Apocrine Carcinoma of the Breast

A Morphologic and Immunocytochemical Study

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The mode of recognition and hence the frequency of apocrine differentiation in breast carcinomas, assessed on purely morphologic grounds, remains uncertain. One hundred consecutive cases of breast carcinoma were studied in order to establish the incidence of this type of tumor. With the use of an immunocytochemical method for the detection of GCDFP-15, a protein present in apocrine epithelium and in the fluid of tension cyst of the breast, the presence of apocrine differentiation was confirmed in 4 cases initially diagnosed as apocrine carcinomas on histologic grounds. Eight additional cases contained immunoreactive cells: 1 contained 10% of positive cells scattered throughout the tumor, and the other 7 cases were only focally positive. In 4 of these latter cases positive staining was confined to the *in situ* component. The ultrastructural findings in 2 cases of apocrine carcinoma are discussed in order to link the morphologic features for recognizing this tumor type and the presence of the antigenic apocrine marker. (Am J Pathol 1986, 123:532–541)

THE NOTABLE discrepancies in the literature concerning the morphologic features of apocrine carcinoma of the breast have recently been stressed.[1]

The definition and consequently the reported incidence of these tumors varies considerably. McDivitt et al[2] included this entity under the group of "relatively rare carcinomas."

Frable and Kay,[3] in a survey which covered a 16-year period, stated that apocrine carcinoma accounts for 1% of mammary carcinomas. A lower incidence (0.3–0.4% of cancers) was suggested by Azzopardi[4] if carcinomas of the breast are considered "apocrine" only if they are composed largely of easily recognizable apocrine-type epithelium.

Fisher et al,[5] in their study of 1000 cases of breast carcinoma, did not find any pure cases considered worthy of the designation of apocrine carcinoma. They stated that "only 2.2 per cent of carcinomas contained varying numbers of cells with oxyphilic granular cytoplasm remiscent of those composing apocrine glands." In addition, they were inclined to consider that these changes represented oxyphilic, rather than apocrine metaplasia, a view previously held by Hamperl.[6] Similarly, Bonser et al,[7] who gave an incidence of 14.5%, were not convinced that "pink cell carcinomas" could be equated with apocrine metaplasia. More recently, Haagensen et al[8] suggested that the basic criteria for a diagnosis of apocrine carcinoma of the breast should include acidophilia of the cytoplasm, large size of the neoplastic cells, and cytoplasmic "snouts" projecting into the lumina of glands. Using these criteria, they found that no fewer than 60% of carcinomas studied had apocrine features.

These very varying views emphasize the lack of objective diagnostic criteria for reliable light-microscopic identification of apocrine carcinomas.

Ultrastructural studies have also failed to establish reliable diagnostic criteria. Roddy and Silverberg[9] concluded, on the basis of ultrastructural analysis of the case of apocrine carcinoma, that the tumor cells had some features of apocrine epithelium but also resembled oncocytes. Ahmed[10] stated that there was ultrastructural resemblance between the cells of apocrine carcinoma

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of the breast and the cells of the normal apocrine glands of the skin.

In an ultrastructural study of 6 cases of apocrine carcinoma of the breast, which constituted 0.4% of their cases, Mossler et al[11] found that the neoplastic elements possessed an extensive rough endoplasmic reticulum and numerous (400–600 μ) osmiophilic, membrane-bound granules. Ultrastructural study of a case of invasive lobular carcinoma with immunologic evidence of apocrine differentiation[1] showed that only 5% of neoplastic elements contained osmiophilic membrane-bound granules, whereas most of the cells contained numerous empty vesicles, a prominent Golgi apparatus, and large mitochondria with incomplete cristae.

Recently Mazoujian et al,[12] using an immunoperoxidase technique, were able to localize an apocrine gland-related antigen to specific tissue sites. This antigenic marker, called gross cystic disease fluid protein (GCDFP-15), is a unique glycoprotein initially isolated from the fluid of the breast cysts. It is present in apocrine glands at all sites, including the apocrine glands of the axilla and metaplastic apocrine epithelium in the breast. With the development of this marker, a more objective diagnostic criterion was introduced which enabled Mazoujian et al[12] to demonstrate that 14 of 30 breast carcinomas they studied were of apocrine type, including 12 of 16 cases diagnosed as apocrine carcinomas on morphologic grounds.

More recently, with the use of morphologic as well as immunologic criteria, the spectrum of apocrine carcinomas of the breast has been broadened by the demonstration of apocrine changes in certain cases of lobular carcinoma, both *in situ* and invasive.[1]

In an attempt to establish more reliable and objective criteria of apocrine differentiation in breast carcinomas, we compared the histologic and immunocytochemical findings in 100 unselected cases of mammary carcinoma. Two additional cases were studied by electron microscopy. The results constitute the basis of this paper.

Materials and Methods

Selection of Cases

A series of 100 consecutive case of invasive carcinoma of the breast was studied. Sixty cases were from the files of the Department of Pathology, University of Bologna, and 40 cases were from the files of the Imperial Cancer Research Fund Breast Cancer Unit at Guy's and New Cross Hospitals, London.

Estrogen receptor (ER) assay was carried out on all the cases with the use of the dextran-charcoal radioimmunologic technique. The 60 cases from Bologna were assayed in the Istituto di Cancerologia of Bologna University, and an international standardized procedure was used.[13] In 25 of these cases the radioimmunologic content of progesterone receptors (PR) was also assayed. Both of these assays were performed on the 40 cases from London at the Imperial Cancer Research Fund Laboratories.

The age of the patients, the size of the tumors, and the lymph node status of all patients were also recorded.

Histology

All cases were reviewed and classified by one of us (V.E.). The tumors were graded according to Bloom and Richardson.[14]

Immunocytochemistry

In the immunocytochemical study, the immuno-β-galactosidase technique[15] was used.

