Adenoid cystic carcinoma of the breast: prevalence, diagnostic criteria, and histogenesis

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SYNOPSIS Three cases of adenoid cystic carcinoma have been identified in a 10-year review of 2686 cases of breast carcinoma. The criteria necessary for diagnosis have been reviewed with particular reference to cribriform intraduct carcinoma and adenocarcinoma of the breast with a small, dark, 'basaloid'-cell pattern. The most important single diagnostic criterion of adenoid cystic carcinoma is a biphasic cellular pattern which may be aided by the demonstration of two types of mucin—stromal acid mucopolysaccharide and ductal neutral mucopolysaccharide. This tumour most frequently presents as a painful or tender mass near the areola, and it carries a uniquely favourable prognosis when compared with similar tumours elsewhere in the body. Actomyosin has been demonstrated in all three tumours by an immunofluorescent method, and this supports a predominantly myoepithelial origin.

Adenoid cystic carcinoma (adenocystic carcinoma, cylindroma, basaloid carcinoma) is best known as a tumour of salivary glands though it infrequently also occurs at other sites in the body—the tracheo-bronchial tree, nasopharynx, maxillary sinus, uterine cervix, and the skin. The tumour is characteristically made up of small, dark, ovoid cells with a sieve-like or cribriform pattern of growth, and small cysts may form. These cells resemble the basal cells of epithelial surfaces or myoepithelial cells. In addition, small, duct-like structures are also seen. The well-differentiated cytological features belie a tendency to infiltrate, recur, and metastasize. The prognosis is generally poor (Evans and Cruickshank, 1970).

Galloway *et al* (1966) reported nine cases of adenoid cystic carcinoma occurring in the breast, none of which recurred or metastasized after mastectomy. Since that time numerous reports have appeared, mainly from the United States and the European continent, which have confirmed the excellent prognosis at this site. These have been summarized in table I. Single case reports have been omitted except those which illustrate some unusual feature. The rarity of this tumour in the breast and the difficulty of distinguishing it from other lesions, notably intraduct carcinoma, sclerosing adenosis,

and epitheliosis, have been repeatedly emphasized (Cavanzo and Taylor, 1969; Friedman and Oberman, 1970; Lusted, 1970). Histogenesis remains doubtful, and ultrastructural studies have been inconclusive (Koss *et al*, 1970; Woyke *et al*, 1970).

Recent interest in adenoid cystic carcinoma of the breast and the diagnostic problems associated with it have stimulated us to review our own material of breast tumours over a 10-year period in order to assess prevalence and to review criteria for diagnosis.

We have also undertaken an investigation of the possible myoepithelial origin of this tumour with the use of immunofluorescent techniques.

Materials and Methods

During the 10 years from 1961 to 1970 some 2686 cases of breast carcinoma were seen at this institute. All the sections were reviewed in a search for adenoid cystic carcinoma and tumours closely resembling it. The term adenoid cystic carcinoma is the one recommended by the World Health Organization in preference to other synonyms (Thackray and Sobin, 1972). Twenty-six were found in which this diagnosis might have been considered by a reasonably experienced pathologist. The blocks from these cases were re-cut and stained with haematoxylin-eosin, periodic acid-Schiff (PAS) reaction with and without diastase, alcian blue at pH 2.6, combined alcian blue-PAS (Mowry, 1956)

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Reference	No. of Cases	Age Range (av.)	Sex	Duration of Symptoms
Nayer (1957)	1	39	F	1 yr
O'Kell (1964)	3	47-76 (59)	F	8 d-6 mth
Galloway <i>et al</i> (1966)	9	44-80 (53)	F	2 d-15 yr
Wilson and Spell (1967)	1	54	F	3 mth
Cavanzo and Taylor (1969)	21	31-69 (50)	F	Few weeks-many years
Elsner (1970)	7	38-80 (50)	F	2 mth-12 yr
Friedman and Oberman (1970)	5	53-76 (63)	F	7 d-6 mth
Koss <i>et al</i> (1970)	5	41-77	F	
Lusted (1970)	4	42-65 (52)	F	2 wk-11 yr
Woyke <i>et al</i> (1970)	1		M	
Hopkins and Tullis (1972)	3	33-53 (43)	F	3-5 mth
Verani and van der Bel-Kahn (1973)	2	63-78 (52)	F	6 wk-10 yr
			M	

Table I Adenoid cystic carcinoma of the breast: a summary of salient features in 62 cases

and phosphotungstic acid-haematoxylin. A study of this material resulted in the identification of three cases of adenoid cystic carcinoma, 19 cases of cribriform intraduct carcinoma, and four cases of 'basaloid' tumour. We have not experienced any difficulty in distinguishing well-differentiated ductal adenocarcinoma, sclerosing adenosis or epitheliosis from adenoid cystic carcinoma.

