Virchows Arch (1996) 428:319–324

ORIGINAL ARTICLE

Eugene F. Ruffolo · Horacio M. Maluf
Frederick C. Koerner

Spindle cell endocrine carcinoma of the mammary gland

Received: 26 February 1996 / Accepted: 25 April 1996

Abstract We report the pathological characteristics of a variant of mammary endocrine tumour, predominantly formed from cytologically bland spindle cells. This neoplasm grows as a red, well defined mass lacking the usual macroscopical characteristics of breast cancer. Within smoothly contoured aggregates arranged in an insular pattern, delicate capillaries and collagen bundles support the neoplastic epithelial cells. Most of the tumour cells possess a slender spindle shape and form a solid or fenestrated sheet, but a few appear cuboidal and create glands. Immunohistochemical studies demonstrate that the spindle cells and the glandular cells constitute a single population. Both types of cells stain for neuroendocrine markers (chromogranin, synaptophysin, and CD 57), carcinoembryonic antigen, keratin 8/18, S-100 protein, and receptors for oestrogen and progesterone. Many of the tumour cells possess argyrophilic granules, and electron microscopy may reveal dense core granules.

Key words Breast · Neoplasm · Neuroendocrine · Spindle cells

Introduction

Although spindle cell neoplasms of the breast arise only rarely, they do not usually cause difficulties in classification. Most are either sarcomas or spindle cell carcinomas, and in both cases the marked cytological atypia makes the diagnosis of malignancy obvious. Spindle cell proliferations exhibiting minimal cytological atypia, however, regularly create diagnostic confusion. Many prove to have a myoepithelial origin, but occasionally the spindle shape of the cells reflects endocrine, rather than myoepithelial, differentiation. The formation of spindle cells occurs regularly in endocrine tumours of many organs; spindle cell carcinoid tumours of the lung and medullary carcinomas of the thyroid stand out as well-recognized examples. Students of mammary pathology seem to have overlooked this phenomenon, for the literature relating to breast tumours contains only passing references to the presence of spindle-shaped cells in endocrine tumours, and no mention at all of endocrine differentiation of spindle cell neoplasms. In this report, we describe and illustrate three cases of the latter type, discuss the relevant diagnostic possibilities, and suggest an approach to the classification of such tumours.

E. F. Ruffolo (✉) · F. C. Koerner
James Homer Wright Laboratory of Pathology,
Massachusetts General Hospital, Fruit Street,
Boston, MA 02114, USA

H. M. Maluf
Pathology and Laboratory Medical Service,
Veterans Administration Medical Center,
1030 Jefferson Avenue, Memphis, TN 38104, USA

Materials and methods

Three cases reviewed by the authors in consultation form the basis of this report. The surgical records and the pathological reports provided information about the patients, the operative procedures, and the specimens.

Patients

The three women whose tumours we describe were 58, 74 and 75 years of age at the time of diagnosis. Each presented with a palpable mass that proved to be a tumour. One patient underwent a re-excision of the breast biopsy cavity and dissection of the axillary lymph nodes, which did not disclose residual carcinoma, and post-operative radiation therapy. The second patient received radiation treatments without further surgery. The third patient did not receive any subsequent therapy. All three patients remain free of recurrence after intervals ranging from 27 to 48 months.

Methods

The original tissue sections, processed in the usual fashion and stained with haematoxylin and eosin, were used to elucidate the morphological characteristics of the tumours. For immunohistochemical studies, we stained paraffin sections using a conventional ABC technique and primary antibodies directed against the following antigens: smooth muscle actin (Sigma, St. Louis, Mo., 1:2400), S-100 protein (DAKO, Carpenteria, Calif., 1:550), kera-

tin 8/18 (Becton Dickinson, San Jose, Calif., 1:5), carcinoembryonic antigen (DAKO, 1:700), chromogranin (Boehringer Mannheim, Indianapolis, Ind., 1:100), synaptophysin (Biogenex, San Ramon, Calif., 1:5), CD 57 (AMAC, Wesbrook, Me., 1:25), oestrogen receptor protein (Abbott, North Chicago, Ill., 1:4), and progesterone receptor protein (Abbot, 1:10). (The polyclonal carcinoembryonic antigen antiserum contains antibodies directed against a non-specific cross reactive antigen.) We carried out Grimelius staining according to a method that incorporates microwave heating [16] and mucin staining, by means of Meyer's mucicarmine method. Ultrastructural studies were performed in the usual fashion using tissue retrieved from the paraffin blocks.