GCDFP-15 antiserum (kindly donated by Dr. D. E. Haagensen, Boston), diluted 1:5000, was the primary antiserum employed. This is the same antiserum as was used by Mazoujian et al[12]; its specificity was extensively discussed by Haagensen and co-workers.[8]

Controls included normal rabbit serum as a primary antiserum. In addition, tissues from cases of cystic disease of the breast containing apocrine epithelium were stained with each batch of slides tested for the presence of GCDFP-15.

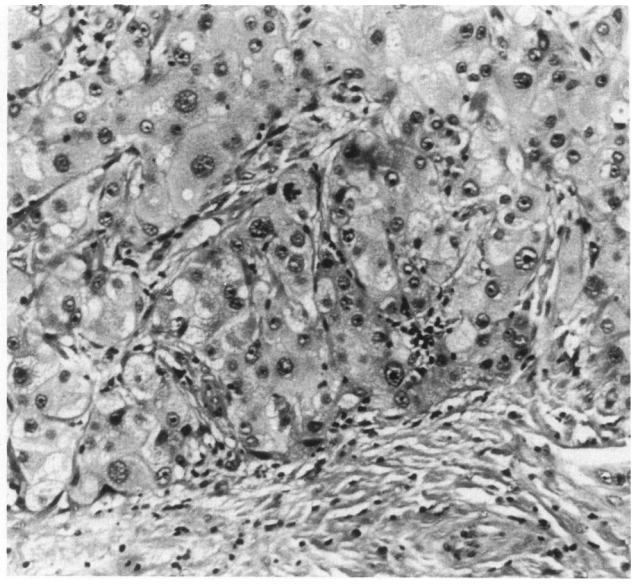
The results of the immunologic staining were assessed by two observers independently (G.B. and V.E.); and where discrepancies occurred, the cases were classified by mutual agreement.

Cases were classified as follows: Group A, cases in which positive staining was observed in the majority of the tumor cells; Group B, cases in which positive

Table 1—Immunoreactivity for GCDFP-15 in 100 Breast Carcinomas

		Reaction for GCDFP-15		
Type of tumor	Number	A	B	C
NOS	77		6	71
Apocrine	4	4		
Invasive lobular	6			6
Medullary	4		1	3
Mucoid	3			3
Invasive comedo	2		1	1
Invasive cribriform	2			2
Metaplastic	1			1
Carcinoid-like	1			1
Total	100	4	8	88

Group A, positivity in most of the cells; Group B, patchy positivity or diffuse positivity in a minority of the cells; Group C, negative cases.



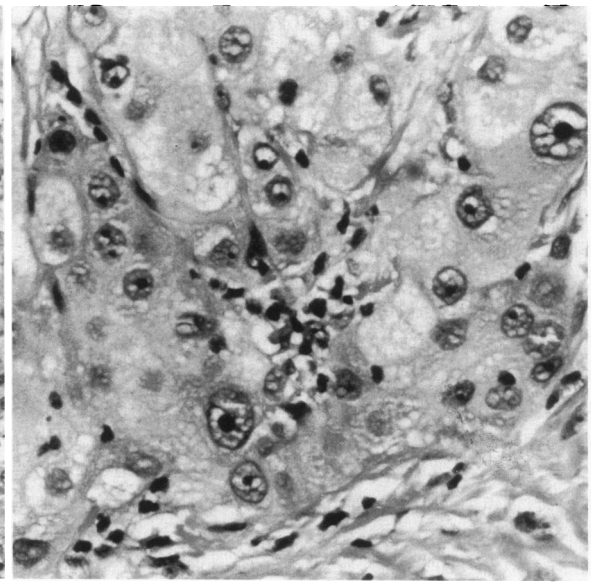


Figure 1—Case 1. The cytoplasm of the neoplastic cells is copious, and the cell margins are distinct. (H&E, × 100) **Figure 2**—At higher magnification, the same case as in Figure 1 displays cells with round nuclei and prominent nucleoli. The cytoplasm is granular and a hint of foaminess is also visible. (H&E, × 350)

staining was confined to one area of the tumor or was present more diffusely in a minority of cells only; Group C, cases which were entirely negative.

Electron Microscopy

Two cases outside the consecutive series were studied by electron microscopy. They were selected because on hematoxylin and eosin (H&E) staining they had histologic characteristics of apocrine carcinomas and showed intense and diffuse positive staining with GCDFP-15 antiserum. The tissue was fixed in Carson's buffered formalin[16] and postfixed in 1% phosphate-buffered osmium tetroxide and then dehydrated and embedded in Epon-araldite mixture. Thin sections were cut with a diamond knife, stained with uranyl acetate and Reynold's lead citrate, and examined in an electron microscope at 80 kv.

Results

As shown in Table 1, 77 tumors were classified as infiltrating duct carcinomas NOS,[17] 6 as lobular carcinomas, 4 as medullary carcinomas, and 3 as mucoid carcinomas.

Four cases were tentatively identified as apocrine carcinoma by the use of Azzopardi's criteria[4]: ie, neoplastic cells with copious, variably granular eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli (Figures 1 and 2). Two tumors were classified as invasive cribriform carcinoma,[18] and 2 cases, as invasive comedocarcinoma in which the majority of the tumor was *in situ* and the invasive component comprised only a small proportion of the tumor. One "metaplastic carcinoma" showed an invasive ductal component merging with a spindle cell component. One tumor with an organoid structure was classified as carcinoidlike.[19]

Immunocytochemistry

Group A: Positive Staining in Most of the Cells (Table 2)

In the 4 cases tentatively identified as apocrine carcinomas on light microscopy, most of the neoplastic cells stained with GCDFP-15 antiserum. Between 60% and 80% of tumor cells were positively stained. Staining was present diffusely within the cytoplasm. In addition,

Table 2—Diffusely Immunoreactive Cases (Group A)

Case	Age (years)	Size (cm)	Grade	LN	% of positive cells	ER (fmol/mg)	ER (fmol/mg)
1	69	2.5	II	0/16	60	18	72
2	64	2.5	III	11/15	Over 80	0	0
3	70	2.5	II	0/12	Over 80	33	0
4	78	2	II	15/15	60	240	60