Specific antiserum to actomyosin prepared from calf aorta was raised in rabbits and supplied to us by Professor J. F. Hampe, Pathological-Anatomical Laboratory, Amsterdam, The Netherlands. This was applied to deparaffinized sections with an indirect immunofluorescent technique utilizing anti-rabbit immunoglobulin raised in sheep. The results were viewed in a Leitz Ortholux microscope with appropriate filters, and the identity of the structures seen was checked by phase contrast. All three adenocystic carcinomas were subjected to immunofluorescence microscopy together with two cases each of intraduct carcinoma and of 'basaloid' tumour. Sections from normal myocardium and skeletal muscle, which had been stored for approximately the same period as the test cases, were used as controls.

Results

ADENOID CYSTIC CARCINOMA
Brief clinical details are summarized in table II for comparison with table I. There are no conclusions to be drawn from three cases, but they do fall into the overall pattern of cases summarized in table I. In two patients the tumour arose in the nipple area and was tender. All three tumours were rounded and fairly well defined. The cut surface was cystic in one case. All three patients are alive and well and free of recurrence nine, six, and three years later. One patient (case 3) had had an 'ordinary' adenocarcinoma of the contralateral breast removed one year previously.

Histology

All three tumours showed a lobulated pattern of growth with finger-like extensions into surrounding tissues (fig 1). A Swiss cheese or sieve-like cribriform pattern was invariably present but some of the lobules were solid or reticular in structure. Larger 'cysts' were present in one case. Perineural infiltration was not seen.

The cellular component was of two types. The

Case	Age	Sex	Duration (weeks)	Presentation	Site	Size (cm)	Treatment	Course
1	61	F	4	Tender mass	Periareolar	3 x 1	Radical mastectomy	Alive and well 6 yr later
2	38	F	8	Mass	Upper outer quadrant	2	Local excision followed by radiotherapy	Alive and well 9 yr later
3	48	F	6	Tender mass	Lateral to nipple	2	Radical mastectomy	Alive and well 3 yr later

Table II Brief details of three cases of adenoid cystic carcinoma of the breast

Presentation	Site	Size (cm)	Treatment	Course
Tender or painful mass in four cases	4 near areolar	0.6-3	Radical mastectomy	Dead of disseminated malignant disease 13 yr later. No necropsy
			Radical mastectomy	Two alive and well 1 yr and 1 yr 3 mth later. One died of metastases 3½ yr later
			Radical mastectomy	All alive and well; four patients up to 7½ to 15 yr
Mass in breast 'sometimes tender'	Near nipple	2-8 1-5	Simple mastectomy	Local recurrence 7½ and 15½ yr later
			Local excision (4)	Local recurrence in 2; death from unrelated causes in 2; rest alive and well 2-14 yr later
			Simple mastectomy (3) Radical mastectomy (13) Unknown (1)	
Painful mass in two cases	3 periareolar	2-4	Simple mastectomy (1)	Metastasis to lung in one case after 6 yr; rest alive and well 2-14 yr later
			Radical mastectomy (6)	One died of heart disease; four alive and well 1-4 yr later
			Simple mastectomy (4) Radical mastectomy (1)	
Painful mass in one case		5-8	Radical mastectomy	Alive and well 2-10 yr later
			Radical mastectomy	One local recurrence after 22½ yr. All alive and well up to 39 yr later
Tender mass in two cases	2 subareolar 1 subareolar	1.8-3 2-3	Radical mastectomy	All alive and well 2-13 yr later
			Radical mastectomy	Axillary lymph node metastasis in one; both died of metastases

Table I—continued

bulk of these tumours was made up of small, dark cells, 4-8 μ m in size, oval or elongated in shape, with regular dense nuclei and scanty cytoplasm. The 'cysts' within the lobules were invariably surrounded by such cells (fig 2). In addition, scanty, duct-like structures were also present lined by a single layer of cuboidal cells with paler nuclei and more abundant, finely granular cytoplasm. Though not fully differentiated, these resembled normal breast ductules (fig 3). They were present in all three cases but were found only after prolonged search, usually within smaller masses. Mitoses were rarely seen anywhere in these tumours and necrosis was absent.

