Virchows Arch. A Path. Anat. and Histol. 388, 175–186 (1980)

Virchows Archiv A

The Ultrastructure of Medullary Carcinoma of the Breast

Ali Ahmed
Department of Pathology, University of Manchester, Manchester M13 9PT, England

Summary. Three cases of medullary carcinoma complying with strictly defined criteria have been examined by electron microscopy. These carcinomas are characterised by the presence of light and dark tumour cells which exhibit prominent organelles and well-developed Golgi complexes but lack secretory activity. The essential stromal cellular infiltrate of macrophages, lymphocytes and plasma cells contains macrophage–lymphocyte clusters suggesting the existence of an immune response. Also present in the stroma are blood vessels lined by high-endothelial cells of the type said to facilitate lymphocyte migration.

It is suggested that light and dark tumour cells with well-developed organelles but absent secretory activity, macrophage-lymphocyte clusters and stromal high-endothelial venules represent specific ultrastructure features of typical medullary carcinoma associated with good prognosis.

Key words: Breast – Medullary carcinoma – Electron microscopy.

Introduction

Medullary carcinoma is an infrequent type of breast carcinoma which has been said to be associated with relatively good prognosis (Moore and Foote 1949; Richardson 1956). More recently, Ridolfi et al. (1977), by applying strict diagnostic criteria, have clearly shown that medullary carcinoma represents a distinct morphological entity with a significantly better prognosis than the ordinary infiltrating ductal carcinoma. Three cases of medullary carcinoma fulfilling these diagnostic criteria have been examined by electron microscopy with the particular purpose of defining specific ultrastructural features of such tumours.

Offprint requests to: Department of Pathology, Stopford Building, University of Manchester, Manchester, M13 9PT, England

0340-1227/80/0388/0175/$02.40

Material and Method

Tissue was obtained at the time of frozen section diagnosis from three cases of medullary carcinomas which on paraffin sections fulfilled the strict criteria defined by Ridolfi et al. (1977). Small fragments of tissue were fixed in 4% glutaraldehyde buffered with 0.1 sodium cacodylate pH 7.4 for 4 h. After fixation, the glutaraldehyde was decanted and the tissue washed in sodium cacodylate buffer containing 3 mM $CaCl_2$. The tissue fragments were then post-fixed in osmium tetroxide (buffered at pH 7.4) for 1 h, prior to dehydration and embedding in Araldite. Sections 0.5–1 μm thick were stained with alkaline toluidine blue for tissue selection. Thin sections were double-stained with lead citrate and uranyl acetate and examined in an AEI EM 6B electron microscope with an accelerating voltage of 60 kV.

Results

The histological appearances of the tumours comply with the typical medullary carcinoma (Ridolfi et al. 1977) namely the presence of predominately syncytial growth pattern, completely circumscribed margins and a moderate to marked mononuclear stromal infiltrate (Fig. 1). Another noteworthy but less well known feature is the presence, at the periphery of tumour cell masses, of smaller more elongated cells with denser cytoplasm and nuclei (Fig. 2) (Azzopardi 1979).

At ultrastructural level, many of the closely packed tumour cells exhibit electron-lucent cytoplasm which is rich in organelles comprising many mitochondria often arranged in small groups, profiles of rough-surfaced endoplasm reticulum, free ribosomes and well-developed Golgi complexes (Fig. 3). Occasional tumour cells contain lipid bodies and others show glycogen deposits. However, secretory vesicles are rarely seen and intracytoplasmic lumina are infrequent.

The oval or round nuclei show a relatively smooth nuclear membrane and occasionally contain prominent nucleoli. Nuclear inclusions, cytoplasmic invaginations and perichromatin granules, as seen in infiltrating ductal carcinoma (Ahmed 1978) are relatively uncommon.

The relatively straight plasma membranes of tumour cells show fairly frequent desmosomal contact (Fig. 3) and occasional interdigitations.

Intermingled among the light electron-lucent tumour cells are dark cells with electron-dense cytoplasm and nuclei. The cytoplasm of dark tumour cells contains focal aggregates of polyribosomes as well as dilated rough-surfaced endoplasmic reticulum. Golgi complexes, as in light tumour cells, are also prominent in dark tumour cells (Fig. 3) but secretory activity is minimal or completely absent. Frequent desmosomal contacts are present between light and dark tumour cells. These dark tumour cells completely lack morphological features of myoepithelial cells namely cytoplasmic filaments with dense bodies, and pinocytotic vesicles. Such dark tumour cells are often located at the periphery of tumour cell masses (Fig. 4).

