Perifollicular Xanthomatosis as the Hallmark of Axillary Fox-Fordyce Disease

An Evaluation of Histopathologic Features of 7 Cases

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Background: Fox-Fordyce disease (FFD) or apocrine miliaria is a rare condition with features that are characteristic clinically but not histopathologically. It is traditionally described as a condition that shows infundibular plugging, acanthosis, parakeratosis, spongiosis, and a nonspecific infiltrate. The so-called retention vesicle, which reputedly involves the apocrine duct, is often difficult to find. Recently, 4 uncontrolled observations were described (infundibular dyskeratotic cells, vacuolar alteration, cornoid lamella–like parakeratosis, and perifollicular foamy macrophages). In this study, we evaluated both established and new histopathologic criteria for the diagnosis of FFD and searched for other meaningful findings.

Observations: Most established features were observed in both patients with FFD and control patients. All cases occurred during 1995 through 2005. No unequivocal retention vesicle was identifiable in any case. Infundibular vacuolar change and cornoid lamella–like parakeratosis were not corroborated as being diagnostically meaningful. Few dyskeratotic cells were seen in some patients with FFD and in control patients. Perifollicular foam cells were noted in most patients with FFD but not among control patients. These cells expressed CD68 but lacked expression of carcinoembryonic antigen, gross cystic disease fluid protein 15, and periodic acid–Schiff with diastase digestion. Perifollicular mucin, fibrosis, and mast cells in the infiltrate were also observed.

Conclusions: The established histopathologic attributes of FFD are nonspecific, and a retention vesicle is difficult to find even in level sections. In contrast, perifollicular foam cells are a distinct, relatively consistent, and specific feature of FFD. We contend that perifollicular foam cells represent a useful hallmark of FFD.

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Fox-Fordyce disease (FFD) is a rare condition typically composed of skin-colored follicular papules in apocrine skin, most commonly involving the axillae and areolae of postadolescent women. The histopathologic features are traditionally characterized as follicular plugging with associated infundibular acanthosis, parakeratosis, and spongiosis, coupled with a nonspecific infiltrate. The so-called sweat retention vesicle has been reputed to be the singular diagnostic feature. Although the clinical features of FFD are relatively characteristic, rendering a specific histopathologic diagnosis is less straightforward. The search for a retention vesicle via conventional serial sections is often frustrating if not futile, although transverse sectioning can be used to demonstrate a vesicle. However, this approach is not amenable to use in routine diagnostic work.

Recently, Boer1 published uncontrolled observations regarding 4 cases. Findings included scattered infundibular dyskeratotic cells, vacuolar alteration at the junction between infundibular epithelium and its adventitia, and cornoid lamella–like parakeratosis within the infundibular plug. Furthermore, Boer and a colleague4,7 noted an infiltrate of foamy macrophages surrounding the infundibular and apocrine ducts, which she believed represented a specific manifestation of FFD. Independently, Kossard and Dwyer8 reported on a case termed axillary perifollicular xanthomatosis that was thought to represent FFD. Historically, Osment10 in 1979, mentioned histiocytes with foamy granular cytoplasm in the vicinity of degenerated ducts in association with FFD and, thus, the findings of Boer4 and Kossard and Dwyer8 were not entirely novel.

Boer4,7 speculated that apocrine secretion trapped by infundibular plugging may

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be spewed into adjacent tissue through spongiotic epithelium. Per this hypothesis, perifollicular macrophages subsequently ingest the secretions and assume a foamy appearance. This theory is unproved.

The purpose of our study was to evaluate both traditional and recently described histopathologic criteria and to search for other meaningful findings. Using special stains (including immunoperoxidase stains), we also sought to gain insight into pathogenesis.

