

# The Cytology of Pancreatic Foamy Gland Adenocarcinoma

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## Abstract

All cell block specimens from pancreatic fine-needle aspirations (FNAs) obtained between January 1, 2002, and June 30, 2003, were reviewed for foamy gland adenocarcinoma (FGA). All smears from these cases were reviewed for cytologic features, including those previously noted in conventional pancreatic adenocarcinoma.

Fifty-two cell block specimens showed adenocarcinoma. Of these, 12 (23%) showed histologic features of FGA. This pattern predominated in 6 cases and was present focally in 6 cases. Although there were relatively low nuclear/cytoplasmic (N/C) ratios, other features of adenocarcinoma were present universally, including loss of cohesiveness, nuclear overlap or loss of “honeycomb” architecture, anisonucleosis (>4 to 1), irregular nuclear contours, prominent nucleoli, and atypical chromatin. Background necrosis was present in 8 cases. Distinct cell borders were present in 9 cases, and foamy cytoplasm was present in all cases.

Pancreatic FGA is a recently described histologic pattern of pancreatic adenocarcinoma. It is not uncommon, and we identified the pattern, at least focally, in 23% of our FNA cell blocks. Although cytologic samples show low N/C ratios, most cytologic features of conventional pancreatic adenocarcinoma are present, and the diagnosis presents little additional difficulty.

The use of endoscopic ultrasound (EUS) has facilitated sampling of pancreatic lesions by fine-needle aspiration (FNA).<sup>1-5</sup> Although the features of usual pancreatic ductal adenocarcinoma (PDA) have been well described, occasional cases might present diagnostic challenges.<sup>6-9</sup> The foamy gland pattern of PDA (foamy gland adenocarcinoma [FGA]) is a recently described histologic pattern characterized by cells with abundant clear, “microvesicular” cytoplasm; basally located, irregular, hyperchromatic nuclei; and a brush border–like zone created by apparent apical cytoplasmic condensation.<sup>10</sup> The pattern seems to have no clinical or biologic relevance in and of itself; however, owing to its somewhat bland appearance, it can present diagnostic challenges histologically, especially with small biopsy specimens. To assess whether these same difficulties affect cytologic interpretation, we searched for all cases of FGA present in cell block sections from pancreatic FNA at our institution. We then evaluated the cytologic features of 12 consecutive cases.

## Materials and Methods

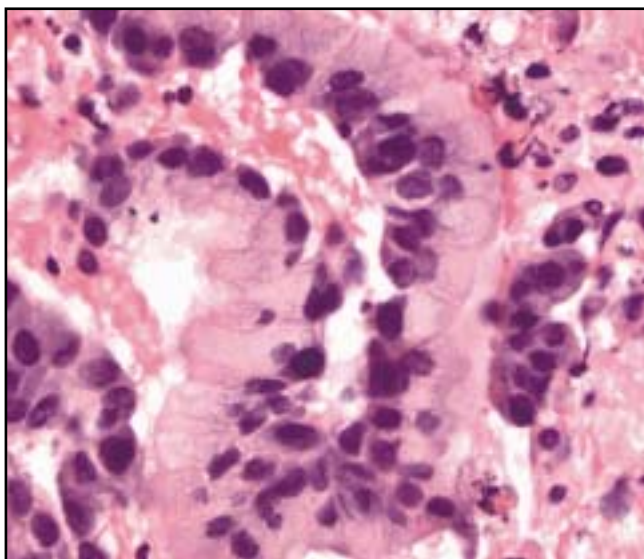
EUS was performed by the usual methods. Pancreatic FNA was performed with 22- and 25-gauge needles. Air-dried, rapid Romanowsky–stained slides; ethanol-fixed, Papanicolaou-stained slides; and formalin-fixed, paraffin-embedded cell blocks were prepared at the discretion of the pathologist attending the procedure (E.B.S., R.H.B., S.M.D., or M.W.S.). Cell blocks were made by permitting aspirated material to clot on a slide and then scraping it into 10% buffered formalin. This material then was

processed by routine histologic methods, and H&E-stained sections were made.