The stromal cellular infiltrate consists of lymphocytes, macrophages and occasional plasma cells. The lymphocyte population predominates and consists of heterogenous group of small, medium and large lymphocytes (Fig. 4). Many of the lymphocytes are arranged in close association with macrophages to form

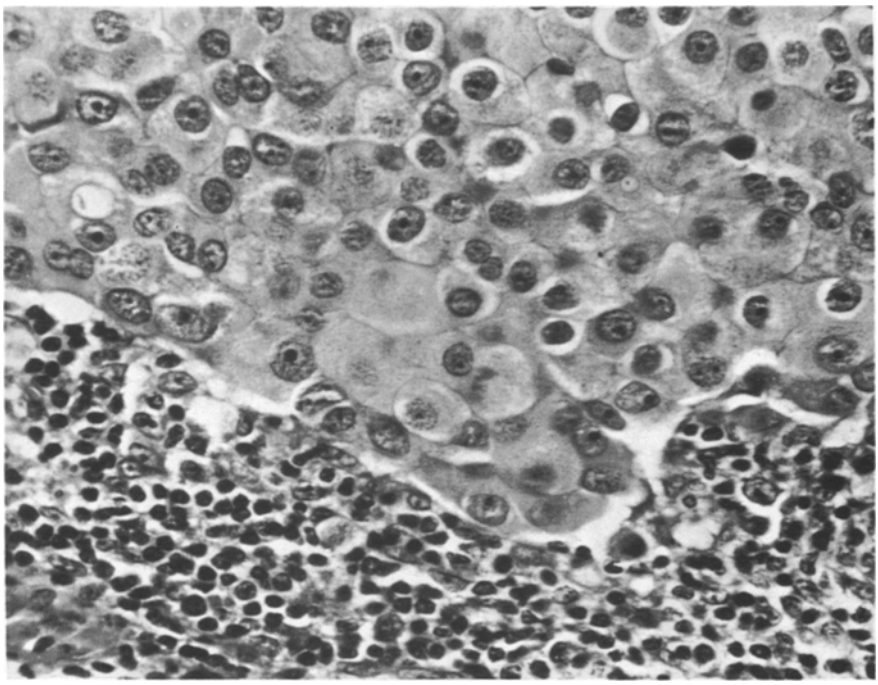

Fig. 1. Medullary carcinoma. The tumour cells show a syncytial growth and are associated with a dense mononuclear infiltrate. H&E, ×350

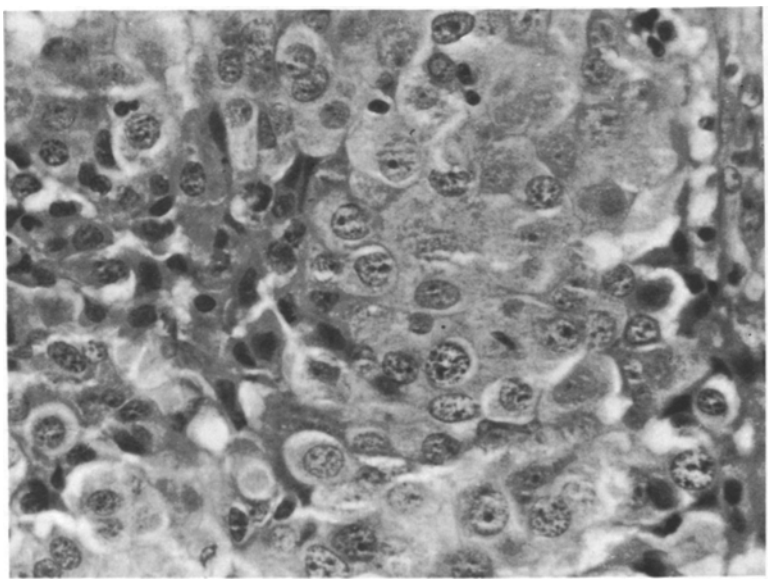

Fig. 2. Medullary carcinoma. Note the peripheral, dark elongated tumour cells. H&E, ×350