METHODS

Biopsy specimens from 7 patients coded as having FFD were retrieved via a search of the computerized database of the University of California, San Francisco, Dermatopathology Service for the years 1995 through 2005. All specimens had been originally evaluated using conventional hematoxylin-eosin–stained sections, and many had been evaluated by level sections. All histopathologic features deemed important in prior studies were tabulated for each patient. Immunoperoxidase staining for CD68, carcinoembryonic antigen (CEA), and gross cystic disease fluid protein 15 (GCDFP-15) were completed in 3 specimens. The antibody vendors and dilutions used are as follows: CD68 (Dako North America, Inc, Carpinteria, California) at 1:4000; CEA, polyclonal (Dako North America, Inc) at 1:20; epithelial membrane antigen (Dako North America, Inc) at 1:240; and GCDFP-15 (Georg Fischer Signet, El Monte, California) at 1:20. Pretreatment with antigen retrieval solution (pH 6.0) (Dako North America, Inc) was performed. The Envision detection system (Dako North America, Inc), using horseradish peroxidase, was used. Periodic acid–Schiff with diastase digestion (PAS-D) and colloidal iron stains were also completed in selected instances.

Axillary skin specimens from other conditions (inflammatory and noninflammatory) were also retrieved for use as controls. The histopathologic features associated with FFD were tabulated using control tissue. The control tissue included the spongiosis associated with inflammatory and noninflammatory conditions. Spongiosis in FFD was often mild and focal. We did not identify an unequivocal retention vesicle in any of our case patients. A questionable space was observed in 1 case patient, but we favored a sectioning artifact when a portion of a duct was cut through in deeper sections.

REPORT OF CASES

All 7 specimens came from axillary lesions of women. Six of the patients were 16 to 34 years old and 1 was 58 years old. In 4 of the 7 patients, FFD was suspected clinically (Table 1).

TRADITIONALLY DESCRIBED HISTOPATHOLOGIC FEATURES

The histopathologic findings in the patients with FFD and the control patients are presented in Table 2 and Table 3. The conventional features of dilation, hyperkeratosis, parakeratosis, spongiosis, and acanthosis of the infundibulum and lymphohistiocytic infiltrates were observed (Figure 1A) in the patients with FFD. These features were also noted in our control patients in an almost similar proportion to case patients (Figure 1B).

Spongiosis and acanthosis, although present in all patients with FFD, were observed mostly in our controls who had inflammatory conditions. Spongiosis in FFD was often mild and focal. We did not identify an unequivocal retention vesicle in any of our case patients. A questionable space was observed in 1 case patient, but we favored a sectioning artifact when a portion of a duct was cut through in deeper sections.

RECENTLY DESCRIBED FEATURES

We were unable to corroborate the presence of the cornoid lamella–like parakeratosis and vacuolar change of the infundibulum, as Böer described. The parakeratosis noted in 2 patients with FFD did not form a cornoid lamella. There were hints of squamatization of the infundibular basal layer in some of our case patients, but no clear vacuolar change was observed. Scattered dyskeratotic cells were present in 6 of the patients with FFD either in the infundibular epithelium or within the hyperkeratotic plug. Dyskeratosis was hard to find, with only 2 to 4 cells in a section and present only in 35% of the microscopic-level sections examined. Interestingly, rare dyskeratotic cells were also seen within the infundibula in 2 of our controls and in some of the additional HS cases.

Varying numbers of foam cells were noted in 6 of the 7 patients. In most of the case patients, these cells were numerous and readily identifiable, whereas 1 case patient had fewer and less prominent foam cells (Figure 2 and Figure 3). The cells were arranged in aggregates surrounding the infundibulum and the apocrine duct. The cell borders were discernible and cytoplasm was abundant and finely vacuolated or almost granular, yielding a foamy appearance with a grayish blue or amphophilic hue. The nuclei were pale and somewhat ovoid or sometimes slightly irregularly shaped. Sparse to moderate lymphohistiocytic infiltrates were seen in the same distribution, but multinucleate cells were not prominent. The foam cells were observed in 64% of the microscopic-level sections examined.

One HS specimen showed some resemblance to the foam cells near the infundibulum. By examining additional cases of HS and suppurative folliculitis, we noted that resemblance to the peri-infundibular foam cells was due to either cells with abundant somewhat stringy cytoplasm with indistinct cell walls in an edematous stroma or cells with clear but nonfoamy cytoplasm. These cells were widely distributed in the dermis and the subcutis.
rather than being confined to peri-infundibular and periductal areas. In addition, the HS specimens had a much denser mixed-cell infiltrate in the lower dermis and subcutis, with areas of necrosis.

