Adenoid Cystic Carcinoma of the Breast

Data from the Connecticut Tumor Registry and a Review of the Literature

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The case records of the Connecticut Tumor Registry were reviewed from 1952–1982. There were 37 cases of adenoid cystic carcinoma of the breast (ACC) from a total of 40,350 invasive breast tumors. Patient survival, complications, and pathologic sections were reviewed. Only 14 of 27 surgical pathology slides available for review could be confirmed histologically as ACC. All patients were white females with a mean age of 64 years. The tumor remained localized to the breast in all cases. Nine patients had either radical or modified radical mastectomy, four patients had either simple mastectomy or lumpectomy, and one patient refused treatment. There was no evidence of axillary node involvement, metastases, or local recurrence after excision. At the time of follow-up, nine patients were alive and disease free and four died of disease unrelated to their breast cancer. The one patient who died of breast cancer had a radical mastectomy and survived 11.7 years after diagnosis. It is concluded that ACC has a favorable biologic behavior characterized by a prolonged clinical course and good prognosis. Simple mastectomy is all that is required as initial treatment, and a chest x-ray and thorough physical examination looking for local recurrence is all that is needed for follow-up.

ADENOID CYSTIC CARCINOMA of the breast is a rare histologic form of breast cancer, comprising in most series less than 1% of all mammary cancers. Approximately 106 documented cases of adenoid cystic carcinoma have been reported to date, and all have emphasized the favorable prognosis of this type of cancer.[1–28]

The Connecticut Tumor Registry was established in 1941 and includes records on all malignant neoplasms diagnosed in residents of Connecticut since 1935. All hospitals in Connecticut routinely report to the Registry information on all newly diagnosed cancers, and the Registry maintains an annual follow-up on all the reported cases. The aim of this study was to analyze the data of the Connecticut Tumor Registry with regard to adenoid cystic carcinoma of the breast to assess further the histologic features and clinical behavior of this type of breast tumor.

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Materials and Methods

The case records of the Connecticut Tumor Registry were reviewed from 1952–1982. In the 30-year period, a total of 40,350 invasive breast tumors were diagnosed among Connecticut residents of both sexes. There were 37 listed cases of adenoid cystic carcinoma of the breast (<0.1%). Most of the living patients at the latest follow-up were seen in the last 3 years. One patient with adenoid cystic carcinoma was lost to follow-up after 1970. Follow-up information for all patients was obtained from hospital records, the patient's physician, or by patient interview over the telephone. The original surgical pathologic sections of the primary tumor, axillary lymph node, and adjacent breast tissue were retrieved from their respective institutions for review.

In five cases, immunohistochemistry was performed using the peroxidase-anti-peroxidase (PAP) method[29] against cytokeratin, keratin, S-100 protein, epithelial membrane antigen, and smooth muscle myosin.

Results

Pathologic Review

The surgical pathology slides of 27 of 37 cases identified as adenoid cystic carcinoma cases were available for review. However, only 14 of the 27 cases (52%) could be confirmed histologically as being adenoid cystic carci-

TABLE 1. *Clinical Features of 14 Cases of Adenoid Cystic Carcinoma of the Breast*

Patient	Sex	Age	Site	Primary Treatment	Survival (yrs)	Status	Cause of Death
1	F	65	RUO	Radical mastectomy	11.67	D	Carcinoma of breast
2	F	81	RUI	Simple mastectomy	12.67	D	Pneumonia
3	F	58	RUI	Radical mastectomy	12.17	L	
4	F	78	LLC	Radical mastectomy	5.00	D	Acute myocardial infarction
5	F	60	RUI	Modified simple mastectomy	9.25	L	
6	F	63	RC	Modified radical mastectomy	7.33	L	
7	F	80	LUI	Modified radical mastectomy	7.00	D	Carcinoma of ovary
8	F	49	RUO	Excision only	5.58	L	
9	F	56	RUO	Modified radical mastectomy	6.17	L	
10	F	47	RUO	Modified radical mastectomy	4.33	L	
11	F	77	LC	Modified radical mastectomy	3.50	D	Generalized atherosclerosis
12	F	78	LUO	Refused surgery	2.17	L	
13	F	50	LUO	Modified radical mastectomy	1.67	L	
14	F	51	RUO	Partial mastectomy with nodes	2.50	L	