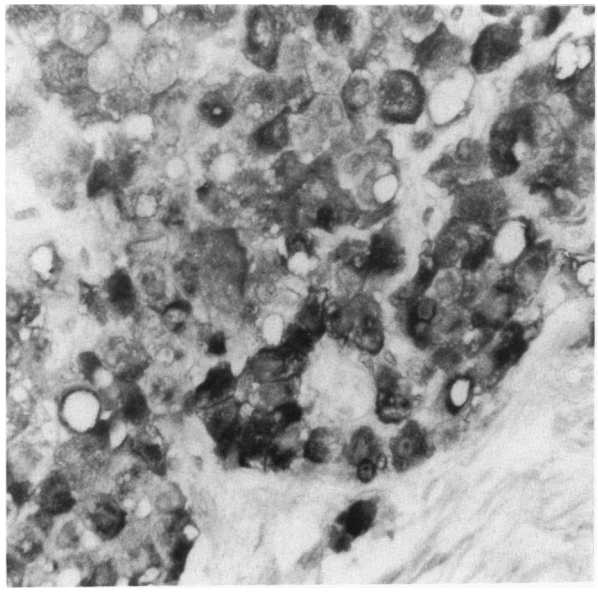


Figure 3—Most of the cells show cytoplasmic positivity. (Anti-GCDFP-15 immuno-β-galactosidase; nuclei slightly counterstained with neutral red, ×200)

several intracytoplasmic lumens (ICLs) also contained immunoreactive material (Figure 3).

Three of this group of 4 cases were Grade 2 tumors, and 1 was a Grade 3 tumor. Most of the neoplastic cells had round, regular nuclei, often with a single prominent nucleolus (in Grade 3 carcinomas the nuclei were less regular). A few tumor cells, however, had nuclei which were intensively hyperchromatic and did not contain visible nucleoli. Mitotic activity was variable from case to case. The cytoplasm was generally abundant, with distinct margins, variably granular, and ranged tinctorially from lightly to deeply eosinophilic.

Group B: Cases With Patchy Positive Staining or Diffuse Staining in a Minority of Cells Only (Table 3)

Eight cases were included in this group. In 1 case (Case 5), while positive cells were present in most areas of the tumor, only about 10% of cells reacted positively. When serial sections were stained alternatively with H&E and by the immunocytochemical method, it was impossible to identify on the routinely stained sections the cells which corresponded to those staining positively with the GCDFP-15 antibody.

In 4 tumors positive staining was confined to the *in situ* component (Cases 6–9). Only part of the *in situ* component stained positively. In 3 cases, the tumor cells which gave a positive reaction differed morphologically from the *in situ* tumor cells, which were unstained (Figure 4). The positive cells were larger, with granular, more eosinophilic cytoplasm, rounded nuclei, and prominent nucleoli. In the fourth case (Case 9) the positive focus was barely visible on the H&E section.

In a further 3 cases (Cases 10–12), positive cells were localized to a focal area of the invasive tumor. The positive cells were easily identifiable on the H&E-stained sections because they were cytologically different from the nonreactive cells. In 2 cases (Cases 10 and 12) the positively staining cells had the same appearance on H&E sections as those already described in the positive *in situ* lesions. In the third case (Case 11), classified as atypical medullary carcinoma,[20] the H&E section showed that the immunocytochemically positive elements corresponded to cells with a distinctly foamy cytoplasm (Figures 5 and 6), very similar to that observed in the apocrine variant of invasive lobular carcinoma described by Eusebi et al.[1]

Group C: Negative Cases

As shown in Table 1, 88 tumors were negative with the immunocytochemical technique. Three of these cases did show some positive staining; but because this was confined to a very few cells (a maximum of 10), they were regarded as essentially negative.

The 6 cases of invasive lobular carcinoma were all negative with the immunocytochemical technique. This is consistent with provious work[1] in which it was found

Table 3—Cases With Lesser Degrees of Immunoreactivity (Group B)

Case	Age (years)	Size (cm)	Grade	LN	Immunocytochemical positivity	ER (fmol/mg)	PR (fmol/mg)
5	58	0.7	II	0/9	10%*	0	ND
6	52	2	II	8/10	Focal, DCIS	79	ND
7	35	1.8	II	0/15	Focal, DCIS	61	ND
8	70	4	II	0/6	Focal, DCIS	39	19
9	78	4.5	Invasive comedo	0/34	Focal, DCIS	9	0
10	75	2	II	2/5	Focal, invasive	523	166
11	39	1.5	Medullary carcinoma	0/21	Focal, invasive	0	38
12	73	1.5	III	2/11	Focal, invasive	30	0

* Diffuse in 10% of cells.
DCIS, ductal carcinoma *in situ*; ND, not done.

