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A histopathological and ultrastructural study of eccrine porocarcinoma with special reference to its subtypes

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Summary. Five cases of eccrine porocarcinoma were studied by light and electron microscopy. Histopathologically, these could be classified into two types; the common and the giant cell type. The common type was characterized by almost uniform medium-sized cuboidal tumour cells and a formation of well-developed intracytoplasmic lumina. A broad diversity of histopathological and ultrastructural features was seen in these tumours. The tumours of the giant cell type consisted of mononuclear polygonal cells and bizarre giant cells. This type was considered to be an undifferentiated form of porocarcinoma.

Key words: Eccrine porocarcinoma – Ultrastructure – Giant cell – Elastic fibre – Globular filamentous body

Introduction

Since eccrine porocarcinoma was first described as epidermotropic eccrine carcinoma by Pinkus and Mehregan (1963), many studies have been reported on its histopathological features (Mishima and Morioka 1969; Shaw et al. 1982; Mehregan et al. 1983; Puttick et al. 1986; Santa Cruz 1987; Abenoza and Ackerman 1990). These are as follows: the presence of well-demarcated tumour cell nests extending from the epidermis to various levels of the dermis, the presence of poroma-like tumour cells with nuclear pleomorphism that have clear cuboidal cytoplasm often containing glycogen, frequent and often abnormal mitotic figures, foci of intercellular duct-like lumina and/or intracellular canaliculi formation, variable keratinization, and proliferation of tumour cells in discrete forms and/or in groups within the epidermis (epidermotropism). However, few reports on the ultrastructural features of this tumour have been published (Turner et al. 1982; Mehregan et al. 1983; Bottles et al. 1984). In the present study, five cases of eccrine porocarcinoma were examined to delineate the histopathological and ultrastructural characteristics of this tumour.

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Materials and methods

Specimens were obtained from five patients with eccrine porocarcinoma. The clinical findings on these five cases are summarized in Table 1. The patients were four men and a woman, ranging in age from 62 to 83 years. The lesions were located mostly on the lower extremity and in one case on the breast. The skin lesions were an infiltrated verrucous plaque (cases 1, 5), a slightly elevated flat nodule (case 2), multiple infiltrated plaques or nodules (case 3) or a polypoid lesion (case 4). Inguinal lymph node metastases were present in three cases (cases 1–3). One patient (case 3) was troubled by lymphoedema of the affected extremity. The histological diagnoses were eccrine porocarcinoma (cases 1–3, 5) and anap-

Table 1. Summary of five patients with eccrine porocarcinoma

Case	Age (years)	Sex	Tumour location	Duration (months)	Size (cm)	Lymph node metastasis	Follow-up
1	77	M	Thigh	60	2.0 × 2.0	+	Died of disease, 5 months
2	73	M	Foot sole	36	2.5 × 2.5	+	Died of disease, 12 months
3	62	M	Thigh	4	4.0 × 4.0	+ Lymphoedema of affected extremity	Died of disease, 3 months
4	83	F	Breast	54	0.9 × 0.9 × 0.4	+	Alive, 55 months, radiation
5	71	M	Leg	6	1.0 × 1.0	–	Alive, 28 months