The 'cysts' contained loose, fibrillar or mucoid material often with a capillary blood vessel in the centre, and sometimes with peripheral condensation adjacent to surrounding tumour epithelium (fig 2). In some, this process had led to hyalinization either in a lace-like or globular pattern, resembling the pattern seen in a 'mixed' tumour (pleomorphic adenoma) (fig 4). The duct-like structures showed tubular lumina that did not communicate with 'cysts' and were free of fibrillary material, capillaries or hyalin.

Histochemistry

The contents of the 'cysts' gave a strong positive reaction with alcian blue and were PAS negative in contrast to the contents of the duct-like structures which were weakly positive with alcian blue and strongly positive with PAS. In the combined alcian blue-PAS preparations, the 'cysts' were alcian blue positive and the ducts PAS positive (table III). The PTAH stain failed to demonstrate myofibrils though

Tumour	PAS	Alcian Blue	PAS + Alcian Blue
Adenoid cystic carcinoma	Ducts + 'Cysts' ±	'Cysts' + +	Ducts PAS + 'Cysts' alcian blue +
Cribiform intraduct carcinoma	Ducts and 'cysts' + +	Ducts and 'cysts' +	Ducts and cysts PAS +
'Basaloid' tumour	'Cysts'	'Cysts' +	'Cysts' alcian blue +

Table III Summary of staining reactions for acid and neutral mucopolysaccharides

some scattered granular staining was seen in some areas. The media of small blood vessels stained strongly positive.

Immunofluorescence

A strong, though scattered cytoplasmic fluorescence was seen in all three tumours, generally in small cell masses (figs 5-6) and was equal in intensity to the reaction given by the smooth muscle media of small blood vessels in the same sections (figs 7-8) and by skeletal muscle and myocardium in the control sections.

CRIBIFORM INTRADUCT CARCINOMA

Whole tumours or selected areas within them gave rise to differential diagnostic difficulty in 19 such cases. The resemblance to adenoid cystic carcinoma proved, however, to be superficial on detailed examination. Cribiform intraduct carcinomas also formed distinct masses but these were rounded rather than lobulated in outline, and a basement membrane could usually be demonstrated.

Fig 1

Fig 1 Lobulated masses of adenoid cystic carcinoma of the breast with characteristic 'Swiss cheese' pattern and finger-like extensions into stroma (Haematoxylin-eosin $\times 35$).

Fig 2

Fig 2 Small, dark, uniform cells enclosing 'cysts' which contain loose, fibrillar material (Haematoxylin-eosin $\times 85$)

Fig 3 Duct-like structures (Haematoxylin-eosin $\times 220$).

Fig 4 Hyalinization of the stroma within 'cysts' gives rise to pleomorphic adenoma-like pattern (Haematoxylin-eosin $\times 138$).

Fig 5 Adenoid cystic carcinoma viewed by phase contrast ($\times 138$).

Fig 6 Adjacent section stained for actomyosin by immunofluorescence ($\times 138$).

Fig 5

Fig 6

Fig 7

Fig 7 Small blood vessel viewed by phase contrast ($\times 138$).

Fig 8

Fig 8 Same vessel stained for actomyosin by immunofluorescence ($\times 138$).

Fig 9 Detail of cribriform intraduct carcinoma (Haematoxylin-eosin $\times 138$).

Individual tumour cells were larger with variable nuclei, a more open chromatin pattern, and often prominent nucleoli. The cytoplasm was more abundant and finely granular. The cells tended to show a polar arrangement around duct-like or cystic lumina which contained mucus (fig 9). Mitoses and areas of necrosis were frequently present. They stained positively with both alcian blue and PAS, and in combined preparations, with PAS rather than with alcian blue (table III). No immunofluorescent staining was obtained with anti-actomyosin serum in the two cases tested.

'BASALOID' TUMOURS

Four tumours consisted of lobulated masses with a cribriform pattern but lacked other criteria considered necessary for the diagnosis of adenocystic carcinoma. The tumour cell masses were much more disorderly, and the individual cells were more pleomorphic and lacked a biphasic pattern with small duct-like structures (fig 10). The 'cysts' stained only with alcian blue (table III). Occasional

Fig 10 Cribriform pattern of a 'basaloid' tumour. Note the disorderly arrangement and marked nuclear pleomorphism (Haematoxylin-eosin $\times 138$).

flecks of immunofluorescence to actomyosin were seen but were not considered significant. It is possible that these 'basaloid' tumours (so designated because of their similarity to basal or myoepithelial cells) do, in fact, represent a more malignant or, at any rate, less well differentiated variant of adenoid cystic carcinoma, but this could not be established with certainty and these tumours should remain classified with 'ordinary' adenocarcinoma of the breast.

