Fox-Fordyce Disease Following Axillary Laser Hair Removal

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Background: Fox-Fordyce disease (FFD) is a relatively rare entity with a typical clinical presentation. Numerous studies have described unifying histopathological features of FFD, which together suggest a defect in the follicular infundibulum resulting in follicular dilation with keratin plugging, subsequent apocrine duct obstruction, and apocrine gland dilation, with eventual extravasation of the apocrine secretions as the primary histopathogenic events in the evolution of the disease.

Observations: We describe a case of FFD that developed in a 41-year-old woman 3 months after completing a series of axillary laser hair removal treatments, and we detail the clinical and histopathological changes typical for FFD.

Conclusion: Because defective infundibular maturation has been suggested to play a central role in the evolution of FFD, the close temporal relationship of laser hair therapy with the development of FFD suggests a causal role, which we continue to explore.

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Fox-Fordyce disease (FFD) is an infrequently encountered disease characterized by the eruption of symmetric, variably pruritic skin-colored to yellow folliculocentric papules in skin areas containing apocrine glands, including the axilla, areola, anogenital area, and umbilicus. Fox-Fordyce disease typically affects postpubertal women, and symptoms tend to resolve with menopause, the use of oral contraceptives, or pregnancy. Consistent with the idea that FFD represents a disorder of infundibular keratinization and subsequent apocrine duct obstruction, the disease, and specifically, the pruritus, is often exacerbated in summer months or with exercise or sweating.1-5

Nonablative laser therapy has emerged as a useful approach for selective hair removal.6,8 In the procedure, discrete wavelengths of light target melanin pigment in the hair bulb and shaft. Following selective absorption of laser energy by the melanin, heat dissipates and causes tissue injury.5 Relatively few adverse effects have been reported with laser hair removal. Unwanted pigmentedary changes are the most common, and rarely, paradoxical hypertrichosis may occur.6,7

We report a case of FFD developing in the axillae of a 41-year-old woman 3 months after completing treatment of this area with a hair laser (Candela 755 nm; Candela Corporation, Wayland, Massachusetts). We summarize various histopathologic descriptions of FFD in the literature. Finally, given the close temporal relationship between FFD and laser therapy in the present case, we explore a potential causal relationship between them in the context of previously proposed mechanisms explaining the development of FFD.

REPORT OF CASE

A 41-year-old white woman was seen at our clinic for a 2- to 3-year history of an intensely pruritic papular eruption in her axillae bilaterally. Three months before the onset of her symptoms, she had completed 6 Candela 755 nm laser treatments at an interval of once every 2 months over the course of 14 months to her forearms, axilla, legs, and bikini areas. She denied any adverse reactions during the period of laser treatment. She further denied any similar episodic, pruritic, papular eruptions in the past. Prior to presentation, she had been treated with over-the-counter hy-
drocortisone cream and Lotrimin ( clotrimazole) cream ( Schering-Plough HealthCare Products Inc, Berkeley Heights, New Jersey) without relief. Physical examination revealed multiple, bilateral, monomorphic, follicular, skin-colored to yellow papules (1-2 mm in diameter) confined to the bilateral axillary areas ( Figure 1 ). The remainder of her physical examination results were unremarkable.

She was initially prescribed clobetasol propionate spray, 0.05%, to apply to the affected area twice daily. This alleviated her symptoms but only with regular use. Because her symptoms had not abated, she returned and underwent a punch biopsy of the affected area. She was then given fluocinolone cream, 0.1%, for use as needed for itching; however, she was again corticosteroid dependent for symptomatic relief. To minimize the adverse effects of long-term topical corticosteroid use, she was switched to Protopic ointment, 0.1%, which did not provide any relief of her symptoms and was discontinued. She is currently undergoing a trial with Retin-A Micro ( tretinoin gel] microsphere, 0.04%; Ortho Dermatologics, Los Angeles, California).