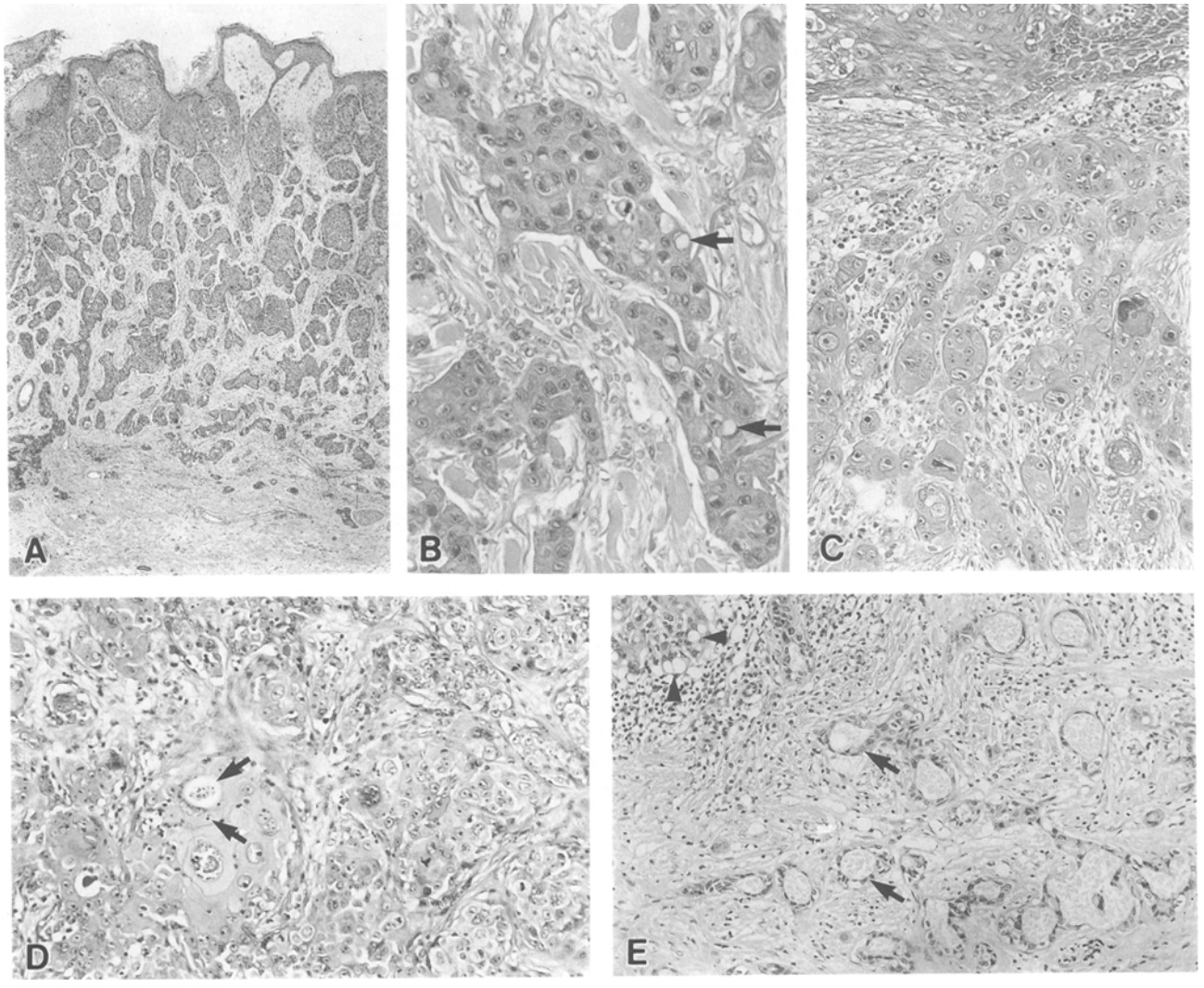

Fig. 1 A–E. Light micrographs of eccrine porocarcinomas: **A** Common type of eccrine porocarcinoma (case 3). Many irregularly shaped tumour cell nests are seen both in the epidermis and the dermis. H & E, ×50. **B** Common type (case 1). Medium-sized polygonal cells with relatively pleomorphic hyperchromatic nucleus. Note pale-staining intracytoplasmic globular inclusions (*arrows*). H & E, ×490. **C** Giant cell type of eccrine porocarcinoma (case 5). Bizarre giant cells with large nuclei and prominent nucleoli can be observed. H & E, ×250. **D** Giant cell type (case 4). Mononuclear polygonal cells and bizarre giant cells. Note dense inflammatory infiltration in the stroma and emperipolesis (*arrows*). H & E, ×250. **E** Metastatic foci in the regional lymph node (case 3). Dilated ductal lumens lined by one or two layers of flattened tumour cells (*arrows*). Intracellular lumen formations (*arrowheads*) are also seen in the solid metastatic tumour nests. H & E, ×125

lastic carcinoma (case 4). The final diagnosis of case 4 was established by enzyme histochemistry. Cases 4 and 5 showed neither systemic leucocytosis nor anaemia, and had no abnormal blood chemistry values. In case 5, serum carcinoembryonic antigen level was slightly elevated (6.5 ng/ml). Case 4 developed repeated lymph node metastases on his left axilla 7, 18 and 30 months after the removal of the primary skin lesion. The lymph nodes were dissected and irradiated each time. The patient is still alive without further metastasis. In case 5, there is no evidence of local recurrence or metastasis after the operation.