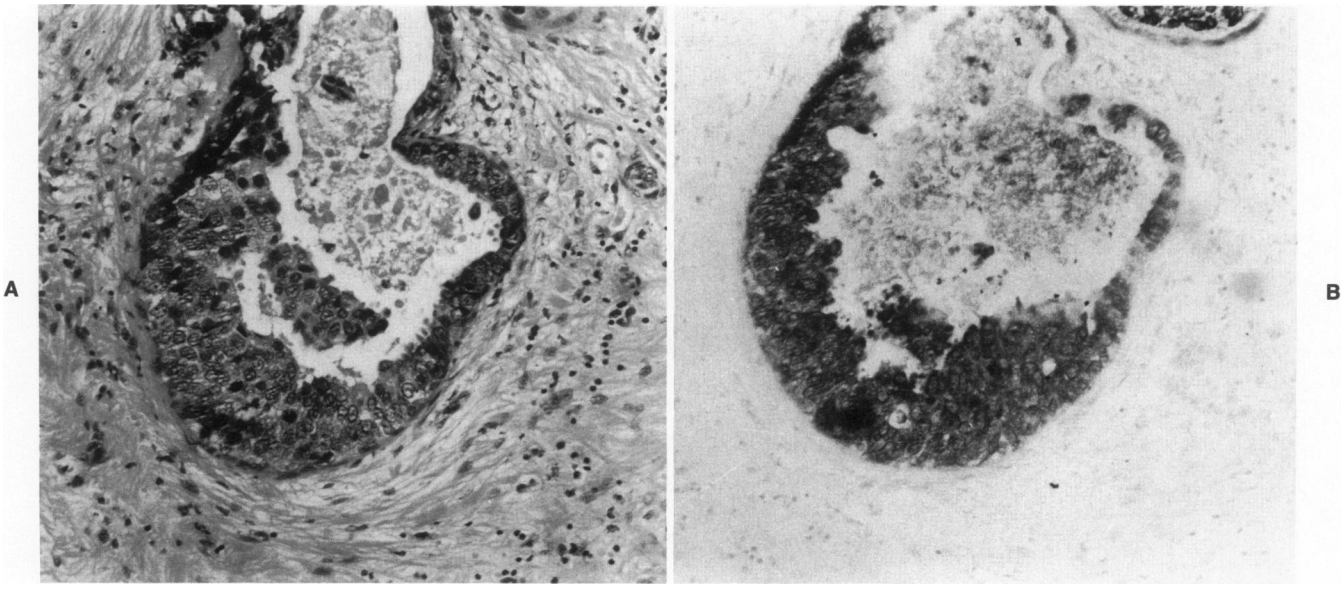


Figure 4—Case 7. This focus of *in situ* duct carcinoma is the only positive area of the neoplastic population. **A**—The cells show eosinophilic granular cytoplasm. (H&E, ×100) **B**—The cells appear intensely stained. (anti-GCDFP-15 immuno-β-galactosidase, ×100)

that the only invasive lobular carcinomas which stained positively for GCDFP-15 were those with histologic features of so-called histiocytoid carcinoma, and no such case was present in this series.

Seven carcinomas NOS which were immunocytochemically negative displayed copious eosinophilic cytoplasm but lacked granularity. The nuclei were variable in shape and contained one to two very small nucleoli.

It is worthy of note that the so-called apocrine snouts present on the luminal aspect of some malignant cells were consistently negative with the immunocytochemical stain. A solitary exception to this was seen in a tumor outside the present series.

Clinical and Other Features

The mean age of the patients was 56.1 (range, 37–84). The mean size of the tumors was 2.1 cm in the longest axis (range, 0.4–7.0 cm). In 43 cases a metastatic de-

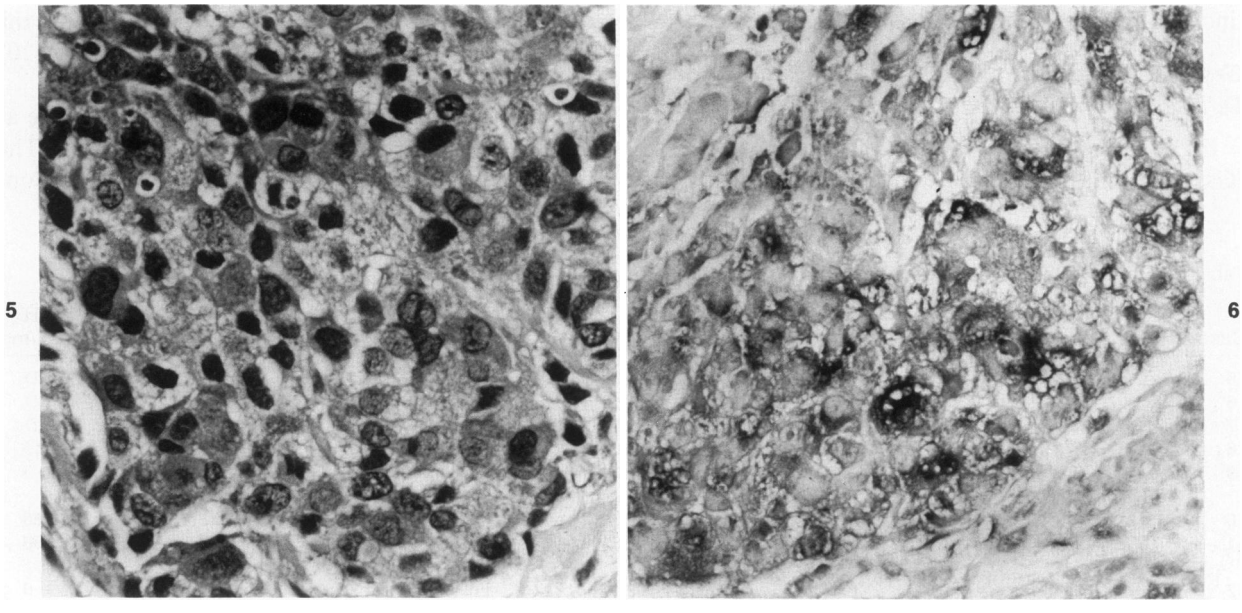
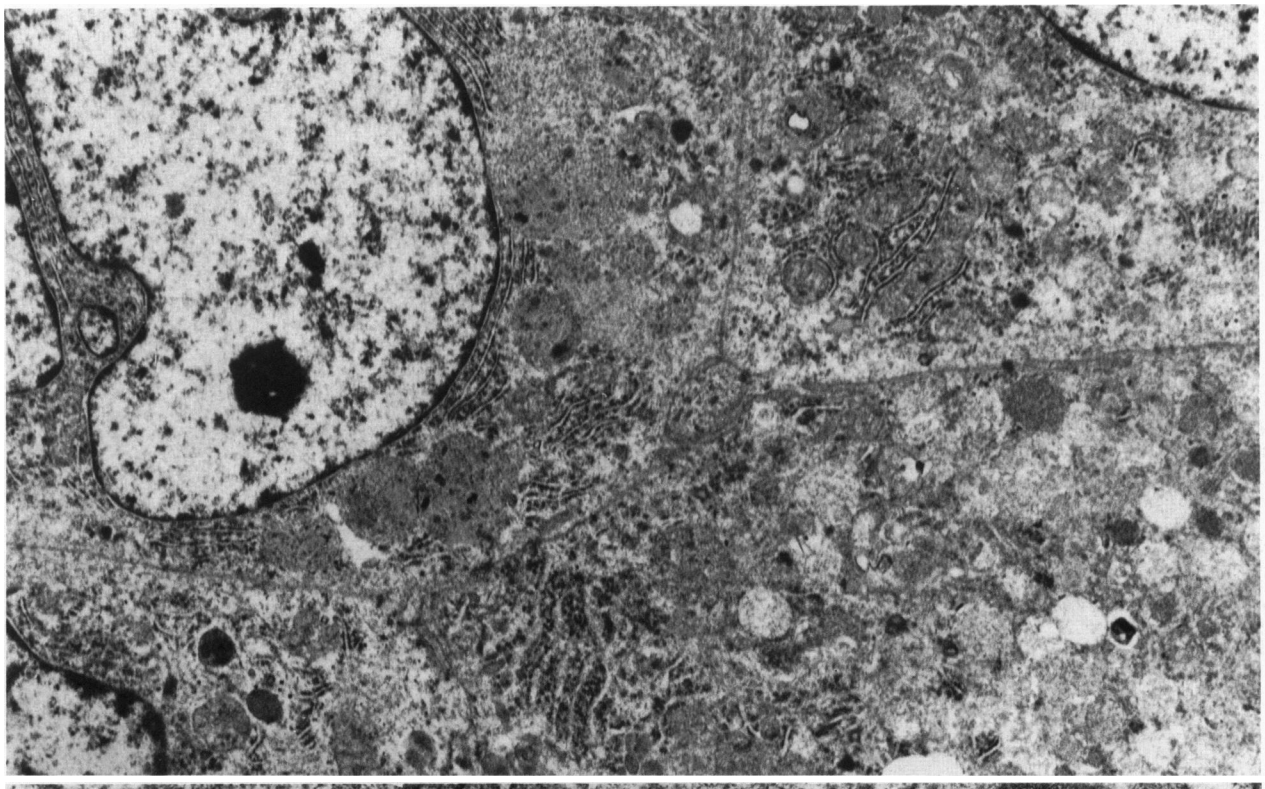