Histologic examination of a 4-mm punch biopsy specimen taken from the right axilla revealed dilation of the follicular infundibulum with a predominantly orthokeratotic plug ( Figure 2A). Focally, a diminutive parakeratotic column—reminiscent of a cornoid lamella—surmounted the dilated infundibulum (not shown). In addition, follicular infundibular keratinocytes exhibited spongiosis and scattered dysmaturation manifested by cells with dense eosinophilic cytoplasm and hyperchromatic nuclei ( Figure 2B). A scant mononuclear cell inflammatory infiltrate surrounded the follicular infundibulum. Minimal interface changes, including focal vacuolar change of the basal keratinocytes, and an associated lymphocyte exocytosis into the follicular infundibulum associated with the areas of dyskeratosis were also present (not shown). Mild perifollicular and periadnexal fibrosis were present in the superficial dermis ( Figure 2B). Distinct perifollicular and peridendal accumulation of foamy histiocytes, or “perifollicular xanthomatosis,” was present ( Figure 2C). In the deeper regions of the dermis, dilated and locally atrophic apocrine glands with entrapped faintly basophilic material were identified ( Figure 2D).

The clinical presentation of FFD is thought to be the manifestation of interrupted apocrine gland secretion due to keratin plugging of the follicular infundibulum at the site of apocrine duct insertion. More than 90% of patients are women, with the majority aged between 13 and 35 years. 1,4 In order of frequency, the sites affected in these patients reflect the endogenous distribution of apocrine glands and include the axillae, genitalia, perineum, areolae, peristernal area, umbilicus, and upper-inner thigh. Patients usually present with a chronic, pruritic eruption of follicular-based, skin-colored, dome-shaped papules. The pruritus is typically episodic and is classically exacerbated by emotional stress, sexual activity, or exercise. In addition to the apparent age and gender bias, further evidence supporting a hormonal contribution to FFD is the documented remission of symptoms with oral contraceptive use and pregnancy. 1,5 Of note, there is typically a reduction of hair growth in affected areas.

Although the precise chronology of events remains formally unproven, several unifying histologic and clinical observations from reports in the literature spanning many decades suggest the following series events in the pathogenesis of this disease. 1,3,5,8–10 There is general agreement that dilation of the follicular infundibulum with hyperkeratinosis and keratin plugging is a common feature of FFD. 1,3,5,8–13,15,16 Keratin plugging may be caused by keratinocyte dysmaturation, manifested by dyskeratosis and parakeratosis—the latter often resembling a cornoid lamella. 1,5,10,15 Blockage of the apocrine duct at the point of entry to the epidermis obstructs apocrine secretion 1 and causes apocrine duct and gland dilation. Continued increase in secretory pressure causes leakage of apocrine duct secretions into the surrounding epidermis, initially producing epidermal spongiosis, and then later, the elusive “retention vesicle.” 4 Finally, with extravasation into the dermis, inflammation and perifollicular foamy histiocytes develop. The latter “perifollicular xanthomatosis” represents the final step in FFD pathogenesis as the body attempts to sequester the lipid-laden apocrine secretions in the cytoplasm of reactive histiocytes. 1,10,14,15 Consistent with these latter events is the observation that the mucinous substance in the papillary dermis, perifollicular xanthomatous histiocytes, and dilated apocrine glands all exhibit positive staining results with Alcian blue with a pH of 1 or 2.5. 15

Despite this relatively coherent explanation, formal proof of this process is lacking. Furthermore, the inciting event that sets the aforementioned chain of events into motion remains elusive. The prominence of epidermal dyskeratosis and parakeratosis observed in numerous studies has led to the suggestion that defective infundibular maturation ultimately underlies FFD, giving rise to infundibular dilation with keratin plug formation and secondary apocrine duct blockage. 1,10 Consistent with this model is the historical observation of a cornoid lamella-like structure and interrupted hair growth.
in patients with FFD. However, the precise reasons underlying this dysmaturation phenotype and the basis for its apparent restriction to the apocrine duct portal remain unclear.