For light microscopy, specimens were processed routinely. The staining methods employed were; haematoxylin and eosin, periodic acid-Schiff (PAS) with and without diastase digestion, Mowry's colloidal iron with and without bovine testicular hyaluronidase digestion, elastic van Gieson, Congo red and azan Mallory. The enzyme histochemical demonstration of amylophosphorylase, succinic dehydrogenase, β-glucuronidase, and acid phosphatase was carried out on the fresh frozen sections (case 4). Immunohistochemical studies using the standard avidin-biotin technique (Hsu et al. 1981) were performed on paraffin-embedded sections of case 1 employing two commercially available monoclonal antibodies to cytokeratin: MA902 (Enzo) reacting with low-molecular-weight cytokeratin of 54 kDa, at a dilution of 1:3000; and MA903 (Enzo) reacting with high-molecular-weight cytokeratins of 68, 58, 56.5 and 56 kDa, at a dilution of 1:3000. A digestion with 0.03% protease (Sigma, St. Louis, Mo.) for 60 min was employed prior to incubation with the antibodies.

For electron microscopy, the specimens from primary skin lesions in four cases (nos. 1, 3–5) were cut into several smaller pieces, fixed in 2.5% glutaraldehyde for 2 h, and postfixed in 2% osmium tetroxide for 2 h. Both fixatives were buffered with 0.1 M cacodylate buffer, pH 7.4. After dehydration in graded concentrations of ethanol, blocks were embedded in epoxy resin. Ultrathin sections were made on a Porter-Blum MT-1 ultramicrotome, stained with uranyl acetate and lead citrate, and examined in a JEM-100 CX electron microscope.