Results

Macroscopical examination

The macroscopic appearance of the nodules did not suggest malignancy to the examining pathologists in any of the three cases. They described the masses as "well circumscribed" and "well encapsulated", and one patholo-

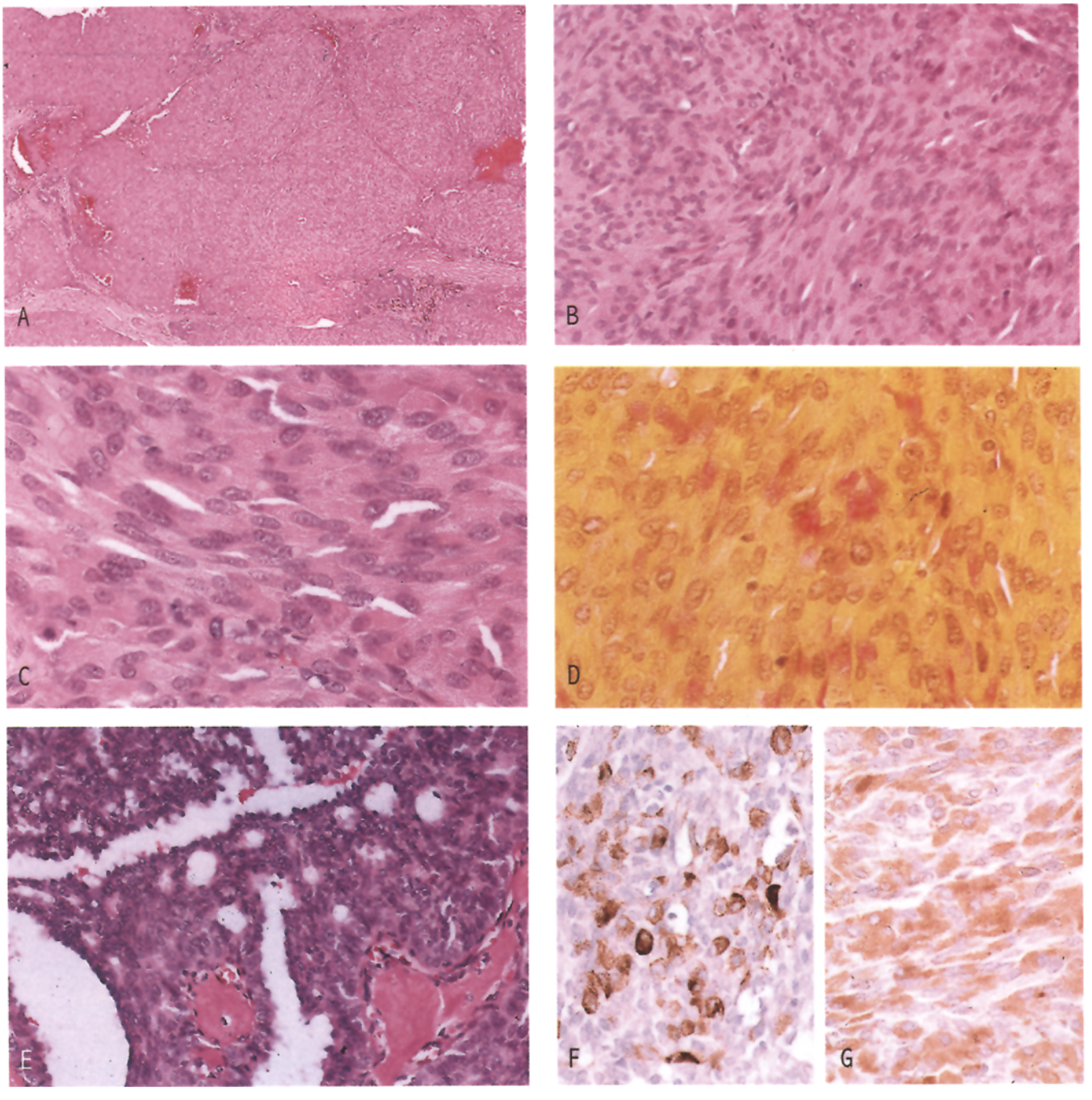

Fig. 1 **A** The tumour forms as a well-defined, lobulated nodule with an insular pattern. The tumour cells form tightly cohesive fascicles and fenestrated sheets (**B**); they possess a spindle shape and oval, bland nuclei (**C**). **D** A mucicarmine stain discloses intracellular and extracellular mucin. **E** Spindle cells and glandular cells intermingle. Immunohistochemical staining discloses **F** intense granular staining for chromogranin in case 2 and **G** diffuse cytoplasmic staining for synaptophysin in case 3

Table 1 Mammary spindle cell endocrine tumours: results of special studies

	Case 1	Case 2	Case 3
Grimelius	+	+	+
Chromogranin	+	+	+
Synaptophysin	+	+	+
CD 57	+	+	+
Smooth muscle actin	–	–	–
S-100 protein	–	+	+
Cytokeratin 8/18	+	+	+
Carcinoembryonic antigen	+	+	+
Oestrogen receptor	+	+	+
Progesterone receptor	+	+	+

gist noted a granular surface that he ascribed to "haemorrhagic papillary fronds." All the tumours exhibited a red hue, varying from pink to dark red, and all felt soft. The greatest dimension of the lesions ranged from 0.9 to 1.1 cm.

Conventional microscopy

Microscopical study of each of the specimens revealed a discrete but unencapsulated neoplasm composed of smoothly contoured, cellular aggregates arranged in an insular pattern (Fig. 1A). Within individual nests, delicate fibrovascular strands created an arborizing framework supporting the neoplastic epithelial cells. They formed tightly cohesive whorling fascicles and fenes-