Nonablative laser hair removal relies on “selective photothermolysis,” which targets the melanin pigment in hair shaft cells. The excited melanin pigment in turn transforms the laser light into heat, which then causes damage to the surrounding tissues in a manner that results in hair loss. Acute adverse events include erythema, perifollicular edema, crusting, and perifollicular inflammation. Chronic adverse events, mostly due to “off targeting” of epidermal pigment, include pigmentary alterations. In this context, then, the clinical and histological appearance of FFD in a patient following laser hair removal as reported herein offers potential further mechanistic insights into the pathogenesis of this disease. The close temporal relationship of laser hair removal and FFD development in this patient suggests that the laser therapy induced some form of damage to the follicular infundibulum—either directly or secondary to inflammation. This altered the maturation of keratinocytes (dyskeratosis and/or dysmaturation), leading to keratin plugging with focal parakeratosis and subsequent infundibular dilation. Finally, this mechanical obstruction led to apocrine secretory interruption and leakage. As indicated in the Table, the present case exhibits many of the clinical and histopathologic features of classic FFD. This raises the possibility that FFD represents a reaction pattern: a “final common pathway” for a constellation of different physiologic insults—mechanical and hormonal—that have in common infundibular dysmaturation and obstruction of the apocrine secretory unit.

Consistent with this hypothesis, electrodessication-mediated experimental obstruction of the apocrine duct produces many of the changes seen in FFD. Clinical changes observed in this latter study included apocrine anhidrosis and follicular plugging, while histopathologic changes included focal hyperkeratosis and keratin plugging, apocrine duct and glandular dilation, and periductal fibrosis. Nevertheless, these studies demonstrated that while mechanical duct obstruction lies at the heart of the changes of FFD, infundibular obstruction by itself is insufficient to elicit the full complement of changes.

Figure 2. Histopathologic appearance of Fox-Fordyce disease. A, Dilated follicular infundibulum with hyperkeratosis (hematoxylin-eosin, original magnification ×20). B, Follicular infundibulum with clustered and single dyskeratotic follicular epidermal cells (white arrows indicate area with numerous dyskeratotic cells). Adjacent apocrine duct (black arrow) with periductal fibrosis (asterisk) (hematoxylin-eosin, original magnification ×20). C, Apocrine duct (black arrow) with surrounding mononuclear infiltrate and foamy histiocytes (“perifollicular xanthomatosis”) (hematoxylin-eosin, original magnification ×40). D, Dilation of an apocrine secretory unit (ducts and glands, indicated by black arrow) with adjacent unaffected apocrine secretory unit for comparison (indicated by white arrow) (hematoxylin-eosin, original magnification ×10).
that characterize FFD. In particular, the rupture of the apocrine secretory network, the associated apocrine spongiosis and the resultant lymphohistiocytic inflammatory response were not identified in these studies, suggesting that additional factors, like hormonal changes, underlying or superimposed infections, and genetics may variably conspire to evoke them. It is also unclear why our patient only developed apocrine duct obstruction in her axillae, despite the fact that she had laser therapy to other apocrine-bearing regions. This might reflect differences in the physiologic features of these anatomic sites (in particular, the density of the apocrine secretory units in the axilla compared with the other sites), differences in the susceptibility to laser-induced injury among these areas (fluctuations in laser intensity, associated inflammation) in this patient or additional factors. Future observation of patients receiving laser hair removal is warranted to determine any potential pathophysiologic relationships with FFD and additional relevant disease-modifying factors as we expand our understanding of this interesting disease process.

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Table. Comparison of Features Seen in Idiopathic FFD With FFD Following Laser Hair Removal

<table>
<thead>
<tr>
<th>Feature</th>
<th>Laser-Induced FFD</th>
<th>Classic FFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair follicle</td>
<td>Absent, ablated</td>
<td>Present</td>
</tr>
<tr>
<td>Dilation of the follicular infundibulum</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Follicular hyperkeratosis</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Dyserkeratosis in the follicular infundibulum</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Periductal lymphohistiocytic infiltrate</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Not identified</td>
<td>Typically present</td>
</tr>
<tr>
<td>Perifollicular fibrosis</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Perifollicular and periductal foam cells</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Apocrine secretory unit dilation</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Etiology</td>
<td>Laser and multifactorial</td>
<td>Multifactorial</td>
</tr>
</tbody>
</table>

Abbreviation: FFD, Fox-Fordyce disease.