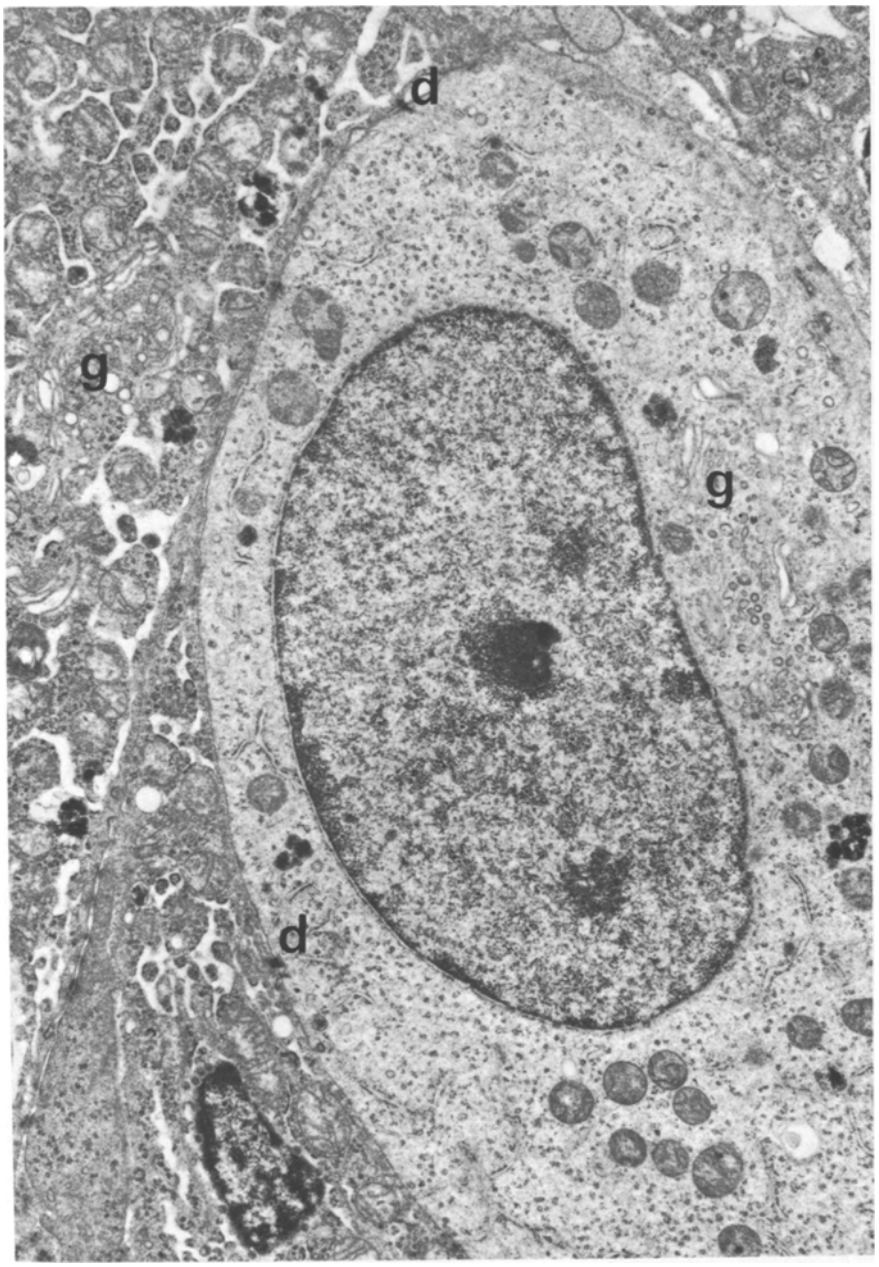

Fig. 3. Medullary carcinoma. A light tumour cell shows prominent organelles and well-developed Golgi complex (*g*). The adjacent dark tumour cell also exhibits prominent Golgi complex (*g*). Note the presence of desmosomes (*d*) between light and dark tumour cells. × 10,000