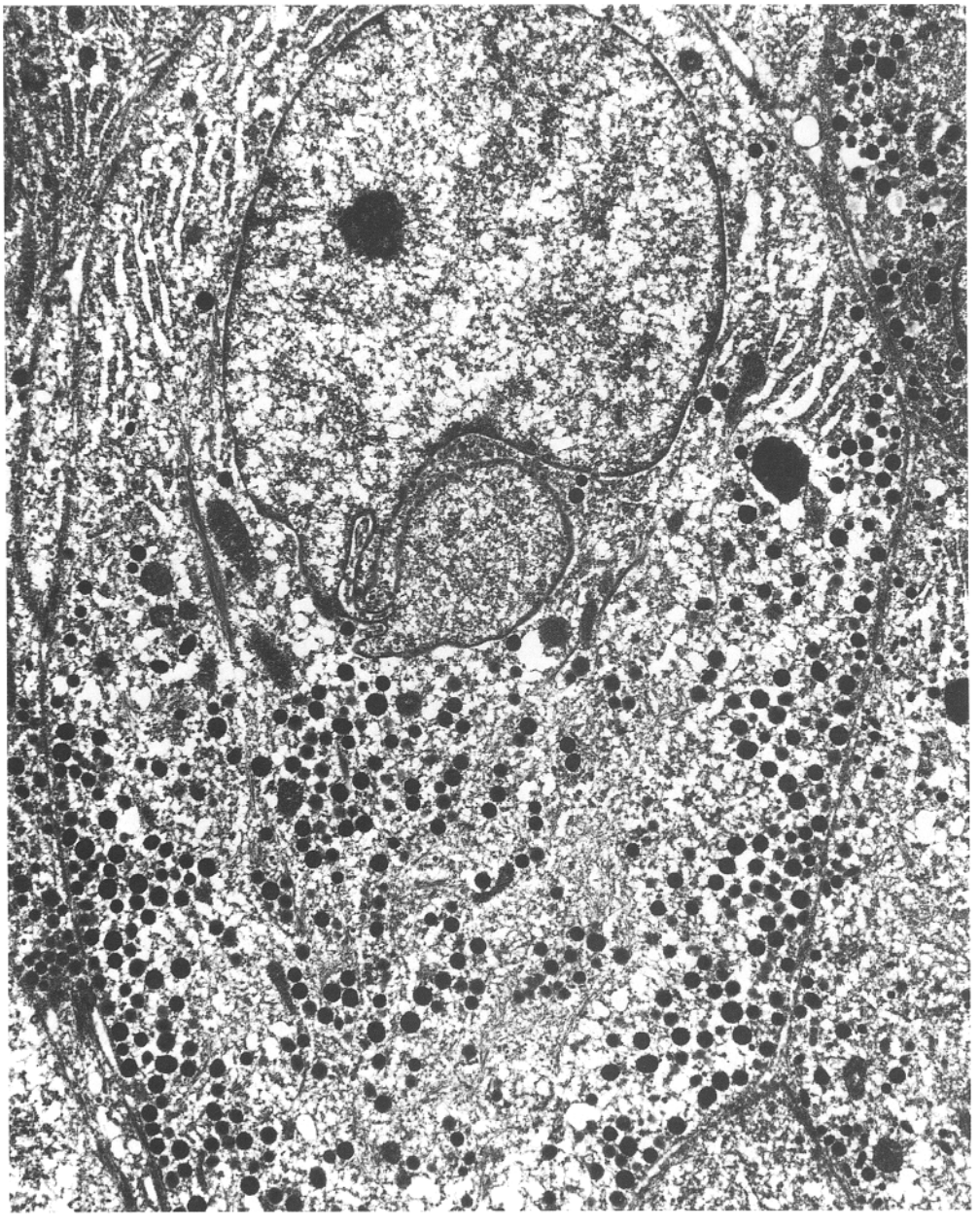

Fig. 2 Most of the cells in case 3 contain characteristic dense core granules

trated sheets (Fig. 1B). Most cells had a tapering, spindle shape (Fig. 1C), but when sectioned in a transverse plane, those with eccentric nuclei looked vaguely plasmacytoid. Around the periphery of some of the nests and adjacent to the stromal cores of a few fronds, the nuclei lined up in a parallel array to produce a "palisade" effect. Near the perimeter of the masses a few neoplastic cells exhibited a polarized, columnar shape and formed glandular lumens. High magnification disclosed the low-grade cytological atypia of the neoplastic cells. The nuclei appeared oval or elongate, slightly enlarged, and smoothly contoured; and they contain stippled chromatin (Fig. 1C). For the most part, the nucleoli appeared inconspicuous; however, small clusters of cells possessed eosinophilic nucleoli of medium size. Normal mitotic figures can be found without a tedious search, but atypical forms did not occur. The cytoplasm appears modest in amount. It stained amphophilic to brightly eosinophilic, and a few cells displayed a fine eosinophilic granularity. The tumour cells produced small amounts of mucin, which became evident with mucicarmine stains (Fig. 1D). The tumour cells did not exhibit necrosis. The stroma in the vicinity of the cell nests consisted of dense collagen and scarce fibroblasts. Haemosiderin deposits and extravasated erythrocytes attested to episodes of haemorrhage. In case 2, the spindle cell proliferation merged with a focus of papillary and cribriform intraductal carcinoma (Fig. 1E), verifying the ductal origin of the neoplasm. We found the assessment of invasion difficult. On superficial consideration, the smooth contours and vaguely lobular pattern of the neoplasm give the impression that the tumour cells resided in expanded and confluent terminal duct-lobular units. This interpretation seems unlikely, however, since the nests look too large and their arrangement too irregular for them to be accepted as distended glandular structures. Tissue apart from the tumours showed only commonplace fibrocystic changes.