RUO = right upper outer. LLC = left lower center. LUI = left upper inner. RUI = right upper quadrant. LUO = left upper outer. RC = right center. LC = left center. D = dead. L = living.

noma. The diagnosis in the remainder varied from infiltrating ductal with cribriform duct carcinoma *in situ* (7 cases), papillary carcinoma (3 cases), mucinous carcinoma (2 cases), and lobular carcinoma (1 case). Interestingly, before 1974, only three of the 13 reviewed cases were confirmed histologically as being adenoid cystic carcinoma, an accuracy rate of only 23% in making the diagnosis. By contrast, after 1974, 11 of the 14 reviewed slides had the correct diagnosis of adenoid cystic carcinoma, an accuracy rate of 79%.

Clinical Data

Table 1 provides a summary of the clinical features of the 14 confirmed cases of adenoid cystic carcinoma. At the time of diagnosis, the age distribution of patients ranged from 47–81 years with a mean of 64 years. All patients were white females. The main presenting symptom was a mass in the breast. The tumor remained localized to the breast in all adenoid cystic carcinoma cases with nine cases found in the right breast and five cases found in the left breast. Of the 14 adenoid cystic carcinoma cases with known subsite, 10 were specified in the upper half of the breast, and of these, five were in the outer quadrant.

Nine patients had either a radical or modified radical mastectomy, four patients had either simple mastectomy or lumpectomy, and one patient refused treatment. Despite the different treatment modalities there was no reported evidence of axillary node involvement, metastases, or local recurrence after excision.

The follow-up interval ranged from 1.67–12.67 years with a mean of 6.5 years. At the time of follow-up, nine patients were alive and disease free and four patients died of diseases unrelated to breast cancer. The patient who reportedly died of breast cancer had a radical mastectomy at the initial presentation and survived 11.7 years after diagnosis. However, confirmation of the cause of death and even the evidence of recurrence or metastases could not be obtained.

Histology

The overall microscopic pattern of adenoid cystic carcinoma seen in these patients, and as emphasized by previous reports in the literature, is identical to that tumor seen in the salivary gland, upper respiratory tract, and other sites. Briefly, these tumors are composed of two morphologic cell types: (1) cuboidal epithelial cells with rather abundant cytoplasm and pale nuclei; these line tubular duct-like structures that contain neutral polysaccharides (PAS positive, diestase sensitive); and (2) myoepithelial cells, which are larger than the epithelial cells although they have less cytoplasm and a more densely staining nucleus; these cells elaborate acid mucopolysaccharides (alcian blue positive) and abundant basal lamina material, thereby effecting a prominent stromal component, giving rise to a cylindromatous appearance, focally or throughout the individual tumor. This stroma may occasionally show metaplastic changes, thus mimicking the pleomorphic adenoma of salivary gland.

Dependent on the degree of cellular proliferation and the extent of stromal expression by the myoepithelial cells, several patterns of growth may be seen in adenoid cystic carcinoma of the breast. The tubular pattern (Fig. 1) recapitulates the appearance of infiltrating duct-like structures, lined by a single layer of epithelial cells. Proliferation of either cell type may result in solid nests (Fig. 2), again with a round to oval duct-like outline; if stromal material is elaborated by proliferating myoepithelial cells, "cysts" are evident within these nests, mimicking a cribriform appearance. With a more extensive stromal component,

