Xanthomatous Fox-Fordyce Disease
Ching-Wen Huang  Po-Hsuan Lu  Yu-Hung Wu  Yang-Chin Lin

Fox-Fordyce disease is a rare, pruritic disorder characterized by multiple flesh-colored follicular papules, usually affecting the apocrine gland-bearing areas of young women. The typical histopathologic features include a keratotic plug in the dilated follicular orifice and spongiosis of the infundibular epithelium. However, recently, another histopathologic observation has been reported, that of numerous foamy histiocytes in the peri-infundibular dermis. Patients with this xanthomatous form of the disease, have yellow as well as flesh-colored papules. We report a 27-year-old woman with mildly itchy follicular papules in both axillae, mammary areolae and the pubes for one year. Histology revealed numerous xanthomatous cells in association with a few lymphocytes surrounding the follicular infundibulum, consistent with a diagnosis of xanthomatous Fox-Fordyce disease. (Dermatol Sinica 24: 220-223, 2006)

Key words: Fox-Fordyce disease, Xanthomatous cells, Apocrine miliaria

福斯佛代斯氏病是一個罕見的皮膚疾患，臨床症狀是在年輕婦女頂漿腺聚集區域發生具有癢感的多顆膚色小丘疹。病理組織的典型發現包括毛囊開口有過度角化的現象，在毛囊漏斗部可見海綿樣水腫的變化，在近來的文獻報告中亦發現可以存在有泡沫狀組織細胞聚集在毛囊漏斗的周圍。我們報告一位27歲的女性，在一年前開始在兩側腋下，乳暈及恥骨部位出現多個丘疹伴隨皮膚的輕微搔癢。病理切片下可見毛囊漏斗部周圍有大量黃色瘤細胞與少量淋巴球的浸潤，在回顧相關的文獻後我們診斷其為黃色瘤樣型的福斯佛代斯氏病。 (中華皮誌 24: 220-223, 2006)
Fox-Fordyce disease, also known as apocrine miliaria, is a chronic papular eruption affecting skin with apocrine sweat glands. Over 90% of patients have been women between the ages of 13 and 35 years. Rarely, the disorder has been reported in prepubescent and postmenopausal patients. We report a woman with typical manifestations of the xanthomatous form of Fox-Fordyce disease.

CASE REPORT

A 27-year-old woman presented with a 1-year history of a slightly itchy skin rash in both axillae. The pruritus was aggravated by exercise. The patient was otherwise in good health. No other family members had a similar dermatologic condition. On examination she had multiple pale yellow or skin-colored follicular papules in the axillae and on the areolae and mons pubis (Fig. 1). The papules were surrounded by normal skin. A biopsy specimen was obtained from a papule in the left axilla. The tissue sections showed an acanthotic epidermis with hyperkeratosis, focal parakeratosis, and intrafollicular keratinous plugs (Fig. 2, 3). There was infiltration of lymphohistiocytes around the follicular infundibulum but no spongiosis of the follicular epithelium was found on multiple sections. A remarkably large number of xanthomatous cells were present in the perifollicular dermis (Fig. 4), with a few scattered lymphocytes interspersed between these foamy histiocytes. No xanthoma cells were seen.

Fig. 1
Multiple pale yellow and skin-colored follicular papules in the axilla.

Fig. 2
Biopsy specimen from a yellow papule in the left axilla shows hyperkeratosis, parakeratosis and acanthosis. A lymphohistiocytic infiltrate is present around the follicular infundibulum. (H & E stain, x40)

Fig. 3
Keratotic plugs block the dilated follicular ostia. (H & E stain, x100)

Fig. 4
Numerous foamy macrophages around the entrance of the apocrine duct into the hair follicle. (H & E stain, x200)
in the interfollicular papillary dermis. Based on the clinical manifestations and histopathologic findings, xanthomatous Fox-Fordyce disease was diagnosed.