Immunohistochemistry and silver staining

Table 1 presents the results of special studies. None of the tumour cells reacted with the anti-actin antibody, whereas the blood vessels stained intensely. All of the tumours exhibited staining with neuroendocrine markers. Figure 1F, G illustrates representative staining for chromogranin and synaptophysin, respectively. Both the number of positive cells and the intensity of the reaction vary from case to case, perhaps because of differences in specimen handling. Within each tumour, the glandular cells showed the same immunophenotype as the spindle cells, although the two cell types varied in the intensity of staining for certain molecules. The reaction for carcinoembryonic antigen, for example, appears to have been intense in most of the spindle cells but only faint in the glandular cells. In each case, the Grimelius method revealed many heavily granulated cells.

Electron microscopy

Despite the suboptimal tissue preservation, it was possible to evaluate the tumour in cases 2 and 3. The cells retained their overall spindle shape and possessed a somewhat eccentrically located nucleus with finely dispersed chromatin. The cytoplasm contained numerous dense core granules throughout, with a tendency to cluster in a subplasmalemmal location (Fig. 2). Granules were present in more than 80% of the cells in case 3, and in less than 5% in case 2. Also noted in the cytoplasm were occasional lysosomes, rough endoplasmic reticulum, and tonofibrils.

Discussion

A review of pertinent publications discloses that other pathologists have encountered cases more or less like the ones in this report. In fact, Papotti et al. [9] proposed the creation of a specific subtype of endocrine tumour (type E) to encompass their single example composed of spindle cells. Fetisoff et al. [5] described a complex invasive endocrine neoplasm displaying colloid and cribriform areas as well as foci in which "the neoplastic cells were fusiform to plasmacytoid .... evocative of a spindle-cell carcinoid." Maluf et al. [8] illustrated two in situ and invasive endocrine carcinomas containing large numbers of spindle cells. Tavassoli has seen "several similar examples", two of which appear in her textbook [19] as Figs. 9–24 and 9–25. Finally, the recently described solid variant of papillary carcinoma [7, 12] frequently includes a few elongated cells. It seems clear that occasional endocrine tumours of the breast contain a small number of spindle cells and that in rare cases such cells constitute the predominant population.

We believe that morphological characteristics permit the recognition of most spindle cell endocrine carcinomas of the breast; however, in the light of their uncommon occurrence and their overlapping characteristics, other diagnoses must be considered. Based on purely theoretical grounds, alternatives include spindle cell proliferations of connective tissue, epithelium, and myoepithelium. From a practical point of view, most of the lesions in the first two categories do not require serious consideration. Spindle cell sarcomas, for example, have both an infiltrative growth pattern and a sufficient degree of anaplasia to ensure that they are not confused with the tumours we describe. The diagnosis of leiomyoma might also come to mind, but smooth muscle cells have characteristic oval nuclei and their cytoplasm lacks the eosinophilic granules found in spindle cell endocrine carcinomas. Rare carcinomas lacking endocrine qualities consist predominantly of spindle-shaped cells, but these non-endocrine spindle cell carcinomas exhibit additional features not observed in the carcinomas we describe: squamous differentiation, pseudovascular spaces, and an infiltrative manner of growth. Conventional ductal-type epithelial hyperplasia poses a more realistic diagnostic al-

ternative, especially since the smoothly contoured nests of an endocrine tumour could be mistaken for the enlarged terminal duct-lobular units of ductal hyperplasia and the spindle shape of the cells could be misinterpreted as a manifestation of myoepithelial differentiation. The distinction can be made by observing the presence of stromal cells, mitotic figures, and endocrine characteristics. Conventional ductal-type epithelial hyperplasia represents a proliferation limited almost exclusively to epithelial cells without supporting collagen fibres. Mitotic activity of hyperplastic cells is observed only in unusual circumstances, and endocrine differentiation does not occur to any significant extent. Spindle cell endocrine carcinomas, in contrast, possess a fine, fibrovascular skeleton, display division figures, and exhibit endocrine features.