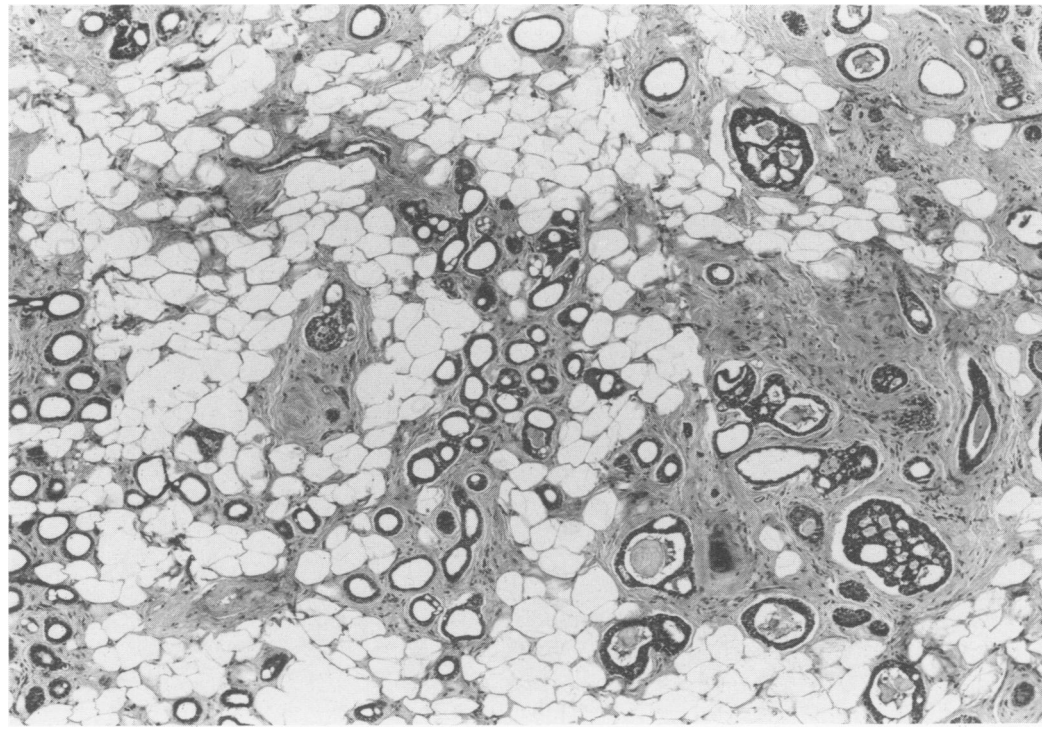

FIG. 1. Infiltrating adenoid cystic carcinoma with predominantly tubular pattern (original magnification ×40, from Case 13).

the cylindromatous pictures occur (Fig. 3). Generally, although one pattern was often predominant, cribriform and/or tubular areas were evident in all cases, even in those cases that showed largely a solid growth pattern. The cylindromatous pattern was clearly identified in only a few tumors.

Despite the gross appearance of being well circumscribed, many cases showed microscopic extension of tu-