**DISCUSSION**

Fox-Fordyce disease was first described in 1902 by George Henry Fox and John Addison Fordyce. It is characterized by discrete, firm, flesh-colored papules affecting the axillae, the pubes, labia, perineum, mammary areolae and less frequently the umbilicus or presternal area. Pruritus is activated by emotional excitation, sexual activity, and exercise. Sparsity of axillary hair is common.

In 1956, Shelley and Levy described the histopathologic findings and suggested that the disease is caused by keratinous obstruction of the follicular ostia. Associated spongiosis of the infundibulum at the entrance of the apocrine duct into the hair follicle is characteristic. There may also be chronic inflammatory cell infiltrates in the dermis.

Recently, a variation of Fox-Fordyce disease has been reported. It presents in typical fashion but microscopically includes a dense infiltrate of xanthomatous cells in the peri ductal tissue. Böer et al. reported a 32-year-old woman with multiple pruritic yellow perifollicular papules in the axillae, perimammary region, and mons pubis. A skin biopsy specimen had foamy histiocytes in the vicinity of the duct, as well as a keratotic plug blocking the dilated duct of an apocrine gland. These authors called this xanthomatous Fox-Fordyce disease. They attributed the yellow color of the lesions to the foamy cells in the infiltrate, the same histology as is seen in xanthomas.

Kossard and Dwyer reported a similar case in a 40-year-old woman with mild pruritic pale yellow follicular papules in the axillae. On biopsy, there was an expanded perifollicular connective tissue sheath with abundant xanthoma cells but no intrafollicular keratinous plug or follicular spongiosis. They proposed the name “axillary perifollicular xanthomatosis resembling Fox-Fordyce disease”. However, they thought it might be a different entity from Fox-Fordyce disease because of the lack of intense pruritus and the typical sweat retention vesicle.

However, in 2004 Böer reported four more patients with the same findings. He thought Fox-Fordyce disease should not be conceived of merely as a spongiotic dermatitis of the infundibular epidermis because spongiosis may be totally absent. Rather, a common clinical presentation may be produced by a varied histopathology, including follicular spongiosis, cornoid lamellation, xanthomatous infiltrates in the peri-infundibular dermis, and vacuolar changes at the dermo-epidermal junction. The spongiosis is an inflammatory response to keratinous obstruction of the hair follicle and apocrine duct. A xanthomatous cell infiltrate may be the result of chronic inflammation of the follicular epithelium, leading to a release of cytoplasmic lipids which are then phagocytosed by histiocytes. According to this view, the pathology may vary depending on the degree of inflammation, resolution, or chronicity of the lesions.

Although the pathology may vary, the classic appearance of the eruption makes the diagnosis straightforward. There may occasionally be confusion with lichen nitidus, eruptive syringoma, contact dermatitis, infectious folliculitis, or pseudofolliculitis of the axillae. In such cases, skin biopsies with traditional or transverse sectioning are useful for diagnosing this follicular-based dermatosis.

The pathogenesis of the keratinous obstruction in apocrine-rich follicles in Fox-Fordyce disease is unknown. A hormonal link has been postulated due to the high prevalence in women (reportedly with a female-to-male ratio of 9:1) and clinical improvement during pregnancy or after menopause. However, no hormonal abnormality has been demonstrated, and the disorder has occurred in prepubertal girls.

There is no definitive treatment for this chronic disorder. Because of the follicular occlusion, therapies used in other follicular disorders, including topical tretinoin cream, topical
steroids, antibiotics, clindamycin, ultraviolet light, electrocoagulation, laser, and oral isotretinoin have all been tried, with variable results. 

Surgical excision is reserved for cases resistant to local therapies, but it is seldom recommended.

In conclusion, our case adds to the literature another description of the histopathology in a case of Fox-Fordyce disease. Familiarity with the typical presentation of this rare cutaneous disease as well as the varied pathology underlying it should be helpful in making a correct diagnosis.

REFERENCES