All slides from pancreatic FNA cell blocks made between January 1, 2002, and June 30, 2003, were reviewed. All cases with the histologic features of FGA were identified (criteria used were those described by Adsay et al<sup>10</sup> and included all of the following: cells with abundant clear microvesicular cytoplasm; basally located, irregular, hyperchromatic nuclei; and a brush border–like zone created by apparent apical cytoplasmic condensation). It was noted whether the foamy gland pattern predominated (>50% of total malignant tissue) or was a minor component of the overall histologic features (<50% of total malignant tissue). All cytologic slides from cases with FGA were reviewed for cytologic features of conventional PDA, including the following: (1) loss of “honeycomb” architecture or nuclear overlap, (2) anisonucleosis (>4 to 1), (3) irregular nuclear contours, (4) prominent nucleoli, (5) clumped chromatin, (6) background necrosis, and (7) cellular discohesion. Foamy cytoplasm, nuclear/cytoplasmic ratios, and the presence of prominent cytoplasmic borders also were noted.

## Results

On review, 52 cases of PDA were identified in cell block preparations from pancreatic FNAs, representing 17% of the total pancreatic FNAs (n = 305) and 57% of the total cases diagnosed as PDA (n = 91) at our institution. Twelve of these (23%) showed histologic features, at least focally, of FGA. In 6 cases, this pattern predominated, whereas in the other 6, the pattern was present focally **Image 1**.



**Image 1** Foamy gland adenocarcinoma. Cell block preparation showing typical features of this pattern (H&E, ×400).

The mean ± 1 SD age of the patients with the foamy gland pattern of adenocarcinoma was 69.3 ± 9.1 years. There were 4 men and 8 women. Cytologic features of conventional PDA were present in all cases and are summarized in **Table 1**, **Image 2**, **Image 3**, and **Image 4**.

## Discussion

The diagnosis of pancreatic adenocarcinoma portends a poor prognosis regardless of whether the patient is to undergo pancreatoduodenectomy.<sup>11</sup> Because the diagnosis implies likely death from disease and the possibility of a difficult and unpleasant surgical procedure, cytopathologists are wary when making the diagnosis using FNA or brush specimens. Possibly for this reason, the specificity of the diagnosis of PDA by FNA is very high.<sup>1,4,8,12-18</sup>

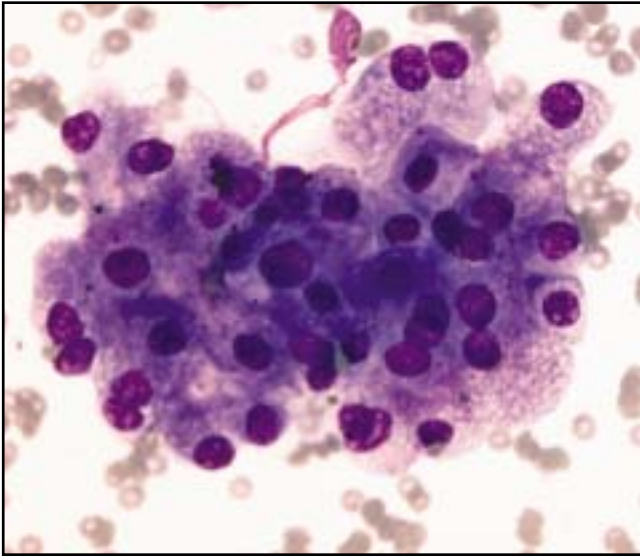
The sensitivity of pancreatic FNA for the diagnosis of PDA also is relatively good: 70% to 80% of cases will be recognized by FNA.<sup>1,4,8,12-18</sup> A recent study investigating false-negative diagnoses found that most of these were due to sampling issues.<sup>4</sup> This finding, together with the relatively high sensitivity and specificity, suggests that despite some of the literature, there is little actual cytologic overlap between benign and malignant disease and that the diagnosis might cause the experienced cytopathologist little difficulty when adequate sampling is achieved.