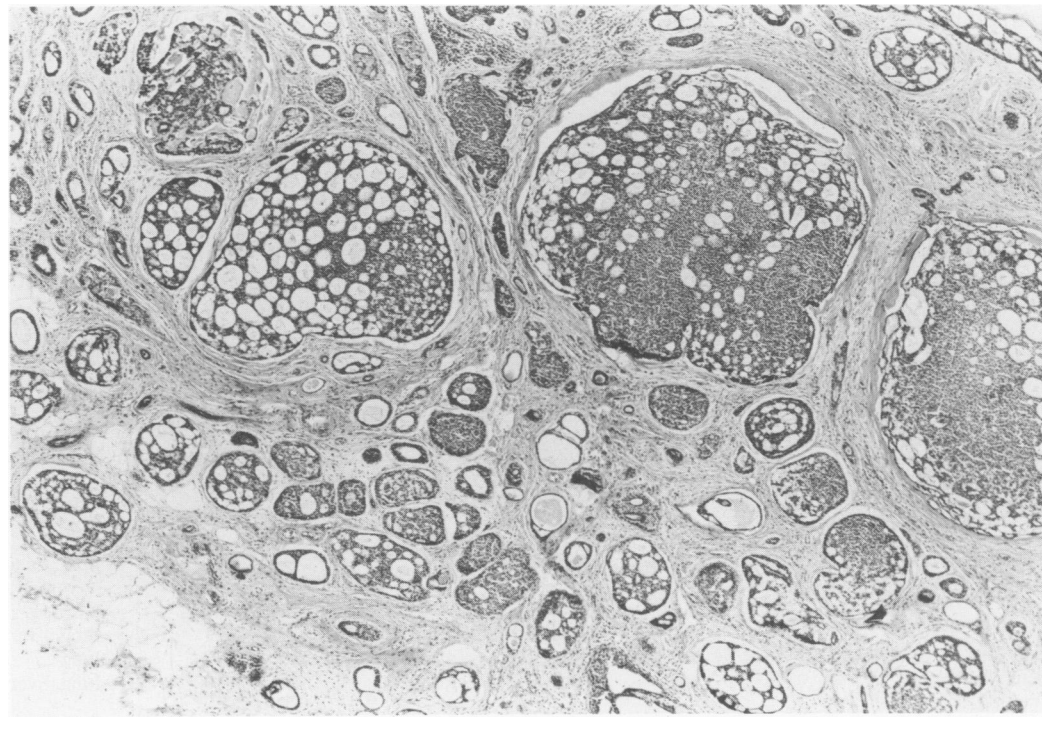

FIG. 2. Cribriform pattern with focal solid growth in adenoid cystic carcinoma (original magnification ×40, from Case 3).

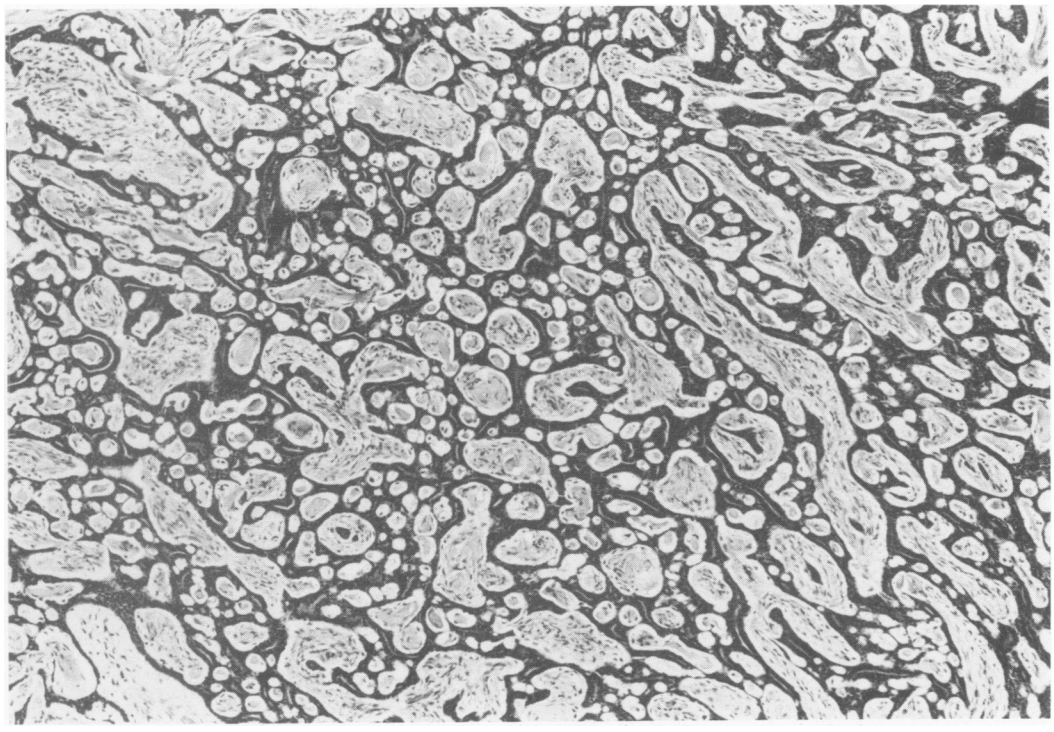

FIG. 3. Cylindromatous growth in adenoid cystic carcinoma with small cystic spaces formed by tumor elaboration of hyaline material (original magnification ×100, from Case 14).