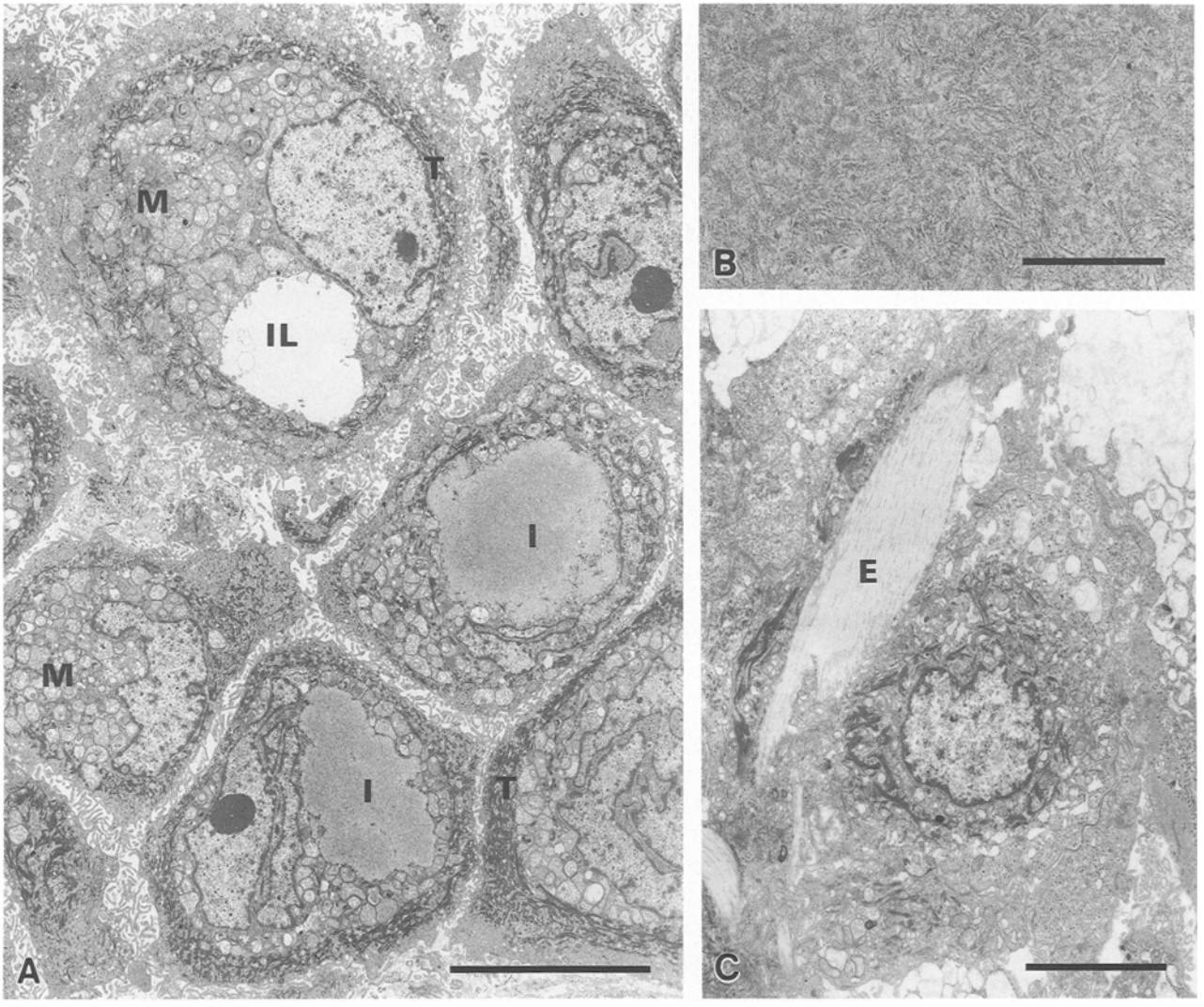

Fig. 2A–C. Case 1. **A** Polygonal-shaped cells in the intradermal tumour island showing numerous mitochondria (*M*) and intracytoplasmic lumen (*IL*) bordered with microvilli in the cytoplasm. Note globular filamentous inclusions (*I*) in the cytoplasm. *T*, Tonofilament. *Bar:* 10 μm. **B** Higher magnification of globular inclusion. Numerous fine filaments are randomly arranged in the amorphous matrix. *Bar:* 0.5 μm. **C** Entrapped elastic fibres (*E*) in the tumour cell nest. *Bar:* 5 μm

Results

In the primary skin lesions, solid tumour nests (cases 1, 3–5) or anastomosing cords of tumour cells (case 2) extended from the epidermis to various levels of the dermis (Fig. 1A), and occasionally invaded in part into the subcutaneous fat (cases 1 and 2). These nests and cords were separated by relatively thick collagenous or loose fibrovascular stroma. In the epidermis, tumour cell nests well-demarcated from the surrounding keratinocytes (cases 1, 3–5) and/or individual tumour cells in discrete form (cases 1, 3, 5) were observed. Several dilated lymphatic spaces were filled with plugs of tumour cells in four cases (nos. 1–4). None of the five cases showed any features of a pre-existing benign lesion.

The cells in cases 1–3 exhibited almost the same morphological characteristics: a relatively uniform pattern of medium-sized polygonal cells with narrow, clear and eosinophilic cytoplasm (Fig. 1B). They had relatively pleomorphic, hyperchromatic nuclei and one or more prominent nucleoli. A few large cells showed a cluster of nuclei. However, the tumour cell nests in cases 4 and 5 were composed of two types of cells: mononuclear polygonal cells and bizarre giant cells (Fig. 1C, D). The polygonal cells showed marked nuclear pleomorphism. The giant cells had a single, bizarre nucleus or two to several nuclei. Both cell types possessed abundant clear cytoplasm. The nucleolus was prominent and sometimes multiple. Frequent mitoses, some abnormal, were observed in all five cases.