Discussion

Nearly a hundred cases of adenoid cystic carcinoma of the breast have been reported in the world literature to date, most of them in the last five years. Table I summarizes some salient features. The age range and the average age of patients are not distinctive. It is a tumour affecting almost exclusively women though two examples in men have been recorded (Woyke *et al*, 1970; Verani and van der Bel-Kahn, 1973). The duration of symptoms is variable but often quite long—months or even many years. It is worth noting that Lusted (1970) had calculated the linear growth rate of the tumour in one case as 2.4 mm per year. Presentation is generally with a mass in the breast. In four of the nine cases reported by Galloway *et al* (1966) the lump was painful and/or tender. Cavanzo and Taylor (1969) comment on their 21 cases that 'the main presenting symptom was a mass in the breast, sometimes tender'. Pain or tenderness was also reported by Friedman and Oberman (1970), Lusted (1970), and Hopkins and Tullis (1972). This was also the case in two of our three patients. The tumour often arises in the nipple area (Galloway *et al*, 1966; Friedman and Oberman, 1970; Hopkins and Tullis, 1972; Verani and van der Bel-Kahn, 1973). This was so in two of our three cases. The size of the tumour is generally 1 to 3 cm, though it occasionally is much larger. Macroscopically it presents as a fairly well defined, sometimes lobulated mass which may be grossly cystic.

The prognosis of adenoid cystic carcinoma of the breast is much better than that of similar tumours elsewhere in the body. Nearly one-third of the patients with tumours at other sites have regional or distant metastases at the time of first presentation, and local recurrence followed by further spread is common; five-year survival, on average, is about 30% (Cavanzo and Taylor, 1969). By contrast, there are very few instances where adenoid cystic carcinoma of the breast has shown a similarly aggressive behaviour. Local recurrence has been recorded in only four cases (Wilson and Spell, 1967; Cavanzo and Taylor, 1969; Lusted, 1970) and metastases in

only five (Nayer, 1957; O'Kell, 1964; Elsner, 1970; Verani and van der Bel-Kahn, 1973) of which two are incompletely documented (Nayer, 1957; O'Kell, 1964). Several authors have advocated local excision or at most simple mastectomy as adequate treatment. Certainly, in one case only has regional lymph node metastasis been found (Verani and van der Bel-Kahn, 1973), and axillary dissection would seem superfluous.

At the outset of this 10-year review of breast tumours it was expected that a number of adenoid cystic carcinomas might be found which had been misdiagnosed. This has not turned out to be the case: only three unequivocal examples were identified. The risk lies not in failure to recognize but in overdiagnosis, which may be stimulated by numerous recent reports. Strict criteria must be used in differential diagnosis, particularly from cribriform intraduct carcinoma which has also been emphasized by Galloway *et al* (1966), Friedman and Oberman (1970), and Lusted (1970). This can be achieved by examination of routine sections stained with haematoxylin-eosin alone, but the demonstration of acid mucopolysaccharides in 'cysts' and of neutral mucopolysaccharides in small duct-like lumina is of additional help. We believe that the 'cysts' represent invaginations of young connective tissue stroma, and this has been previously established by serial sectioning of whole tumours (Lusted, 1970) and by electron microscopy (Koss *et al*, 1970). The main mass of the tumour consists of myoepithelial cells producing acid mucopolysaccharides and fibrillary connective tissue while the scanty duct-like structures probably represent differentiation towards mammary duct epithelium, capable of secreting PAS-positive mucus. This, again, is supported by previous reports on ultrastructure (Eneroth *et al*, 1968; Murad and von Haam, 1968; Koss *et al*, 1970). We consider this biphasic cellular pattern to be the most important single diagnostic criterion of adenoid cystic carcinoma.

The identity of 'basaloid' tumours remains in doubt. We feel that tumours with such appearances should be regarded as variants of 'ordinary' adenocarcinoma unless evidence to support a myoepithelial origin can be found. We have not been able to demonstrate actomyosin in two of four cases.

The histogenesis of adenoid cystic carcinoma is of interest in view of its biphasic histological pattern and distinctive clinical behaviour. The cytological features suggest that it originates from myoepithelial cells, but it also has a secretory, ductal element, and electron microscopy studies have shown evidence of both types of cell. The interpretation of ultrastructural appearances has given rise to some controversy between those who favour a pre-

dominantly ductal epithelial or a predominantly myoepithelial origin (Koss *et al*, 1970). Filamentous material resembling myofibrils has also been demonstrated with phosphotungstic acid-haematoxylin (Friedman and Oberman, 1970), but we have not been able to confirm this.