mor into the surrounding fat. In none of the cases reviewed was perineural invasion noted.

Immunohistochemistry

The immunohistochemical features of mammary adenoid cystic carcinoma were investigated in five cases using PAP immunoperoxidase techniques. Five cases were stained for epithelial membrane antigen (EMA), cytokeratin, S-100 protein, and smooth muscle myosin (SMM). Five cases stained positively for EMA, four stained positively for cytokeratin (one strongly, whereas three showed focal staining), two were positive for S-100 protein, and two were positive for SMM.

These findings support the heterogeneous immunohistochemical characteristics of the lesions and are similar to those described for neoplasms of salivary glands.

Discussion

Our experience with 14 confirmed cases of adenoid cystic carcinoma represents one of the larger series and enables us to draw certain conclusions concerning the biologic features of adenoid cystic carcinoma of the breast.

It is a rare histologic form of breast cancer, comprising in our series, as in others, less than 1% of all breast tumors. However, despite its uncommon occurrence, it can be readily recognized and it is important to distinguish from other forms of breast cancer because of its excellent prognosis. Of the cases drawn from the literature, there have been only seven documented cases of distant metastases associated with adenoid cystic carcinoma (Table 2). All of these reported cases had concomitant pulmonary metastases and up to the interval of follow-up, four of these seven patients died of their metastatic disease.

TABLE 2. *Review of Cases of Adenoid Cystic Carcinoma of the Breast with Distant Metastasis*

References	Age	Sex	Initial Treatment	Time of Metastases (yrs)	Site of Metastases	Follow-up
Nayer[4] (1957)	39	F	Radical mastectomy	8	lung, pleura	dead, 4 yrs
O'Kell[5] (1964)	73	F	Radical mastectomy	3	lung, chest wall, IVC	dead, 1 yr
Elsner[17] (1970)	44	F	Radical mastectomy	6	lung	alive, 6 yrs
Verani and van der Bel-Kahn[22] (1973)	63	F	Radical mastectomy	14	lung, hilar nodes, vertebra, axilary nodes	dead, 3 yrs
	78	M	Modified radical mastectomy	1	lung, liver	dead, 1.5 yrs
Lim et al.[26] (1979)	48	F	Modified radical mastectomy	9	lung	alive, 1 yr
Peters and Wolff[28] (1982)	73	F	Radical mastectomy	10	lung, liver	alive, 2 yrs

TABLE 3. *Review of Cases of Adenoid Cystic Carcinoma of the Breast with Local Recurrence*

References	Age	Sex	Initial Treatment	Time of Recurrence (yrs)	Subsequent Treatment	Follow-up
Wilson and Spell[10] (1967)	54	F	Simple mastectomy	5	*En bloc* resection pectoralis major and axilla	Recurrence to chest wall 10 years later
Cavanzo and Taylor[13] (1969)		F	Local excision	3	Simple mastectomy	Alive, 9 yrs
		F	Local excision	7	Simple mastectomy	Alive, 14 yrs
Lusted[16] (1970)	46	F	Local excision	22.5	Modified radical mastectomy (− axilla nodes)	Alive, 2 yrs
Qizilbash et al.[24] (1977)	28	F	Local excision	0.5	Modified radical mastectomy (− axilla nodes)	Alive, 9.5 yrs
Peters and Wolff[28] (1982)		F	Local excision	8	Wide excision	Alive, 9 yrs
	46	F	Local excision	5	Modified radical mastectomy (− axilla nodes)	Alive, 4 yrs