The tumour cell nests showed an extensive (cases 1–3) or occasional (case 5) intracytoplasmic lumen formation with an eosinophilic cuticular border. There was, however, no such lumen formation in case 4. In three cases (nos. 1–3), some tumour cells contained keratohyalin granules in the cytoplasm, and in two cases (nos. 1, 2), foci of keratinization were observed in some tumour cell nests. The cells of the other two cases (nos. 4, 5) contained no keratohyalin granules.

The cells of three cases (nos. 1, 4, 5) contained consid-

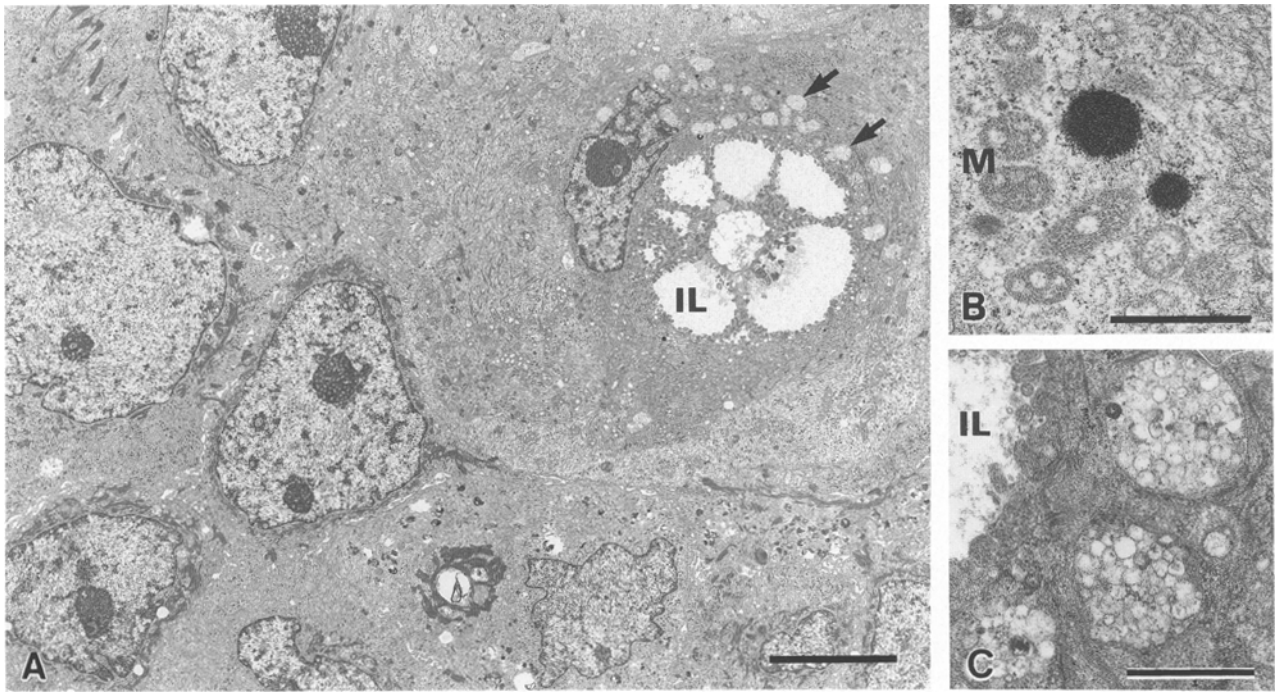

Fig. 3A–C. Case 3. **A** Polygonal tumour cells with irregularly shaped nucleus and prominent nucleoli. Note intracytoplasmic lumina (*IL*) lined with numerous microvilli. Mucous secretory granules (*arrows*) are also seen. *Bar:* 5 μm. **B** Mitochondria with clear vesicles and dense matrix (*M*). Keratohyalin granules are also seen. *Bar:* 1 μm. **C** Mucous secretory granules. *IL,* Intracytoplasmic lumen. *Bar:* 1 μm