Enough tissue was available for immunoperoxidase stains in 3 of the case patients. The foam cells were CD68 in the 3 case patients. Both CEA and GCDFP-15 failed to demonstrate intracytoplasmic positivity. Periodic acid–Schiff with diastase digestion staining was unable to demonstrate the PAS-positive, diastase-resistant material typically seen in apocrine secretion.  

### OTHER OBSERVATIONS

Fibrosis of the expanded perifollicular adventitia was evident in all of the cases and was most notable in the upper half of the adventitia. A lesser degree of fibrosis was also seen in some of the control cases. In 6 of the 7 patients, varying amounts of dermal mucin were observed near the upper half of the follicle. This finding was confirmed with colloidal iron stains. Control patients did not exhibit this pattern of mucin deposition, although 3 had mild mucin deposition that was limited to the papillary dermis.

Varying numbers of mast cells were also found in the upper dermal infiltrates in all patients with FFD; these were perifollicular, perivascular, and interstitial. Mast cells were also seen in all of the control patients, but these were scant and not as prominently seen as in the patients with FFD.

### COMMENT

The traditional diagnostic criteria for FFD are not specific because these features were found commonly in...
cells are not peri-infundibular or periductal in distribution. The xanthomatous eruptive xanthoma is characterized by other features such as free (extracellular) lipid and neutrophils, that aid in distinction from FFD. In instances of diagnostic ambiguity, serum lipid testing could be pursued to resolve the differential diagnosis.

The differential diagnosis also includes perifollicular granulomatous lesions, including the full spectrum of granulomatous perifolliculitis and rosacea. The character of epithelioid histiocytes in a granulomatous infiltrate differs from that of the foamy histiocytes in FFD. Multinucleate histiocytes may also be prominent in granulomas, and this feature was not prominent in our cases.

Our study revealed several new findings, such as perifollicular mucin, adventitial fibrosis, and increased mast cell density, that can be used as clues to the diagnosis of FFD. These features have been mentioned in past works, but curiously these are not mentioned in standard textbook descriptions of FFD.

Our failure to corroborate the value of 3 findings (the retention vesicle, cornoid lamella–like parakeratosis, and vacuolar change) does not necessarily imply that these features do not exist. We believe that many of the histopathologic changes of FFD are focal in space, time, or both. They may be so focal that even level sections fail to demonstrate them. In addition, some changes may occur transiently in lesional evolution and, thus, are not present when a biopsy specimen is obtained. The variability in frequency and degree of expression of various features may be explained by this.

The pathogenesis of FFD remains a subject of debate. The cause remains unknown, and histopathologic studies have not shed full light in this arena. Ackerman and Mone17 question the concept of apocrine miliaria and postulate that FFD is primarily a defect of infundibular keratinization. The finding of dyskeratotic cells fits with this theory but is not firm evidence of a defect in keratinization. The prominence of mast cells in the infiltrate of FFD may also hold pathogenetic significance and may be interrelated with the histiocytic infiltrate because mast cells are also found coupled with histiocytes in atherosclerotic plaques.18

Our immunoperoxidase stains failed to show staining of histiocyte cytoplasm, suggesting that there was no definite uptake of apocrine secretion by the foam cells. The PAS-D staining yielded a similar result. We hoped that special stains would confirm that the foam cells contained phagocytosed apocrine debris, but this proved not to be the case. Perhaps digestion of the secretion by macrophage enzymes precluded a positive result.

In conclusion, our study shows that traditional attributes of FFD are not specific. A retention vesicle is generally difficult to find, even in level sections. Traditional histopathologic criteria provide little help in the diagnosis of this condition. In contrast, our study confirms that perifollicular foam cells are distinct, easily recognizable, and frequently seen. The finding appears to be relatively consistent and specific for FFD. We contend...
that peri-infundibular and periductal xanthomatized cells represent a hallmark of FFD.

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REFERENCES