Axillary lymph node metastasis is even more uncommon with only one patient reported in the literature.[22] This patient was a 63-year-old woman in whom 11 of the 22 examined lymph nodes contained metastases. Despite axillary node involvement, the patient remained free of recurrence for 14 years, then distant metastases developed and she eventually died. The histologic interpretation of this patient's tumor, however, has been the subject of much debate in the literature. Some have questioned whether a coexisting second primary neoplasm was present and responsible for the lymph node metastases.[27] Other authors have also argued that this tumor might in fact be a variant of papillary and cribriform carcinoma.[28]

Despite histologic evidence of tumor infiltration into the surrounding tissues, local recurrence after simple excision is low. There have been only eight documented cases of local recurrence and six occurred after local excision (Table 3). The recurrence interval was as early as 6 months to as late as 22 years after excision. Subsequent treatment varied from a simple mastectomy to a more radical dissection. All axillary nodes examined were negative for tumor. Patients were all alive and well on follow-up except for the patient reported by Wilson and Spell[10] who had a second recurrence on her chest wall 15 years after her initial mastectomy. This latter case was originally reported as one of regional metastasis as well, and this questionable conclusion has been perpetuated in subsequent literature.[26] The significance of this question relates to the otherwise apparent tendency of adenoid cystic carcinoma to metastasize to lung.

Although perineural growth is a distinguishing feature of adenoid cystic carcinoma in other locations and is reported by others as being common in breast lesions, no evidence of perineural invasion could be found in our series. This may explain in part the relatively less aggressive behavior of adenoid cystic carcinoma of the breast compared with extramammary adenoid cystic carcinoma.

In our patients, adenoid cystic carcinoma of the breast was not hormonally sensitive. In fact, in the literature there is only one reported case of estrogen positivity.[30] However, there has not been any reported confirmation of this histologic diagnosis. In addition, there have been only five cases of adenoid cystic carcinoma of the breast reported in men in the literature and none in our series. This probably reflects both the rarity of adenoid cystic carcinoma and rarity of breast carcinomas in men.

Despite its well-characterized histology, adenoid cystic carcinoma can be confused for other more common breast tumors, particularly when one pattern of growth predominates in adenoid cystic carcinoma. The more serious diagnostic error, however, as evident in this review, is mistaking another breast primary for adenoid cystic carcinoma.[31] In our study, this occurred most frequently with cases of infiltrating duct carcinoma with a prominent *in situ* cribriform pattern. In all such cases, invasive tumor of typical duct cell type could be identified on review, and the cribriform pattern could be distinguished from that in adenoid cystic carcinoma by the cytologic characteristics of the duct cells, the tendency to show intraluminal necrosis, and the lack of the mucoid or myxoid stromal material in the lumena (Fig. 4). Cribriform growth in intraductal carcinoma is usually limited to the periphery of the duct spaces, allowing appreciation of the large central lumenal space not seen in cribriform growth of adenoid cystic carcinoma. The lumenal spaces in intraductal carcinoma also often show more variability in shape and placement. The orientation of the cells bridging the lumenal cysts is different, with a tendency towards either a more glandular or a more solid growth with fewer spaces. The cells in intraductal carcinoma are also often noted