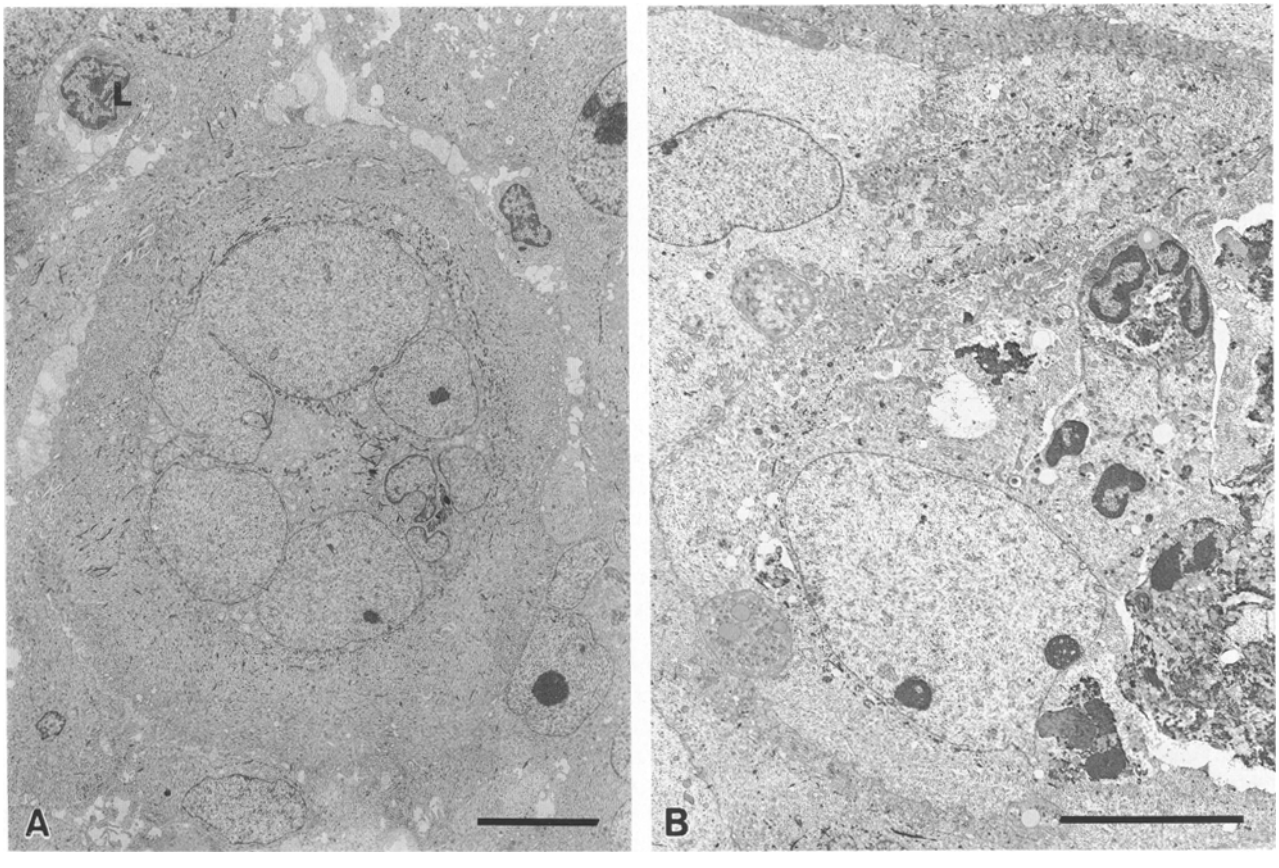

Fig. 4A, B. Case 4. **A** Bizarre giant cell (*G*). The giant cell has several nuclei arranged in a ring-like fashion in the cytoplasm. *L,* Leucocytes. *Bar:* 10 μm. **B** Giant cell containing leucocytes and cellular debris within the cytoplasm. *Bar:* 10 μm