Neoplasms composed of myoepithelial cells constitute the major source of confusion with spindle cell endocrine carcinomas. Myoepithelial neoplasms take two forms: pure myoepithelial proliferations (myoepitheliomas) and mixed myoepithelial/epithelial tumours (adenomyoepitheliomas). Most of the few reported cases of the first group have no striking resemblance to endocrine carcinomas. Tamai [17] described a predominantly non-invasive myoepithelioma, but the presence of comedo-necrosis and polygonal cells containing clear cytoplasm distinguishes this case from those we report. In invasive myoepitheliomas of both benign [1, 4, 10] and malignant [2, 6, 14, 15, 20] types, the neoplastic cells grow as sheets or cords rather than as nests; and tumour cells infiltrate adjacent tissue by permeation rather than in the blunt manner characteristic of our cases. Only the "benign human mammary myoepithelioma" reported by Toth [21] might constitute an exception, but since this tumour contains glands as well as myoepithelial cells, it probably does not represent a purely myoepithelial neoplasm. It seems more reasonable to consider the tumour described by Toth as a combined myoepithelial/epithelial lesion, perhaps an adenomyoepithelioma of the spindle cell type [11, 18, 23]. In this variant of adenomyoepithelioma, the myoepithelial proliferation so predominates that the glandular component becomes virtually inapparent, and the tumour comes to mimic a spindle cell endocrine carcinoma. Both neoplasms can demonstrate low-grade cytological atypia, mitotic activity, peripheral palisading, and a limited degree of gland formation. So closely can these two lesions resemble each other that it might be difficult to separate them on the basis of examination of just a few fields. The intraductal spindle cell adenomyoepithelioma depicted by Tavassoli [18, Fig. 4a], for instance, virtually duplicates selected regions of the neoplasms in our group.

Immunohistochemical studies with special attention to the staining profiles of the glandular and spindle cell components should resolve this problematic distinction. Adenomyoepitheliomas, by their very nature, consist of two types of cells: luminal epithelial cells forming glandular spaces, and myoepithelial cells growing as solid or fenestrated sheets [13, 22, 24, 25]. The luminal cells express epithelial membrane antigen [11] but lack both smooth muscle specific actin [11, 18] and vimentin [23]. The myoepithelial cells exhibit the opposite staining results, and most of the latter cells stain strongly for S-100 protein [11, 18, 22, 23]. Spindle cell endocrine carcinomas, in contrast, consist of a single population of neoplastic cells that adopt different shapes. Immunohistochemical staining of our cases revealed qualitatively similar results in both the glandular and spindle cells, as well as an immunophenotype different from the one described for adenomyoepitheliomas. The tumours we describe lack smooth muscle-specific actin, they show variable staining for S-100 protein, and they produce cytokeratins 8/18 and carcinoembryonic antigen. Moreover, they contain structures and molecules that we do not expect to find in adenomyoepitheliomas: argyrophilic granules, dense core granules, chromogranin, synaptophysin, CD 57, oestrogen receptors, and progesterone receptors. In summary, we suggest that the results of immunohistochemical staining for smooth muscle actin, carcinoembryonic antigen, endocrine molecules, and oestrogen and progesterone receptors will separate spindle cell endocrine carcinomas from adenomyoepitheliiomas. Grimelius staining and ultrastructural examination can provide additional information if needed.