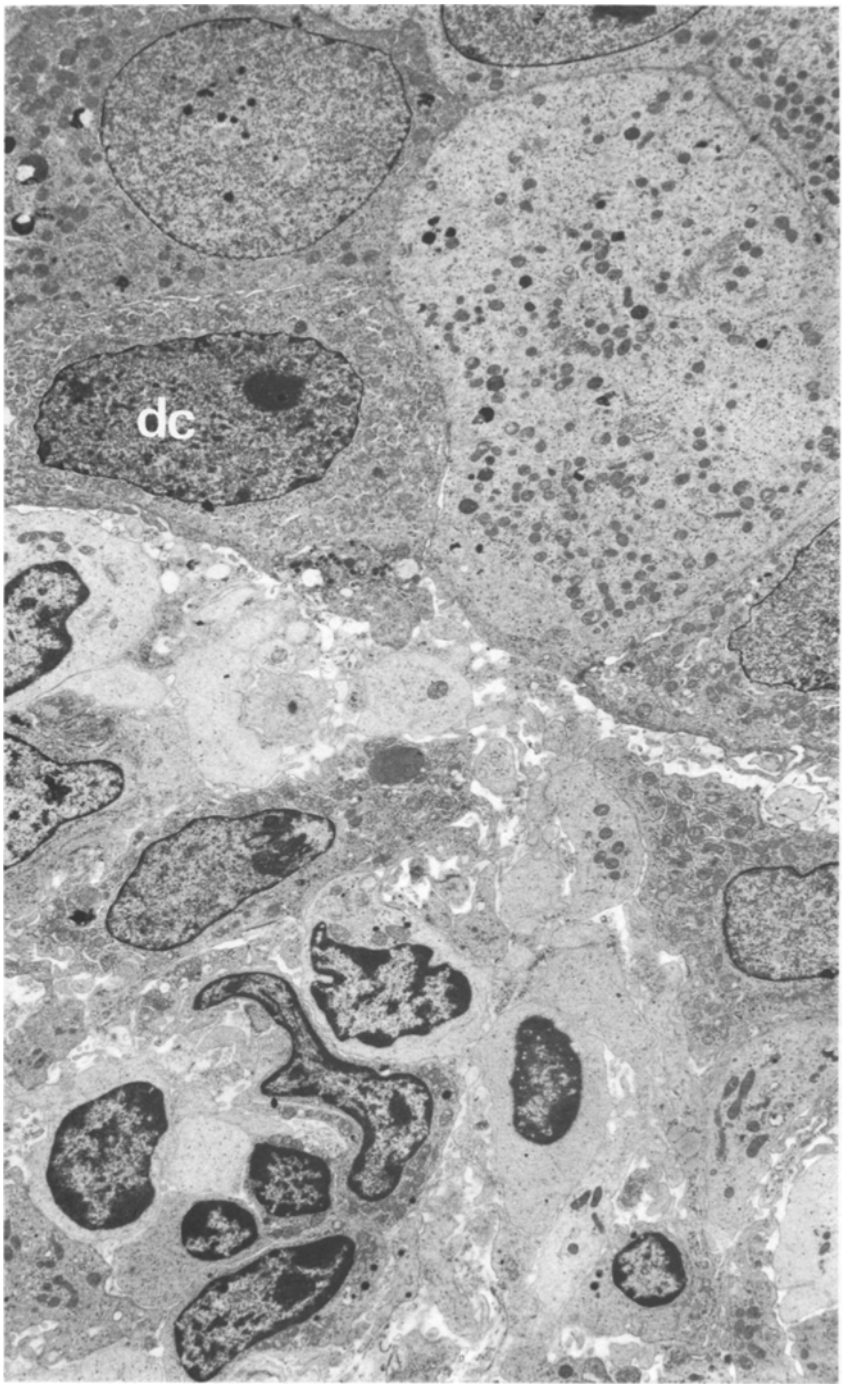

Fig. 4. Medullary carcinoma. The light and dark tumour cells (*dc*) are associated with stromal cellular infiltrate containing macrophages and many lymphocytes. × 3,800

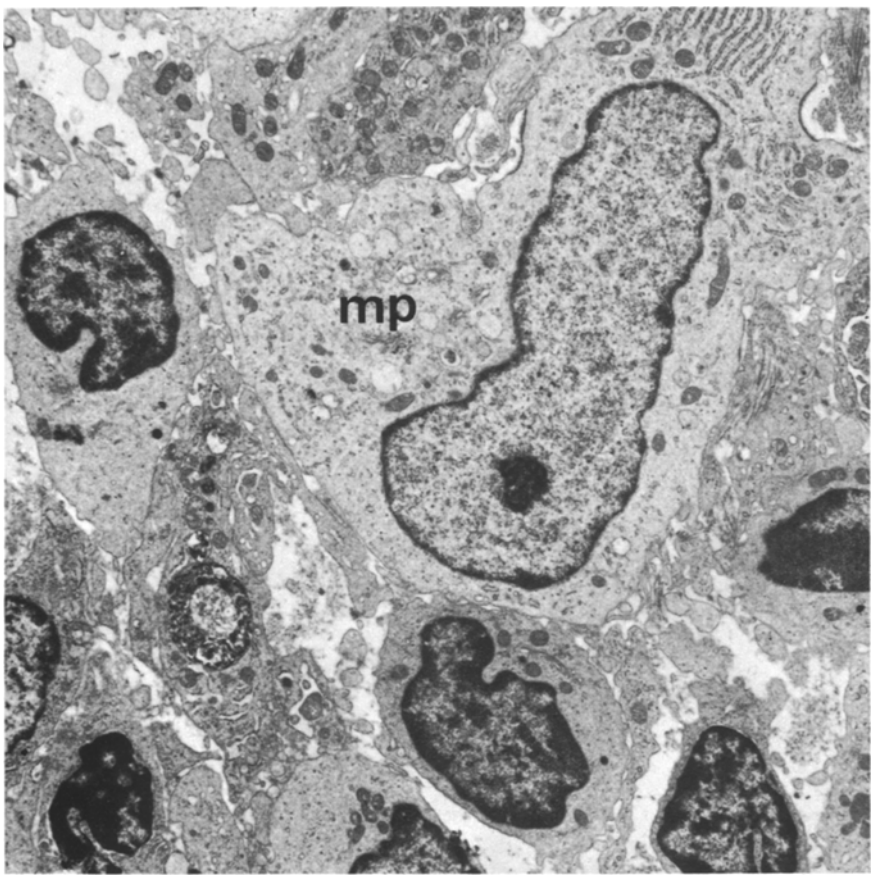

Fig. 5. Medullary carcinoma. A macrophage (*mp*) is surrounded by lymphocytes to form a macrophage-lymphocyte cluster. ×6,250