Figure 5—Case 11. Most of the cells of this area display a foamy cytoplasm. (H&E, ×200) **Figure 6**—The same cells as Figure 5 appear intensely immunoreactive. (Anti-GCDFP-15 immuno-β-galactosidase; nuclei slightly counterstained with neutral red, ×200)



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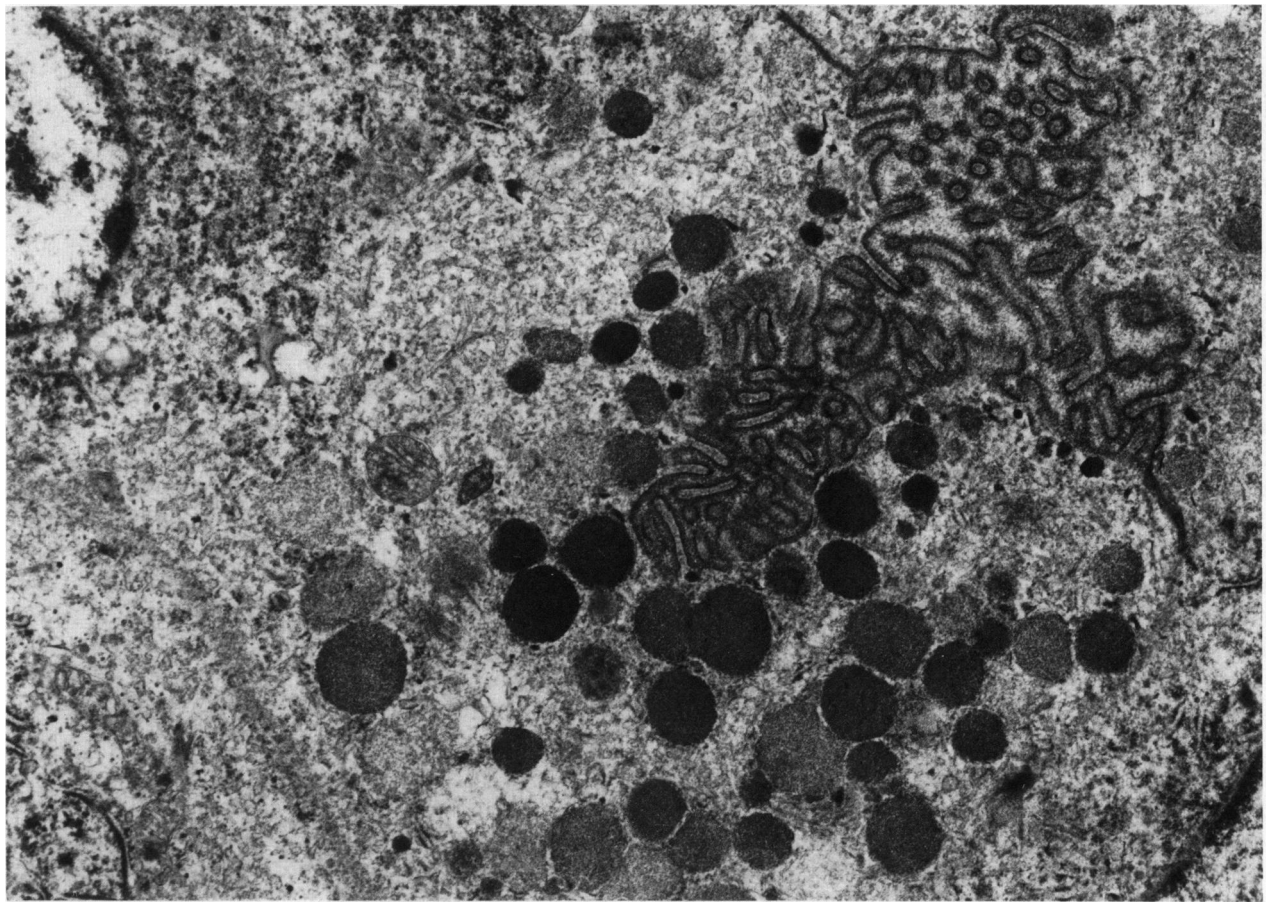