One of the problems that might exist, however, is the relative infrequency with which the pancreas is sampled by FNA at many institutions. EUS allows for somewhat cheaper and possibly easier sampling of pancreatic lesions while at the same time permitting both image-based and tissue staging of disease. For these reasons, EUS is becoming the most common method of sampling the pancreas and might result in pathologists being confronted with an increasing number of pancreatic cytology specimens. At our institution (a medium-sized municipal hospital), the development of an

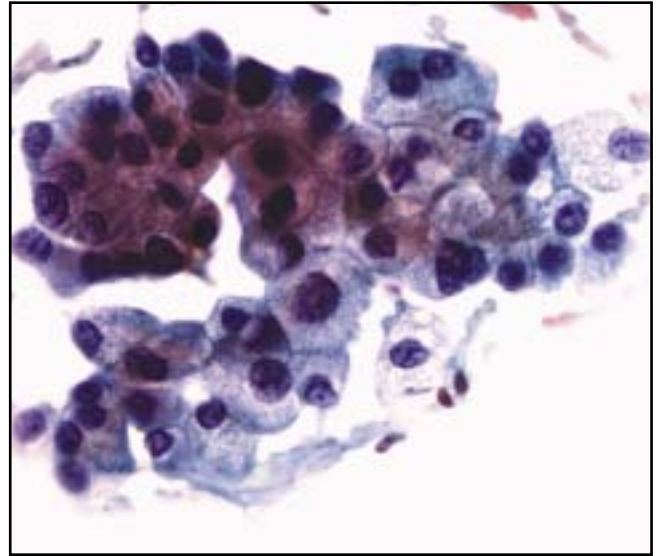
**Table 1**  
Cytologic Features of Pancreatic Foamy Gland Adenocarcinoma

Cytologic Feature	Prevalence in 12 Cases
Nuclear overlap or loss of “honeycomb” architecture	12
Loss of cohesiveness	12
Anisonucleosis (>4 to 1)	12
Irregular nuclear contours	12
Prominent nucleoli	11
Clumped chromatin	11
Background necrosis	8
Prominent cell borders*	9
Presence of foamy cytoplasm*	12
Low nuclear to cytoplasmic ratio (<1 to 3)*	12

\* These features of foamy gland adenocarcinoma were present focally in 6 of 12 cases.



**Image 2** Foamy gland adenocarcinoma. Epithelial cell groups with low nuclear/cytoplasmic ratios, foamy cytoplasm, moderate anisonucleosis, and loss of "honeycomb" architecture (rapid Romanowsky,  $\times 400$ ).

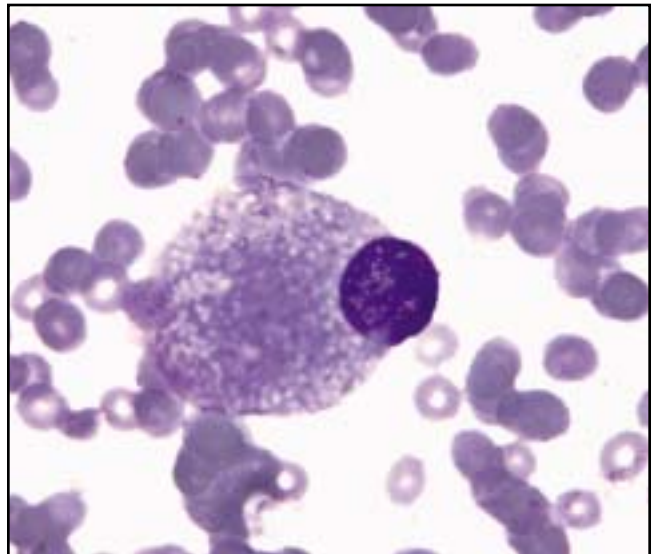


**Image 3** Foamy gland adenocarcinoma with the same features as in Image 2. Note also the well-demarcated cell borders, clumpy chromatin with prominent nucleoli, and irregular nuclear contours (Papanicolaou,  $\times 400$ ).

active EUS service has made PDA the most common malignant diagnosis made by our pathologists.

The qualitative FNA cytologic features that permit the diagnosis of PDA have been well discussed and investigated in depth.<sup>6-9</sup> They include anisonucleosis, nuclear overlap or loss of "honeycomb" architecture, increased nuclear size, irregularity in the nuclear contour, prominent nucleoli, clumped chromatin, cellular discohesion, background necrosis, and the presence of mitotic figures. Undoubtedly, some features are more common than others, and some features have more diagnostic usefulness than others. This has resulted in some authors publishing formulaic methods for diagnosis that might or might not be useful in general practice.<sup>8</sup> Some features of malignancy might be more or less prominent depending on the method used to prepare the slides (eg, air-dried smears, alcohol-fixed smears, liquid-based collection).