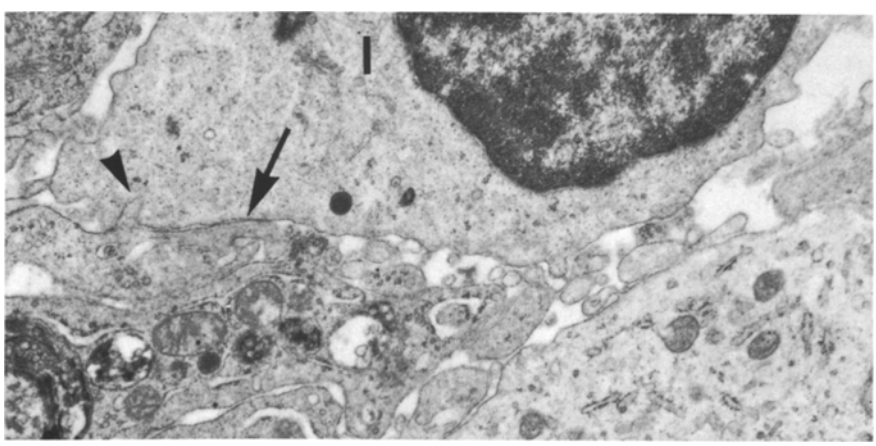

Fig. 6. Medullary carcinoma. Plasmalemmal contact (*arrow*) and occasional interdigitation (*arrowhead*) are seen between a macrophage and lymphocyte (*l*). ×12,500

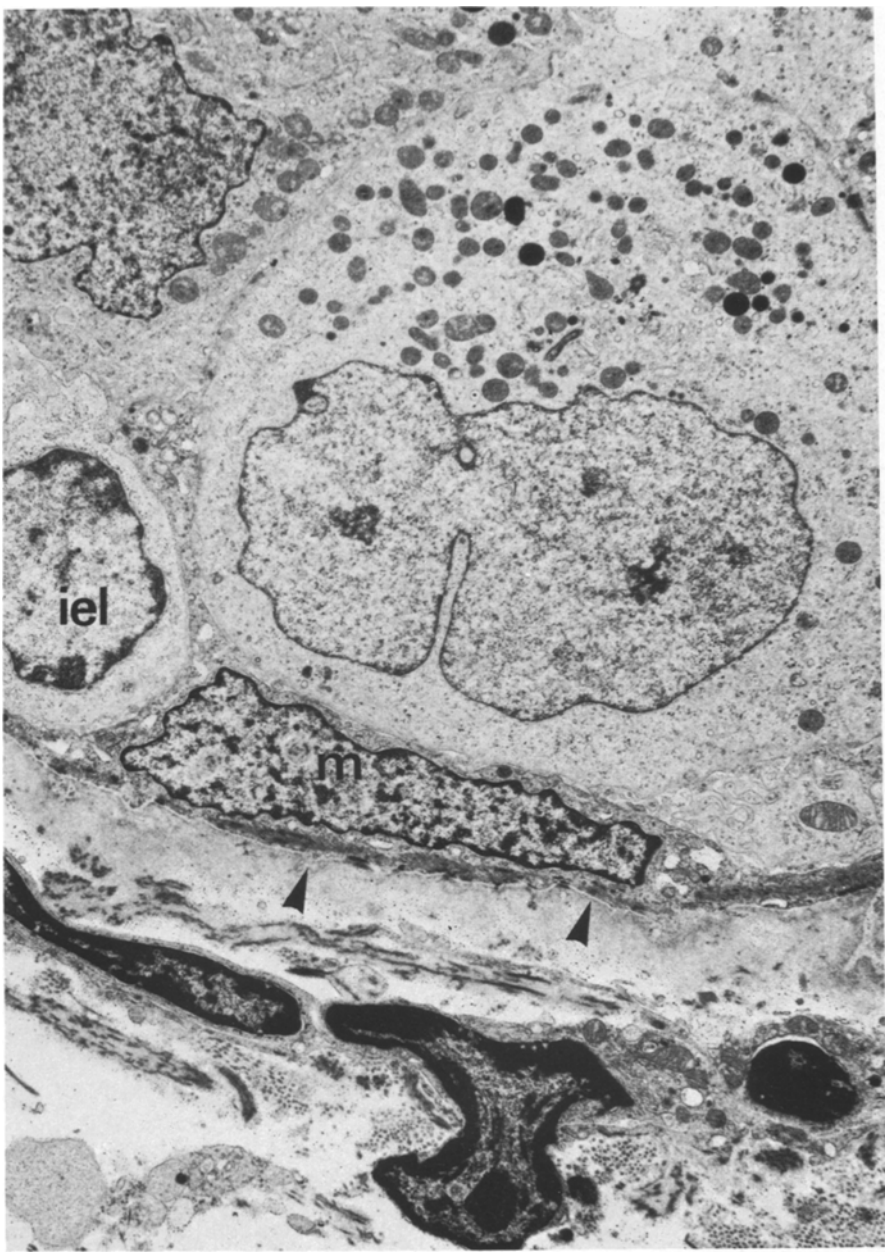

Fig. 7. Medullary carcinoma. An in-situ component shows part of a persisting myoepithelial cell (*m*) with adjacent basal lamina (*arrowheads*). Note the presence of an interepithelial lymphocyte (*iel*). ×8,250