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Figure 7—The neoplastic cells show the cytoplasm rich in organelles and well-defined outlines. Note the paucity of electron-dense granules. (×7200) **Figure 8**—Electron-dense granules, here condensed at a secretory pole of the cell. (×16,500)

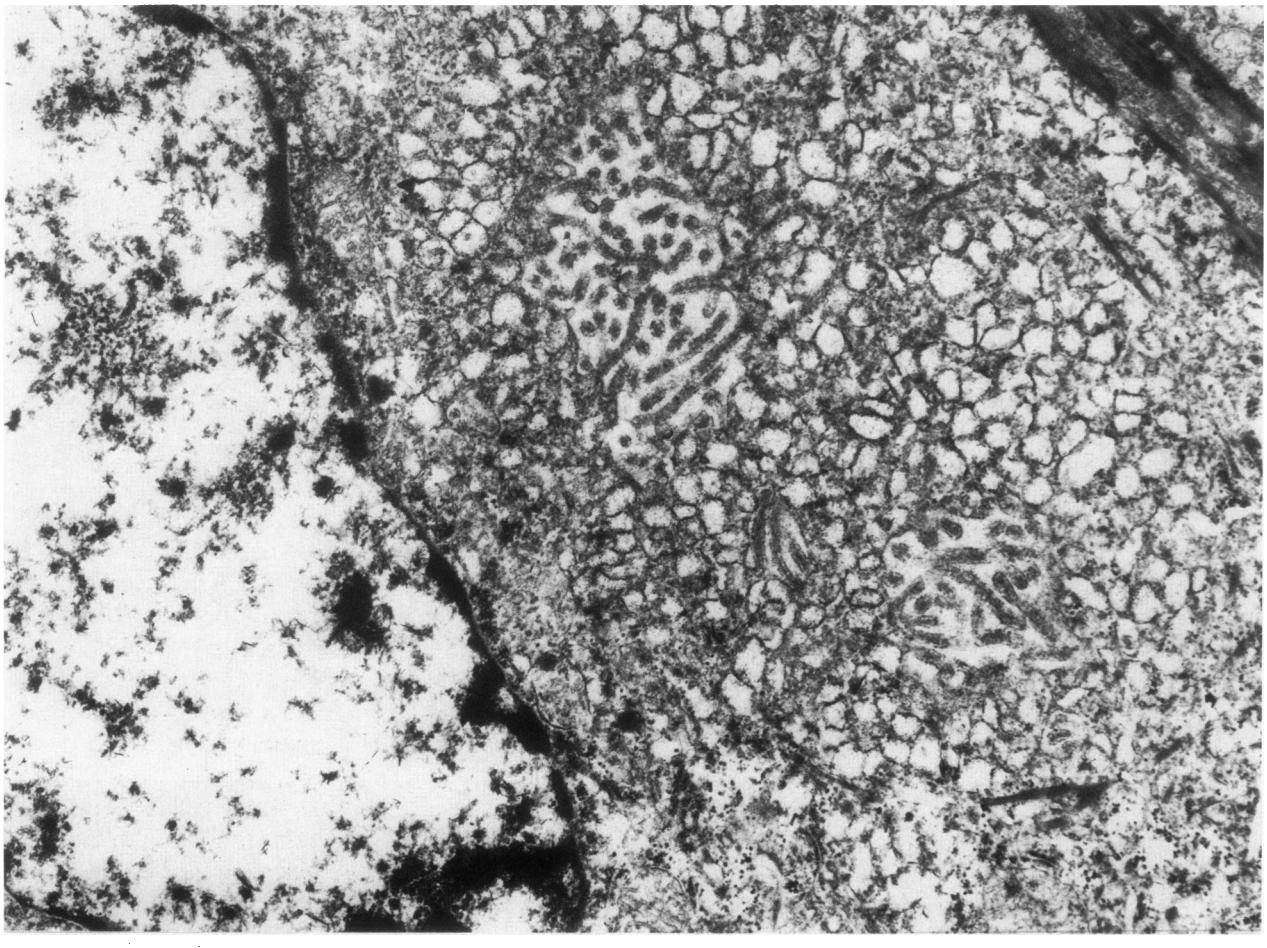

Figure 9—Most of the cytoplasm of this cell is occupied by empty vesicles. Intracytoplasmic lumens with microvilli are also present. (× 16,500)

posit was present in at least one axillary lymph node. Forty-five cases showed uninvolved axillary lymph nodes. In 12 cases no axillary dissection was performed. The ER assay showed the 64% of the cases contained more than 10 fmol/mg protein. Sixty-five cases were also assayed for PR, and 30 cases (46%) contained more than 10 fmol/mg protein.

No statistical differences (chi-square test) were noted when the various clinical and pathologic parameters of the groups of tumors which were positively stained (Groups A and B) were compared with those of the immunologically negative group (C).

Electron Microscopy

The 2 cases studied ultrastructurally showed similar features at both the light- and electron-microscopic levels. In the H&E sections the tumor cells had round nuclei with prominent nucleoli, and their cytoplasm was copious, granular, and showed prominent eosinophilia. The cell margins were well defined. Most of the neoplastic cells appeared immunoreactive for GCDFP-15.

