populations of glandular formations some of which were lined by columnar cells with hints of decapitation secretion while others were lined by cuboidal cells with more clear cytoplasm. The ducts opened directly to the epidermal surface.

Conclusion

Sweat gland biology refers to the morphology, secretory products, innervation, and distribution of eccrine and apocrine glands. The primary function of eccrine glands is thermoregulation via the production of hypotonic aqueous sweat through merocrine secretion [1]. Eccrine glands are present at birth on the entire body with highest concentration on the palms and soles but are not found on the lips, external ear canal, areas of the genitals, and under the nails. Apocrine glands are also present at birth, but differ in their distribution as they are located in axillary, areolar, periumbilical, and anogenital regions [1]. Apocrine glands produce a thicker, oilier substrate rich in odiferous chemicals through decapitation secretion. Secretion from apocrine glands is thought to play a role in olfactory communication.

Eccrine glands are small structures that begin proximally in the dermis with a secretory coil, extend distally with a straight duct that reaches the epidermis, and terminate with an acrosyringium that opens directly to the skin surface by spiraling through the stratum corneum [1, 2]. Eccrine glands show no relation to the hair follicle. Within the secretory coil are myoepithelial cells and so-called 'dark' and 'clear' cells (named for their appearance under electron microscopy). The ductal portion is comprised of a bi-layer of luminal and basal cells. In contrast, apocrine glands are overall larger, but shorter and thicker than eccrine glands [1, 2]. The entire apocrine gland is made up of a monolayer of tall columnar cells, demonstrating characteristic 'decapitation' secretion on microcopy, surrounded by myoepthelial cells. Apocrine glands always open below the surface of the skin by emptying directly into the upper follicular canal of an associated hair follicle. Lastly, intercellular canaliculi between cells in the secretory coil and ducts are found in eccrine glands, but are absent in apocrine glands.

Within the literature, a proposed third type of sweat gland called "apoeccrine" hybridizes eccrine and apocrine features but only develops in adolescence.

Apoeccrine glandular size is overall intermediate and variable between the other two adnexal structures. Like eccrine glands, apoeccrine glands open directly to the skin surface and have high rates of sweat excretion. The secretory coil of apoeccrine cells demonstrate occasional dilation and the tubules have a more gently sloped angularity versus tightly packed apocrine glands. The distal segments of apoeccrine glands more resemble apocrine glands with decapitation secretion from a single layer of luminal cells, whereas proximal regions are more eccrine-like with thinner ducts, intermittent dark cells, and intercellular canaliculi [1, 3]. Immunohistochemical staining can be used to help distinguish the three types of glands, but results vary on antibody and protocol [4-6]. In the original description of apoeccrine glands, it was hypothesized that they derive from pre-existing eccrine glands that acquire apocrine-like features.

The precise role of apoeccrine glands is not known, and their existence is controversial [2, 4, 5, 7]. To date, apoeccrine glands have only been characterized in non-pathologic skin from the axilla of post-adolescents, anogenital regions, and near nasal ala [3, 8]. "Mammary-like eccrine glands" with features of eccrine glands and lactiferous duct apocrine secretion have been found in anogenital areas and may represent the same entity as apoeccrine glands [9]. Apocrine metaplasia exists in several pathologic situations including nevus sebaceous and apocrine hidroadenocarcinoma, among other skin appendageal tumors [9, 10]. Interestingly, nevi sebaceous possess a gradient of metaplasia progressing from the periphery to the center, whereas peri-lesional skin is unchanged - further suggesting that eccrine cells are capable of transitioning toward an apocrine phenotype through an undefined stimulus [9].

Our patient presents a diagnostic challenge both clinically and histopathologically. He had several biopsies from different sites of the body showing morphologically abnormal sweat glands. In particular, the eccrine glands possessed columnar cells and aspects of decapitation secretion – features associated with apocrine glands. The density of the glands was not changed. Whether these glands represent eccrine glands that have undergone apocrine metaplasia, or are true "apoeccrine glands" remains unclear. To our knowledge, no reports have been published of apoeccrine glands existing diffusely in the skin and not associated with an underlying tumor. Because of the widespread distribution of these altered glands, we speculate that there is an unknown systemic or circulating hormone or growth factor leading to metaplasia of existing eccrine glands.

Primary hyperhidrosis typically presents clinically in a focal pattern involving the axilla, palms, and soles, where there is a high density of eccrine glands; excess sweating is episodic (i.e. related to activities or emotional triggers) and ceases with sleep. In contrast, generalized hyperhidrosis is typically secondary to systemic conditions (e.g. hypoglycemia, thyroid disease, hyperthermia) or medications, with sweating persisting during sleep. Importantly, eccrine gland morphology is unaltered in either primary or secondary hyperhidrosis. Clinical studies have shown that patients with hyperhidrosis have a higher concentration of apoeccrine glands as compared to normohidrotic individuals [11]. The secretory rate of apoeccrine glands is also 7-10 times higher than eccrine glands [2, 11]. Of note, our patient is at risk for several causes of secondary generalized hyperhidrosis. He takes several medications known to cause hyperhidrosis including bupropion, insulin, and analgesics (NSAIDs, acetaminophen, and opioids).

Treatment for hyperhidrosis depends on the underlying etiology [12-15]. Hidrosis of the face, chest, and back is usually caused by heat, whereas hidrosis of the palms and soles is typically driven by emotional stress. If episodic, management is aimed towards reduction of psychological or physiological stimuli. When topical antiperspirants such as 20% aluminum chloride hexahydrate are unsuccessful, targeted application of botulinum toxin to the axilla and palms can achieve temporary reduction in hidrosis. Some patients with focal hyperhidrosis have achieved improvement with suction curettage, iontophoresis, microwave thermolysis, ultrasound, laser, and endoscopic thoracic sympathectomy. In addition, systemic agents include anti-cholinergic agents such as oral glycopyrrolate and oxybutynin that counteract activation of glandular secretion.

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