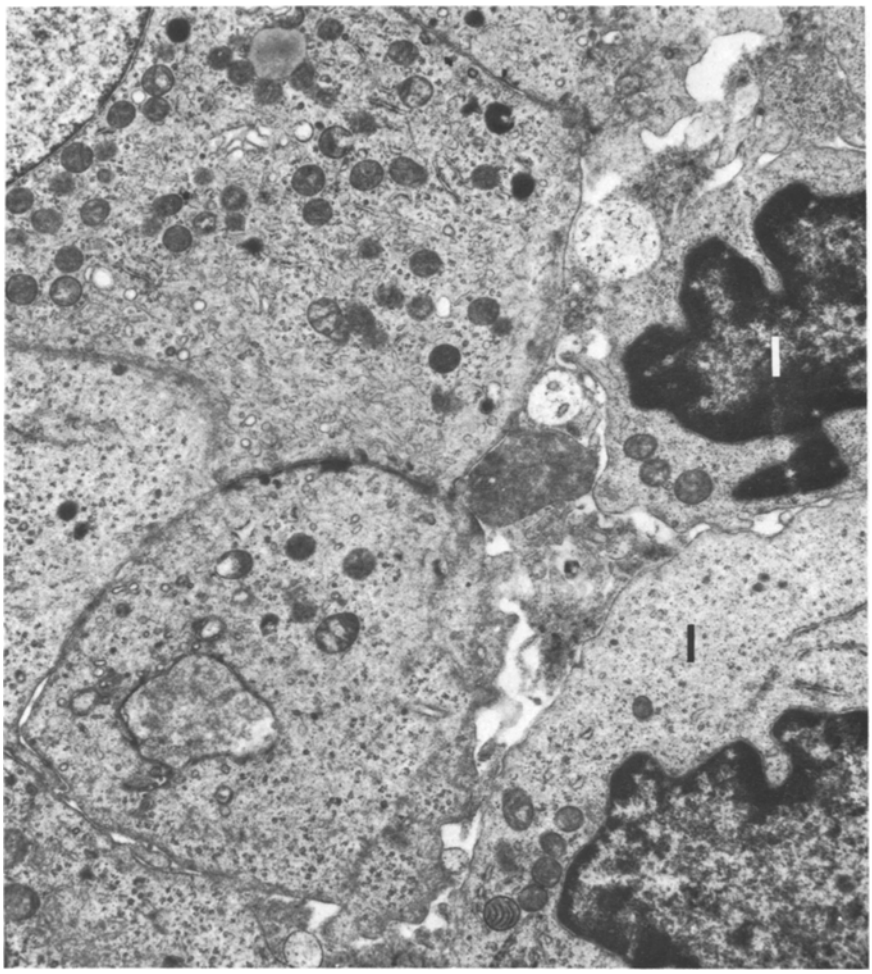

Fig. 8. Medullary carcinoma. Lymphocytes (*l*) are seen near tumour cells with well-preserved organelles. × 10,000

macrophage-lymphocyte clusters (Fig. 5). Some of the lymphocytes show close plasmalemmal contacts with the macrophages (Fig. 6).

Interepithelial lymphocytes are seen among the tumour cells of the rarely described in-situ component present in one of the cases examined (Fig. 7).

Both macrophages and lymphocytes are seen in close proximity to carcinoma cells which, however, do not show morphological evidence of degeneration (Fig. 8).

Another particular feature noted in the stroma of medullary carcinoma is the presence of blood vessels lined by prominent endothelial cells. Occasionally such vessels are seen to be associated with lymphocyte migration (Fig. 9).

