Perifollicular Xanthomatosis as the Hallmark of Axillary Fox-Fordyce Disease

An Evaluation of Histopathologic Features of 7 Cases

Adolfo B. Bormate Jr, MD; Philip E. Leboit, MD; Timothy H. McCalmont, MD

Background: Fox-Fordyce disease (FFD) or apocrine miliaria is a rare condition typically composed of skin-colored follicular papules in apocrine skin, most commonly involving the axillae and areolae of postadolescent women.1 The histopathologic features are traditionally characterized as follicular plugging with associated infundibular acanthosis, parakeratosis, and spongiosis, coupled with a nonspecific infiltrate.2 The so-called sweat retention vesicle has been reputed to be the singular diagnostic feature.3 Although the clinical features of FFD are relatively characteristic,4,5 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.6 However, this approach is not amenable to use in routine diagnostic work.

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.1 The histopathologic features are traditionally characterized as follicular plugging with associated infundibular acanthosis, parakeratosis, and spongiosis, coupled with a nonspecific infiltrate.2 The so-called sweat retention vesicle has been reputed to be the singular diagnostic feature.3 Although the clinical features of FFD are relatively characteristic,4,5 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.6 However, this approach is not amenable to use in routine diagnostic work.

Recently, Boer4 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.9 Historically, Osment,10 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
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 tips of a basal cell carcinoma reexcision, the tips of an excised axillary melanocytic nevus, a follicular infundibular cyst, a case of axillary follicular hyperplasia, 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.

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**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 squamitization 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 supplicative 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 peri-
ductal areas. In addition, the HS specimens had a much
denser mixed-cell infiltrate in the lower dermis and sub-
cutis, 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 dem-
strate the PAS-positive, diastase-resistant material typi-
cally seen in apocrine secretion.11

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 ob-
erved near the upper half of the follicle. This finding
was confirmed with colloidal iron stains. Control pa-
tients 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.

The traditional diagnostic criteria for FFD are not spe-
cific because these features were found commonly in

Table 2. Histopathologic Findings in 7 Female Patients With Fox-Fordyce Disease

<table>
<thead>
<tr>
<th>Histopathologic Findings</th>
<th>Patient No.</th>
<th>Total No. of Patients Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditionally described features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilation of infundibulum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hyperkeratosis of infundibulum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Parakeratosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spongiosis of infundibulum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vesicle within epithelium of infundibulum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphocytes and histiocytes in infiltrate</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Recently described features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornoid lamella-like parakeratosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskeratotic cells in the infundibulum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular alteration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foam cells surrounding infundibulum and/or duct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perifollicular adventitial expansion</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Perifollicular adventitial fibrosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased perifollicular dermal mucin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mast cells in infiltrate</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: +, present; −, absent.

Table 3. Frequency of Features Observed in Level Sections
of Female Patients With Fox-Fordyce Disease

<table>
<thead>
<tr>
<th>Features</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditionally described features</td>
<td></td>
</tr>
<tr>
<td>Dilation of infundibulum</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Hyperkeratosis of infundibulum</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Parakeratosis</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Spongiosis of infundibulum</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Vesicle within epithelium of infundibulum</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes and histiocytes in infiltrate</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Recently described features</td>
<td></td>
</tr>
<tr>
<td>Cornoid lamella-like parakeratosis</td>
<td>0</td>
</tr>
<tr>
<td>Dyskeratotic cells in the infundibulum</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Vascular alteration</td>
<td>0</td>
</tr>
<tr>
<td>Foam cells surrounding infundibulum and/or duct</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Other findings</td>
<td></td>
</tr>
<tr>
<td>Perifollicular adventitial expansion</td>
<td>6 (86)</td>
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Figure 1. Photomicrographs of a patient with Fox-Fordyce disease (FFD) and a control patient. A, Infundibular dilation, hyperkeratosis, parakeratosis, and acanthosis in a patient with FFD (hematoxylin-eosin, original magnification × 200). B, Similar features of hidradenitis suppurativa in a control patient (hematoxylin-eosin, original magnification × 100).
Our control tissue. The elusive retention vesicle, reputed to be a diagnostic hallmark, was not found with certainty in any of our cases. Our study illustrates the difficulty in rendering a specific diagnosis based solely on traditional criteria. With respect to more recently characterized criteria, we were unable to confirm the validity of some of the proposed attributes. For example, infundibular dyskeratotic cells are a nonspecific finding that can be seen in other axillary inflammatory conditions; they are also an infrequent and, thus, insensitive finding.

Our study confirmed that perifollicular and periductal foamy histiocytes represent a sensitive and specific means to recognize FFD. We are unaware of other axillary diseases in which this distinctive alteration can be found. Our study clearly demonstrates that FFD can be readily distinguished from HS.

Various types of xanthomas have been reported to affect the axilla, including flexural plane xanthoma, 12 xanthoma disseminatum, 13 and verruciform xanthoma. 14 Although various xanthomas can be considered in the differential diagnosis of FFD, typically the xanthomatous cells are not peri-infundibular or periductal in distribution. Pirozzi and Gross 15 reported a case of perifollicular xanthomatosis that was claimed to be a manifestation of eruptive xanthoma. 16 The clinical lesions involved the thighs and buttocks but not the axilla. In our experience, the foam cells in eruptive xanthoma do not preferentially involve the peri-infundibular and periductal areas. Eruptive xanthomas are 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, 5,10 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 through the tissue 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 Mones 17 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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Author Contributions: Drs Bormate and McCalmont had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Leboit and McCalmont. Acquisition of data: Bormate, Leboit, and McCalmont. Analysis and interpretation of data: Bormate, Leboit, and McCalmont. Drafting of the manuscript: Bormate and Leboit. Critical revision of the manuscript for important intellectual content: Leboit and McCalmont. Administrative, technical, and material support: Leboit and McCalmont. Study supervision: Leboit and McCalmont.

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Additional Contributions: Beth S. Ruben, MD, identified 1 of the cases.

REFERENCES