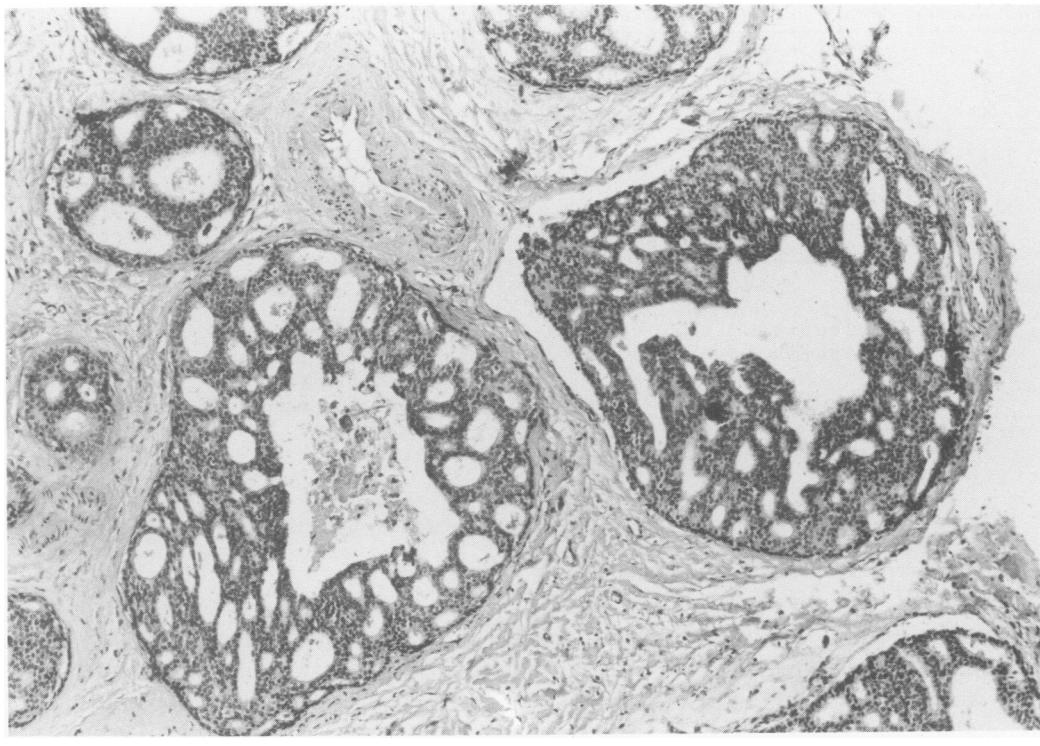

FIG. 4. Cribriform intraductal carcinoma mimicking adenoid cystic carcinoma; note intralumenal necrosis and gland-like orientation of epithelium toward lumenal spaces (original magnification ×100).

to have more abundant, eosinophilic cytoplasm and as mentioned previously, the contents of the cystic spaces differ as well. Mitoses and presence of nucleoli are not useful in differentiation, although generally they are less prominent in adenoid cystic carcinoma.

Papillary carcinoma is also potentially misdiagnosed as adenoid cystic carcinoma, whether it is invasive or not. Usually the intracystic nature of the lesion is notable, and the fibrovascular stroma, although often quite subtle, is distinctly different from the homogeneous, eosinophilic stroma elaborated by the cells of adenoid cystic carcinoma. The nature of the cribriform spaces imparted by the pap-