There is no significant increase in the amounts of stromal collagen and

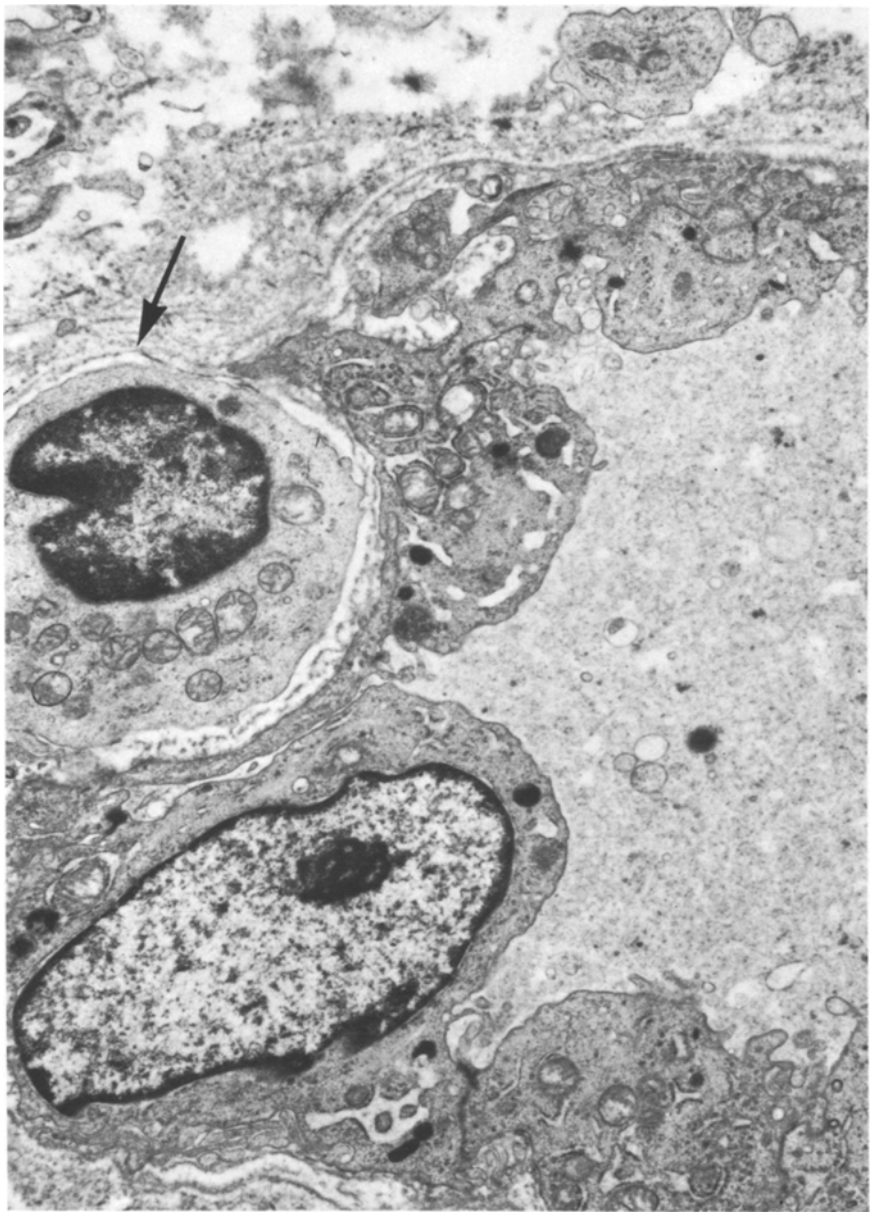

Fig. 9. Medullary carcinoma. A stromal blood vessel is lined by high endothelial cells. Note the closely related lymphocyte which is partially surrounded by basal lamina (*arrow*). ×10,000

elastic tissue. There is also no evidence of calcification among the tumour cells or in the stroma.

Discussion

The histologically distinctive medullary carcinoma of the breast appears also to possess certain specific ultrastructural features.

The light and dark tumour cells observed in the present study were noted in all the previous ultrastructural reports of medullary carcinoma (Murad and Scarpelli 1967; Michaud and Morin 1971; Gould et al. 1975; Fisher 1976), and represent a constant feature of this tumour. The smaller, denser cells seen by light microscopy, the nature of which has been questioned (Azzopardi 1979), most likely represent the dark tumour cells seen ultrastructurally. These dark tumour cells do not show morphological features of myoepithelial cells. Gould et al. (1975) found occasional myoepithelial cells at the periphery of medullary carcinomas. Such myoepithelial cells, however, must be considered to be part of the in-situ component (Fig. 7). It should be pointed out that the presence of an in-situ component, in combination with the other characteristic features, does not in itself preclude the diagnosis of medullary carcinoma (Ridolfi et al. 1977).

On morphological basis, there were considerable similarities between the light and dark tumour cells and the latter did not show evidence of degeneration to account for their electron-density. In a recent study, dark epithelial cells, observed in carcinogen-induced dysplastic changes in tracheal epithelium, were stated to be able to actively incorporate 3H-thymidine and thus provide an argument against the possibility of their being inactive or necrobiotic cells (Klein-Szanto et al. 1980).

Medullary carcinoma cells generally appear to be rich in organelles and in particular possess well-developed Golgi complexes. However, unlike mucin-producing breast carcinoma cells which are also characteristic by the presence of well-developed Golgi complexes (Ahmed 1974), medullary carcinoma cells lack secretory vesicles. The absence of mucin secretion is considered to be another important histological feature of medullary carcinoma (Azzopardi 1979). This lack of secretory activity would also account for the curious absence of calcification in medullary carcinomas which often undergo necrosis. Calcification has been suggested to occur as a result of an active secretory process by breast cancer cells (Ahmed 1975).