We expect that the choice of diagnosis for these spindle cell endocrine neoplasms will prove to be the most contentious aspect of the cases. We considered the diagnosis of "carcinoid tumour", which Cubilla and Woodruff [3] used in their seminal publication describing low-grade endocrine tumours of the breast. The tumours they illustrate do not resemble small intestinal carcinoids, however, and current opinion does not favour the authors' all-encompassing use of this term. Contemporary experts in mammary pathology have therefore abandoned the name carcinoid tumour in this context. They prefer to classify these cancers according to conventional schemes and to indicate the presence of endocrine differentiation as a modifying phase [12]. We also share this philosophy, but it does not provide a ready name for the tumours in this report. Their characteristics differ so substantially from those of conventional breast carcinomas that we would be unhappy about classifying spindle cell endocrine carcinomas as invasive ductal carcinoma, NOS, with endocrine features. Neither do the tumours in our group closely resemble any of the specialized types of ductal carcinoma. There are certain similarities between spindle cell endocrine carcinomas and solid papillary carcinomas [7], and we have encountered one case in which a recurrence of the latter type of carcinoma appeared identical to the former. This single example notwithstanding, the two lesions usually differ in several respects. First, spindle cell endocrine carcinomas grow as compact, rounded, cellular aggregates that first fill and then distend glands; and an arborizing skeleton of delicate fibrous connective tissue supports the neoplastic cells. Solid papillary carcinomas, on the other hand, form blunt papillary structures protruding into cystically dilated ducts, and hyalinized connective tissue forms the

core of many papillae. Second, spindle-shaped cells constitute virtually the entire population in spindle cell neoplasms but only a minor component of most solid papillary carcinomas. Finally, the infiltrating nests of the tumours we describe resemble the co-existing in situ proliferation. The invasive component of solid papillary carcinomas usually takes the form of a cellular mucinous carcinoma rather than the broad, papillary architecture of the in situ component. Since we could find no existing name that satisfactorily describes the three cancers we illustrate, we offer a new diagnosis – spindle cell endocrine carcinoma. This term highlights the essential morphological characteristics of the neoplasms, while sidestepping some of their undefined aspects, such as histogenesis and natural behaviour.

In conclusion, we have described three mammary tumours comprised almost entirely of spindle-shaped cells that display endocrine features. We view these lesions as members of a family of spindle cell epithelial tumours with endocrine differentiation, a group encompassing both low-grade neoplasms that could pass as spindle cell carcinoid tumours and high-grade cancers that duplicate the appearance of pulmonary small cell carcinoma. Like most other endocrine tumours of the breast, the low-grade cancers we report occurred in older women, were characterized by low-grade cytological atypia, and contained oestrogen receptors. Pathologists unfamiliar with this pattern could confuse these carcinomas with spindle cell adenomyoepitheliomas, papillomas, or ductal hyperplasia; however, conventional microscopical characteristics can exclude most of these alternatives, and immunohistochemical findings should resolve any remaining ambiguities. We know little of the natural history of the neoplasm. We hope that this description will lead to more widespread recognition of the lesion and greater appreciation of its clinical characteristics.

Acknowledgements The following pathologists contributed the cases: Dr. Eugene H. Ruffolo, Tampa, Fla.; Dr. Mary Annarella, Milton, Mass.; and Dr. Rosina Lis, Natick, Mass. Dr. G. Richard Dickersin offered advice concerning interpretations of ultrastructural findings. Ms. Ellen Wilson typed the manuscript. Mr. Steve Connelly and Ms. Michele Forrestall assisted with the photography. Phyllis Love performed the immunohistochemistry.