Ultrastructurally, the tumors were composed of large cells with well-defined outlines, cytoplasm rich in organelles, and sometimes ICLs lined by microvilli (Figure 7). A population of cells containing the characteristic cytoplasmic electron-dense membrane-bound granules, similar to those described in previous studies of apocrine carcinomas,[1,10,11] constituted about 10% of the overall neoplastic cell population. These osmiophilic granules, which measured 303–727 nm, were usually randomly scattered in the cytoplasm. The number of granules ranged from only a few per cell to a maximum of 56 (Figure 8). The majority of the neoplastic cells contained numerous empty vesicles of about the same dimensions as the osmiophilic granules. These varied in number, but generally they were abundant and in some cells occupied most of the cytoplasm (Figure 9). Golgi apparatus was prominent, and large mitochon-

dria with incomplete cristae were also seen. The nuclei were rounded, with chromatin condensed against the nuclear membrane, and contained a large nucleolus.

Discussion

In this study of 100 cases of unselected carcinoma of the breast, 12 tumors showed positive staining with GCDFP-15 antiserum by an immunohistochemical technique. In 4 tumors (Group A) 60–80% of the cells stained, but in 8 (Group B) only a minority of the cells were positive.

Mazoujian et al,[12] using the same antiserum at the same dilution employed in this study and an immunocytochemical technique of a similar sensitivity,[15] found that 14 of 30 carcinomas (46%) showed positive staining. This higher percentage of positive cases is probably in part due to an element of selection of the tumors. In their series 16 cases were selected because they showed apocrine features in H&E sections. In addition, 8 cases were pure *in situ* carcinomas. In the present study the number of tumors examined was greater; and, more importantly, the series consisted of unselected consecutive tumors. It would appear that a 12% incidence of positivity of staining with anti-GCDFP-15 antiserum is a more realistic one. Moreover, even this figure includes many cases which showed only very focal positivity.

The 4 tumors of Group A (positive staining in the majority of cells) were selected as composed largely of easily recognizable apocrine epithelium.[4] Tumor cell cytoplasm was copious, variably eosinophilic, and distinctly granular. Most of the nuclei were sharply rounded, contained a large, very prominent nucleolus, and were centrally placed in the cells.

In some breast carcinomas the tumor cells have a copious eosinophilic cytoplasm but lack granularity, and they do not have the nuclear morphologic features described above. While these cases may possibly be exhibiting rudimentary apocrine differentiation, the evidence for regarding such tumors as apocrine is presently inadequate.

Consonant with this interpretation, all 4 tumors regarded tentatively as apocrine on histologic grounds stained diffusely for GCDFP-15 protein in between 60% and 80% of tumor cells. By contrast, the 7 acidophilic tumors lacking cytoplasmic granularity and nuclear characteristics of apocrine carcinomas were negative for GCDFP-15.

Eight other tumors (Group B) showed positive staining with GCDFP-15 antiserum. In 7 cases the staining was focal, and in 1 tumor about 10% of cells scattered throughout the tumor were positive.

In the 7 tumors with focal immunocytochemical staining, this was present in part of the *in situ* ductal component in 4 and in the invasive component in 3 tumors. In 6 of these 7 tumors, there was a corresponding morphologic change in the positively stained foci. Three areas of *in situ* and two of invasive carcinoma contained large granular eosinophilic cells of the type seen as a dominant component in the Group A tumors. A sixth case of atypical medullary carcinoma contained a focus of slightly larger foamy cells, which corresponded to the immunologically reactive area. The case without detectable morphologic change corresponding to the immunoreactive cells contained only a small focus of *in situ* carcinoma with positive staining, but this focus was barely represented in the H&E section.

In 6 of these 7 tumors immunologic positivity was both focal and very limited in amount. In the seventh tumor in Group B (Case 12), slightly more than 50% of the sectional area had the structure of a pleomorphic apocrine carcinoma with more nuclear variability and mitotic activity than the 4 cases in Group A. About one-third of the part of the tumors with an apocrine appearance stained by the immunologic method, demonstrating partial agreement between the two methods. However, the majority of the tumor cells with an apocrine appearance did not stain with the immunologic method, which indicates a lack of complete agreement. This tumor was dominantly apocrine on histologic grounds but not on immunocytochemical grounds.

The eighth case in Group B (Case 5) was exceptional in that immunologic staining was diffusely located but only about 10% of cells were stained. No corresponding morphologic change could be detected in this tumor.

The histologic and immunologic methods for determining apocrine differentiation are largely in agreement in categorizing its presence in individual tumors. Thus, of the 12 tumors which were immunologically reactive, 9 showed histologic apocrine changes. In a tenth tumor, the absence of histologic correlation may have been due solely to the focus in question not being represented in the H&E section. The 2 tumors that constituted genuine exceptions were one with foamy rather than granular cells and Case 5, which contained 10% of immunologically positive cells without histologic changes which could be interpreted as apocrine.

There is less agreement about the identity of individual cells. Apart from the 2 tumors just mentioned in which histologic and immunologic parameters yielded different interpretations, there is other evidence to indicate that the two criteria do not correspond precisely in the assessment of individual tumor cells. In Case 12, only one-third of the part of the tumor ex-

hibiting histologic apocrine change was immunologically reactive. Furthermore, in the 4 Group A tumors where at least 20% of cells were immunologically negative, it was not possible to detect in H&E sections two different cell populations. Therefore, it was not possible to indicate those elements which could correspond to cells which reacted differently with the immunocytochemical method.

It thus appears that while the histologic and immunologic criteria for assessing apocrine differentiation in a tumor are broadly in agreement, the recognition of individual cells by the two methods is not always possible.

The foamy, rather than granular, appearance in the case of the atypical medullary carcinoma is revealing. A similar appearance was seen in 3 of 4 cases of apocrine lobular carcinoma previously reported.[1]

Ultrastructural examination in one of the latter cases showed an abundance of cytoplasmic vesicles of the type and size seen in the 2 cases studied ultrastructurally in the present series. These vesicles appear to be an important electron-microscopic marker of apocrine differentiation in tumors.