Immunological studies on tissue sections are usually performed on fresh frozen, unfixed or cold alcohol-fixed, paraffin-embedded material (Sainte-Marie, 1962). Recent reports, however, have shown that an increasing amount of immunological work is being performed on routine, formalin-fixed, paraffin-embedded material. A study on intracellular immunoglobulins comparing three standard tissue processing methods showed that immunofluorescence from formalin-fixed, paraffin-embedded tissues compared favourably with that obtained using either fresh frozen or the Sainte-Marie method of tissue preservation (Burns *et al*, 1974). We have similarly not experienced any difficulty in demonstrating actomyosin by immunofluorescence in routinely processed tissues.

The demonstration of myofibrils in our three cases of adenoid cystic carcinoma using specific antiserum to actinomyosin and an indirect immunofluorescent technique is strong evidence of a myoepithelial origin of these tumours. The presence of myofibrils by immunofluorescent methods has not been reported previously. We would further suggest that pain and tenderness may also be caused by a contractile, myoepithelial component.

References

- Burns, J., Hambridge, M., and Taylor, C. R. (1974). Intracellular immunoglobulins: a comparative study on three standard tissue processing methods using horseradish peroxidase and fluorochrome conjugates. *J. clin. Path.*, **27**, 548-557.
- Cavanzo, F. J. and Taylor, H. B. (1969). Adenoid cystic carcinoma of the breast. An analysis of 21 cases. *Cancer (Philad.)*, **24**, 740-745.
- Elsner, B. (1970). Adenoid cystic carcinoma of the breast. Review of the literature and clinico-pathologic study of seven patients. *Path. europ.*, **5**, 357-364.
- Eneroth, C. M., Hjertman, L., Moberger, G., and Wersäll, J. (1968). Ultrastructural characteristics of adenoid cystic carcinoma of salivary glands. *Arch. Klin. Exp. Ohr., Nas., Kehlk.-Heilk.*, **192**, 358-368.
- Evans, R. W. and Cruickshank, A. H. (1970). *Epithelial Tumours of the Salivary Glands*. Saunders, Philadelphia and London.
- Friedman, B. A. and Oberman, H. A. (1970). Adenoid cystic carcinoma of the breast. *Amer. J. clin. Path.*, **54**, 1-14.
- Galloway, J. R., Woolmer, L. B., and Clagett, O. T. (1966). Adenoid cystic carcinoma of the breast. *Surg. Gynec. Obstet.*, **122**, 1289-1294.
- Hopkins, G. B. and Tullis, R. H. (1972). Adenoid cystic carcinoma of the breast. *Calif. Med.*, **117** (4), 9-11.
- Koss, L. G., Brannan, C. D., and Ashikari, R. (1970). Histologic and ultrastructural features of adenoid cystic

- carcinoma of the breast. *Cancer (Philad.)*, **26**, 1271-1279.
- Lusted, D. (1970). Structural and growth patterns of adenoid cystic carcinoma of breast. *Amer. J. clin. Path.*, **54**, 419-425.
- Mowry, R. W. (1956). Alcian blue techniques for the histochemical study of acidic carbohydrates. *J. Histochem. Cytochem.*, **4**, 407.
- Murad, T. M., and von Haam, E. (1968). Ultrastructure of myoepithelial cells in human mammary gland tumors. *Cancer (Philad.)*, **21**, 1137-1149.
- Nayer, H. R. (1957). Cylindroma of the breast with pulmonary metastases. *Dis. Chest.*, **31**, 324-327.
- O'Kell, R. T. (1964). Adenoid cystic carcinoma of the breast. *Missouri Med.*, **61**, 855-858.
- Sainte-Marie, G. (1962). A paraffin embedding technique for studies employing immunofluorescence. *J. Histochem. Cytochem.*, **10**, 250-256.
- Thackray, A. C. and Sobin, L. H. (1972). *Histological Typing of Salivary Gland Tumours* (International Histological Classification of Tumours, No. 7). WHO, Geneva.
- Verani, R. R. and van der Bel-Kahn, J. (1973). Mammary adenoid cystic carcinoma with unusual features. *Amer. J. clin. Path.*, **59**, 653-658.
- Wilson, W. B. and Spell, J. P. (1967). Adenoid cystic carcinoma of breast: a case with recurrence and regional metastases. *Ann. Surg.*, **166**, 861-864.
- Woyke, S., Domagala, W., and Olszewski, W. (1970). Fine structure of mammary adenoid cystic carcinoma. *Pol. med. J.*, **9**, 1140-1148.

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