References

1. Bigotti G, Di Giorgio CG (1986) Myoepithelioma of the breast: histologic, immunologic, and electromicroscopic appearance. J Surg Oncol 32:58–64
2. Cartagena N Jr, Cabello-Inchausti B, Willis I, Poppiti R Jr (1988) Clear cell myoepithelial neoplasm of the breast. Hum Pathol 19:1239–1243
3. Cubilla AL, Woodruff JM (1977) Primary carcinoid tumour of the breast. Am J Surg Pathol 1:283–292
4. Erlandson RA, Rosen PP (1982) Infiltrating myoepithelioma of the breast. Am J Surg Pathol 6:785–793
5. Fetissof F, Dubois MP, Arbeille-Brassart B, Lansac J, Jobard P (1983) Argyrophilic cells in mammary carcinoma. Hum Pathol 14:127–134
6. Maiorano E, Rico R, Virgintino D, Lastilla G (1994) Infiltrating myoepithelioma of the breast. Appl Immunohistochem 2:130–136
7. Maluf H, Koerner FC (1995) Solid papillary carcinoma of the breast. A form of intraductal carcinoma with endocrine differentiation frequently associated with mucinous carcinoma. Am J Surg Pathol 19:1237–1244
8. Maluf HM, Zukerberg LR, Dickersin GR, Koerner FC (1991) Spindle cell mucin producing argyrophilic carcinoma of the breast. Histological, ultrastructural and immunohistological studies of two cases. Am J Surg Pathol 15:677–686
9. Papotti M, Macri L, Finzi G, Capella C, Eusebi V, Bussolati G (1989) Neuroendocrine differentiation in carcinomas of the breast: a study of 51 cases. Semin Diagn Pathol 6:174–188
10. Rode L, Nesland JM, Johannessen JV (1986) Case 6: a spindle cell breast lesion in a 54-year-old woman. Ultrastruct Pathol 10:421–425
11. Rosen PP (1987) Adenomyoepithelioma of the breast. Hum Pathol 18:1232–1237
12. Rosen PP, Oberman HA (1993) Tumors of the mammary gland. Atlas of tumor pathology, 3rd ser. Armed Forces Institute of Pathology, Washington, DC
13. Saez A, Serrano T, Azpeitia D, Condom E, Moreno A (1992) Adenomyoepithelioma of the breast. A report of two cases. Arch Pathol Lab Med 116:36–38
14. Schurch W, Potvin C, Seemayer TA (1985) Malignant myoepithelioma (myoepithelial carcinoma) of the breast: an ultrastructural and immunocytochemical study. Ultrastruct Pathol 8:1–11
15. Soares J, Tomasic G, Bucciarelli E, Eusebi V (1994) Intralobular growth of myoepithelial cell carcinoma of the breast. Virchows Arch 425:205–210
16. StatPath (1990) Microwave oven methods in pathology, sect. 6. Statfath, Riverwood, Md, pp 28–29
17. Tamai M (1992) Intraductal growth of malignant mammary myoepithelioma. Am J Surg Pathol 16:1116–1125
18. Tavassoli FA (1991) Myoepithelial lesions of the breast. Myoepitheliosis, adenomyoepithelioma, and myoepithelial carcinoma. Am J Surg Pathol 15:554–568
19. Tavassoli FA (1992) Pathology of the breast. Elsevier, New York, pp 321–326
20. Thorner PS, Kahn HJ, Baumal R, Lee K, Moffatt W (1986) Malignant myoepithelioma of the breast. An immunohistochemical study by light and electron microscopy. Cancer 57:745–750
21. Toth J (1977) Benign human mammary myoepithelioma. Virchows Arch [A] 374:263–269
22. Trojani M, Guiu M, Trouette H, De Mascarel I, Cocquet M (1992) Malignant adenomyoepithelioma of the breast. An immunohistochemical, cytophotometric, and ultrastructural study of a case with lung metastases. Am J Clin Pathol 98:598–602
23. Weidner N, Levine JD (1988) Spindle-cell adenomyoepithelioma of the breast. A microscopic, ultrastructural, and immunocytochemical study. Cancer 62:1561–1567
24. Young RH, Clement B (1988) Adenomyoepithelioma of the breast. A report of three cases and review of the literature. Am J Clin Pathol 89:308–314
25. Zarbo RJ, Oberman HA (1983) Cellular adenomyoepithelioma of the breast. Am J Surg Pathol 7:863–870