Quantitative issues regarding the diagnosis of PDA have not been well discussed. As mentioned, limited sampling seems to be the most common reason for false-negative diagnoses. We have encountered cases that on review show predominantly changes of chronic pancreatitis or simply benign pancreas or gastrointestinal epithelium with rare or even single groups of atypical epithelial cells that show features that generally would be considered consistent with PDA. In these cases, we have been forced to make descriptive diagnoses and suggest clinical follow-up and possibly rebiopsy. We believe this to be especially prudent because pancreatic intraepithelial neoplasia might show features identical to those of PDA and, as yet, has an unknown prevalence and natural history.<sup>19</sup>



**Image 4** Foamy gland adenocarcinoma. Single cell with low nuclear/cytoplasmic ratio and foamy cytoplasm (rapid Romanowsky,  $\times 1,000$ ).

The cytologic features of PDA variants also have been described, including anaplastic, adenosquamous, and mucinous (although most pancreatic mucinous adenocarcinomas actually might be invasive intraductal papillary mucinous neoplasms) carcinoma.<sup>5,20-29</sup> In general, these variants present little problem for the cytopathologist regarding diagnoses because some variants are familiar from other sites (eg, adenosquamous and mucinous), while others have an



obviously malignant appearance with a somewhat limited differential diagnosis (eg, anaplastic carcinoma).

FGA is a recently described pattern, however, and because histologically it can appear deceptively bland, we wondered whether it would pose diagnostic difficulties for the cytopathologist. The histologic features have been mentioned, but the features most likely related to its bland appearance are its low nuclear/cytoplasmic ratios, its abundant foamy cytoplasm, and its often basally located, somewhat small, wrinkled nuclei. Although the cases were shown in the original description to present some difficulty histologically, the pattern was not believed to be a true separate entity because it often was present with more "traditional-appearing" PDA and shared clinical and molecular features with cases of PDA that lacked the foamy gland pattern.<sup>10</sup>

All the cases we were able to identify in our cell block specimens originally were diagnosed as adenocarcinoma, suggesting to us that the diagnosis had not caused much interpretive difficulty. The reasons for this might be 2-fold. First, in half the cases in which we identified this pattern, more typical PDA actually was the dominant pattern. Second, when assessed, the cytologic features associated with conventional PDA were present almost universally. It also should be noted that background mucus is not present in these cases because histologically and histochemically these are not mucinous tumors.<sup>10</sup> Occasionally in the literature, one encounters the term *secretory adenocarcinoma* used synonymously with mucinous adenocarcinoma associated with images closely resembling our material.<sup>30</sup> (There also is a published photomicrograph of a pancreatic adenocarcinoma originally interpreted as benign and then, on review, as "suspicious" that appears to have a foamy gland pattern).<sup>16</sup>

The almost universal presence of conventional PDA features in our cases initially might seem surprising. However, given the prevalence of the pattern (23% of our cases [12/52]), it seems likely that if this pattern had created a diagnostic dilemma, it would have been noted previously. Thus, the prevalence of this pattern in pancreatobiliary adenocarcinomas might explain why the nuclear/cytoplasmic ratio is, in general, not an important criterion for the diagnosis.

Most articles discussing the sensitivity and specificity for FNA diagnosis of PDA have been retrospective, using the surgical specimen as the "gold standard" for the diagnosis. Because specimens that are resected likely represent a biased population, it is difficult to determine the true sensitivity and specificity of FNA. As larger prospective studies obtain information, this may be better described. Stelow et al<sup>31</sup> have shown that optimal specimen handling often permits the preparation of both smears and cell blocks. Because PDA frequently is a fatal disease for which many patients never undergo surgical resection, cell blocks might become the

new histologic gold standard of diagnosis. Furthermore, sampling by FNA might yield more neoplastic tissue than sampling by other methods because it selectively samples malignant epithelial cells from dense reactive stroma. This might even be more important as we become more able to apply various molecular tests to samples. Currently, it is reassuring to know that most PDA and its variants and patterns, including FGA, have cytologic features that are diagnostic by FNA.

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