The few previous ultrastructural studies of medullary carcinoma have included only brief comments regarding the stromal cellular infiltrate. Gould et al. (1975), noted the presence of abundant lymphocytes and Fisher (1976) observed lymphocytes and plasma cells in the stroma. However, neither of these studies described any specific features present in the cellular infiltrate. The finding of macrophage-lymphocyte clusters in the cellular infiltrate is, therefore, of interest. Such clusters have been observed in lymphoid tissue and are considered to be an important event in the initiation and regulation of immune responses (Farr and De Bruyn 1975). The focal close contacts between macro-

phages and lymphocytes may well represent possible sites of interchange of immunological information. Similar sites have been described among lymphoid cells in vivo and in vitro (Holbrook et al. 1977). Further support for the possible existence of an immune response in medullary carcinoma comes from the finding of interepithelial lymphocytes among carcinoma cells of the in-situ component. Interepithelial lymphocytes in mammary ducts have been attributed a possible surveillance role in which antigenic information from the glandular and/or from altered cell surface is developed (Schoorl et al. 1976).

The presence of high-endothelial venules in the stroma of medullary carcinoma is also of interest. Such vessels have been described in lymphoid tissue and are regarded as specialized structures constructed to facilitate lymphocyte migration (Anderson et al. 1976). Similar vessels have not been observed in the stroma of other histological types of breast carcinomas (unpublished observations).

The evidence for the possible presence of in-vivo cytotoxic activity by macrophages and lymphocytes is, as yet, lacking. The tumour cells in contact with macrophages and lymphocytes do not show features of degeneration, an observation also reported previously (Underwood and Carr 1972; Fisher 1976).

Despite the lack of evidence for in-vivo cytotoxic activity, the overall morphological appearances of the stroma in medullary carcinoma strongly suggest that the cellular infiltrate has a functional, immunological significance which is reflected in the prognosis. Ridolfi et al. (1977) found that a better 10 year survival in patients with medullary carcinoma correlated with a more intense cellular infiltrate.

The present observations suggest that light and dark tumour cells with prominent organelles but absent secretory activity, macrophage-lymphocyte clusters and high-endothelial venules represent specific ultrastructural features of typical medullary carcinoma associated with good prognosis.

References

Ahmed A (1974) Electron microscopic observations of scirrhous and mucin-producing carcinomas of the breast. J Pathol 112:177–181

Ahmed A (1975) Calcification in human breast carcinomas: ultrastructural observations. J Pathol 117:247–251

Ahmed A (1978) Atlas of the ultrastructure of human breast diseases. Churchill-Livingstone, Edinburgh, London and New York, p 92

Anderson ND, Anderson AO, Wyllie RG (1976) Specialized structure and metabolic activities of high endothelial venules in rat lymphatic tissue. Immunology 31:455–473

Azzopardi JG (1979) Problems in breast pathology. In: Major problems in pathology, vol 11. WB Saunders Company Ltd, London, Philadelphia, Toronto p 288

Farr AG, De Bruyn PPH (1975) Macrophage lymphocyte clusters in lymph nodes: A possible substrate for cellular interactions in the immune response. Am J Anat 144:209–232

Fisher ER (1976) Ultrastructure of human breast and its disorders. Am J Clin Pathol 66:291–375

Gould VE, Miller J, Jao W (1975) Ultrastructure of medullary, intraductal, tubular and adenoid cystic carcinomas – Comparative patterns of myoepithelial differentiation and basal lamina deposition. Am J Pathol 78:401–416

Holbrook KA, Perkins WV, Glick B (1977) Contact sites between lymphoid cells of the bursa of Fabricius in vivo and in vitro. Anat Rec 189:567–576

Klein-Szanto AJP, Topping DC, Heckman CA, Nettesheim P (1980) Ultrastructural characteristics of carcinogen-induced dysplastic changes in tracheal epithelium. Am J Pathol 98:83–100

Michaud J, Morin J (1971) Ultrastructure d'un epithelioma medullaire de la glande mammaire. Laval Medical 42:496–507

Moore OS Jr, Foote FW Jr (1949) The relatively favorable prognosis of medullary carcinoma of the breast. Cancer 2:635–642

Murad TM, Scarpelli DG (1967) The ultrastructure of medullary and scirrhous mammary duct carcinoma. Am J Pathol 50:335–360

Richardson WW (1956) Medullary carcinoma of the breast: a distinctive tumour type with a relatively good prognosis following radical mastectomy. Br J Cancer 10:415–423

Ridolfi RL, Rosen PP, Port A, Kinne D, Miko V (1977) Medullary carcinoma of the breast. A clinicopathologic study with 10 year follow-up. Cancer 40:1365–1385

Schoorl R, Brutel de la Riviere A, Von dem Borne AEGK, Feltkamp-Vroom TM (1976) Identification of T and B lymphocytes in human breast cancer with immunohistochemical techniques. Am J Pathol 84:529–544

Underwood JCE, Carr I (1972) The ultrastructure of the lymphoreticular cells in non-lymphoid human neoplasms. Virchows Archiv [Cell Pathol] 12:39–50

Accepted May 23, 1980