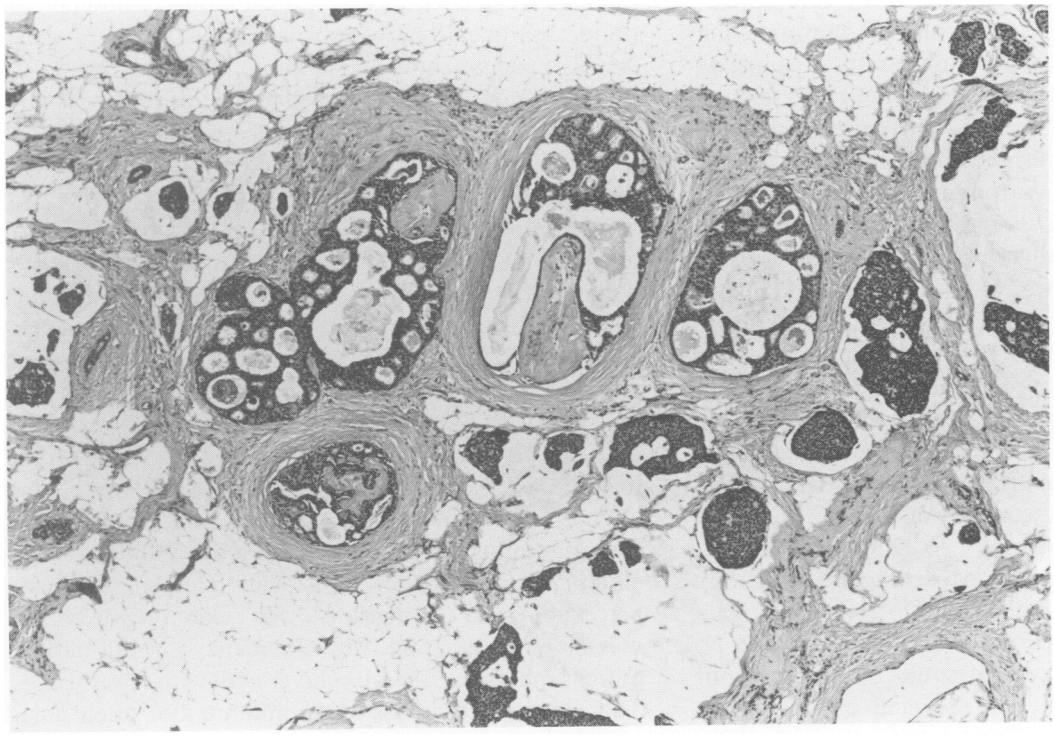

FIG. 5. Mucinous carcinoma with solid nests and cribriform growth; abundant mucin distant from epithelium is evident (original magnification ×40).

illary growth is also different from that of adenoid cystic carcinoma, being typically smaller, more uniform, and frequently more glandular in appearance than in adenoid cystic carcinoma. Solid nests in adenoid cystic carcinoma never achieve the dimensions of intracystic papillary lesions.

Finally, mucinous carcinoma may resemble adenoid cystic carcinoma particularly when the tumor has a prominent cribriform component (Fig. 5). Usually, the typical duct cell growth pattern can be identified focally either intraductally or in its invasive element. More importantly, the character of the mucin production is always distinguishable from the material produced in adenoid cystic carcinoma, being far less intimately associated with tumor cells than in adenoid cystic carcinoma. Additionally, the use of special stains, as advocated by Anthony and James,[23] will demonstrate neutral mucopolysaccharides in mucinous carcinoma as well as in papillary and cribriform carcinoma, while both neutral and acid mucopolysaccharides are evident in adenoid cystic carcinoma. The single case of lobular carcinoma was associated with extensive papillomatosis, which may be confused for the cribriform growth seen in adenoid cystic carcinoma. This should rarely be a diagnostic problem.

Because it is a rare form of breast cancer, the results of different types of breast operations and treatments have been difficult to evaluate. Local excision or simple mastectomy has been recommended by Cavanzo and Taylor,[13] whereas Elsner[17] suggests a modified radical mastectomy saving the major pectoral muscle and the uppermost axillary nodes. From the preceding discussion, however, the favorable biologic behavior of this disease, characterized by a prolonged clinical course and good prognosis, indicates that wide excision alone could be curative in the majority of cases. If one takes into account the very low, but nonetheless existent, rate of local recurrence, most authors would argue for a simple mastectomy. Certainly with the very low complication rate of this procedure, we agree with performing a simple mastectomy. In addition, with only one reported (and controversial) case of axillary node involvement at the initial time of surgery, axillary node dissection would seem unnecessary unless there are clinically enlarged axillary lymph nodes.

Close follow-up after a simple mastectomy is still necessary despite the excellent prognosis of this disease since local recurrence and distant metastases occur, although rarely and generally long after the initial event. Since all cases of distant metastases occurred in the lung, an annual chest x-ray and a thorough physical examination looking for local recurrence is probably all that is needed.

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