Deeply osmiophilic granules, although characteristic of apocrine epithelium, were present in only 5% of tumor cells in the previous study[1] and in 10% of cells of the 2 tumors included in this study. They probably represent the most highly developed marker of apocrine change, present as they are at the luminal pole of benign apocrine epithelium.[22]

Mazoujian et al[21] demonstrated by an immunogold technique that the GCDFP-15 is localized to the ultrastructural vesicles as well as to the osmiophilic granules. The finding of such vesicles and the demonstration of the presence of GCDFP-15 in tumor cells should therefore correspond, and this is indeed the case in our material. Tumor cells with foamy cytoplasm, whether in "histiocytoid" lobular carcinomas[1] or in a focal area of a medullary carcinoma as in this series, may contain abundant vesicles with only a modest number of mitochondria.

On the other hand, the light-microscopic characteristics and, in particular, the cytoplasmic granular eosinophilia, on which a tentative light-microscopic diagnosis of apocrine carcinoma is largely based may well have a different ultrastructural equivalent. It is probably attributable in part to the abundance of mitochondria in the tumor cells, an abundance well documented in apocrine epithelium.[22]

Apocrine carcinomas are mostly variants of ductal carcinoma, while lobular carcinomas more rarely exhibit apocrine differentiation.[1] In lobular carcinomas, apocrine differentiation is usually manifested by the "histiocytoid" type of carcinoma, which is rich in both vesicles and GCDFP-15.

When various clinical, histopathologic, and biochemical parameters associated with tumors that showed positive staining were compared with those of tumors that showed negative staining, there were no statistically significant differences. Mossler et al[11] found an absence of ER activity in their apocrine carcinomas. We were unable to confirm this in our series. Most of the apocrine tumors we studied had ER activity and did not differ in this respect from the common run of breast carcinomas.

The morphologic (light and ultrastructural) criteria outlined, coupled with the immunologic demonstration of GCDFP-15, currently represent the best means of identifying apocrine carcinomas. The present study indicates that, on a submicroscopic basis, vesicles and dense granules appear to correspond to GCDFP-15 content, and there is a suggestion that the mitochondrial content is mainly responsible for the cytoplasmic eosinophilic granularity.

References

1. Eusebi V, Betts CM, Haagensen DE, Bussolati G, Azzopardi JG: Apocrine differentiation in lobular carcinoma of the breast. Hum Pathol 1984, 15:134–140
2. McDivitt RW, Stewart FW, Berg JW: Tumors of the breast, Atlas of Tumor Pathology, Fascicle 2. Washington DC, Armed Forces Institute Pathology, 1968, p 87
3. Frable WJ, Kay S: Carcinoma of the breast: Histologic and clinical features of apocrine tumors. Cancer 1968, 21:756–763
4. Azzopardi JG: Problems in breast pathology, Major Problems in Pathology. Vol 11. London, W.B. Saunders, 1979
5. Fisher ER, Gregorio RM, Fisher B: The pathology of invasive breast cancer. Cancer 1975, 36:1–263
6. Hamperl H: Das sogenannte Schweissdrüsencarcinom der Mamma. Zeitschrift für Krebsforschung 1977, 88:105–119
7. Bonser GM, Dossett JA, Jull JW: Human and Experimental Breast Cancer. London, Pitman Medical, 1961
8. Haagensen CD, Bodian C, Haagensen DE Jr: Breast Carcinoma: Risk and Detection. Philadelphia, W.B. Saunders, 1981
9. Roddy HJ, Silverberg SG: Ultrastructural analysis of apocrine carcinoma of the human breast. Ultrastruct Pathol 1980, 1:385–393
10. Ahmed A: Atlas of the ultrastructure of human breast diseases. New York, Churchill Livingstone, 1978
11. Mossler JA, Barton TK, Brinkhous AD: Apocrine differentiation in human mammary carcinoma. Cancer 1980, 46:2463–2471
12. Mazoujian G, Pinkus GS, Davis S, Haagensen DE Jr: Immunohistochemistry of a gross cyst disease fluid protein (GCDFP-15) of the breast. Am J Pathol 1983, 110:105–112
13. EORTC Breast cooperative group: Revision of the standards for the assessment of hormone receptors in human breast cancer. Eur J Cancer 1980, 16:1513–1515
14. Bloom HJC, Richardson WW: Histological grading and prognosis in breast cancer: A study of 1409 cases of which

359 have been followed for 15 years. Br J Cancer 1957, 11:359–377
15. Bondi A, Chieregatti G, Eusebi V, Fulcheri E, Bussolati G: The use of β-galactosidase as a tracer in immunocytochemistry. Histochemistry 1982, 26:153–158
16. Carson FL, Martin JH, Lynn JA: Formalin fixation of electron microscopy: A reevaluation. Am J Clin Pathol 1973, 59:365–373
17. Fisher ER: The pathologists role in the diagnosis and treatment of invasive breast cancer. Surg Clin North Am 1978, 58:705–721
18. Page DL, Dixon JM, Anderson TJ, Lee D, Stewart HJ. Invasive cribriform carcinoma of the breast. Histopathology 1983, 7:525–536
19. Azzopardi JG, Muretto P, Goddeeris P, Eusebi V, Lauweryns JM: "Carcinoid" tumours of the breast: The morphological spectrum of argyrophil carcinoma. Histopathology 1982, 6:541–569
20. Ridolfi RL, Rosen PP, Port A, Kinne D, Mike V: Medullary carcinoma of the breast: A clinicopathologic study with 10 year follow-up. Cancer 1977, 40:1365–1385
21. Mazoujian G, Warhol HJ, Haagensen DE Jr: The ultrastructural localization of gross cyst fluid protein (GCDFP-15) in breast epithelium. Am J Pathol 1984, 116:305–310
22. Pier WJ, Garancis JC, Kuzma JF: The ultrastructure of apocrine cells. Arch Pathol 1970, 89:446–452

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