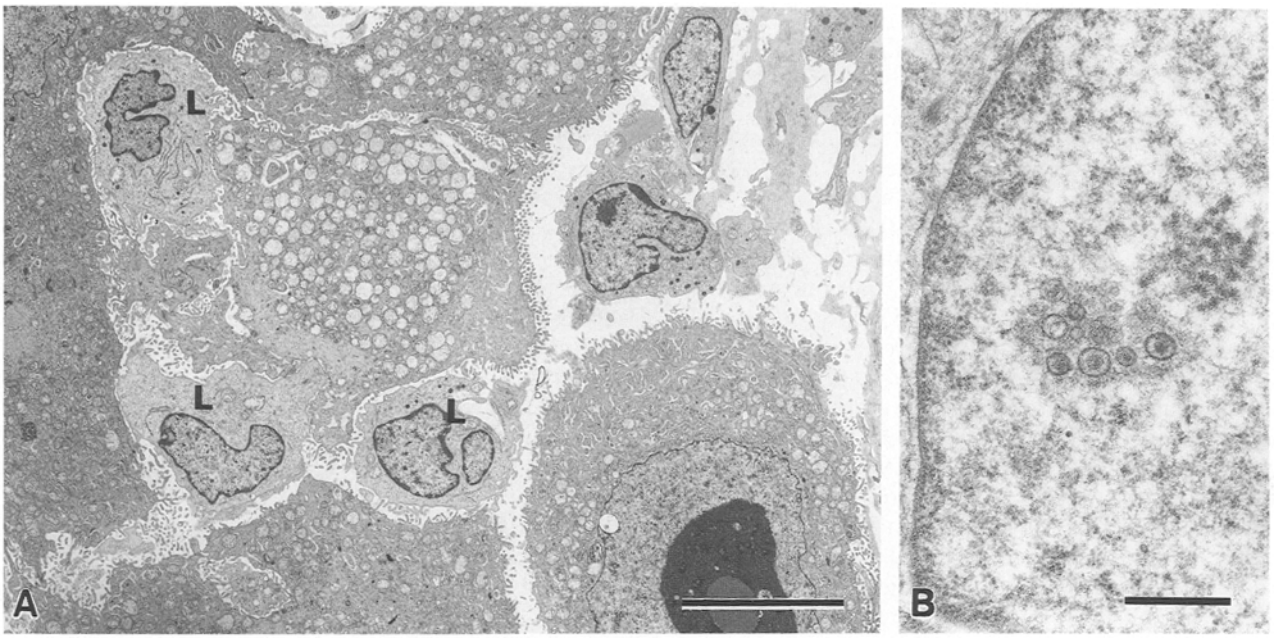

Fig. 5A, B. Case 5. **A** Bizarre giant cells showing a loss of intercellular cohesion with leucocytic infiltration. Note numerous mitochondria and prominent nucleolus. *L*, Leucocytes. *Bar:* 10 μm. **B** Virus-like particles in a nucleus. *Bar:* 0.5 μm

erable numbers of glycogen granules in the cytoplasm. Several cells in the intradermal tumour islands of case 1 showed a pale-staining intracytoplasmic globular inclusion (Fig. 1B), which was PAS and colloidal iron positive, resistant to diastase and hyaluronidase digestion, and negative on Congo red staining.

Mild to moderate lymphoid cell infiltration was scattered throughout the lesion in three cases (nos. 1–3). In case 4, a dense infiltration of lymphoid cells, plasma cells and neutrophils was seen in the tumour stroma. An outstanding findings in this case was the presence of lymphoid cells and neutrophils not only in the intercellular spaces but also within the tumour cells, so-called emperipolesis (Fig. 1D). In case 5, the periphery of the lesion exhibited dense lymphoid cell infiltration mixed with a considerable number of eosinophils, and occasional emperipolesis were observed. In three cases (nos. 1–3), various amounts of elastic fibres were found enclosed within the tumour cell nests.

In the regional lymph nodes of three cases (nos. 1, 3, 4), many metastatic foci of cells closely resembling those in the primary lesion were observed. In cases 1 and 3, extensive intracellular lumen formation, as in the primary skin lesion, was seen. In case 3, several clusters of metastatic foci also produced a dilated ductal lumen lined by one or two layers of flattened tumour cells (Fig. 1E). In case 4, the phenomenon of emperipolesis was also found in the metastatic lesion.

In case 4, the tumour cells showed intense activities of phosphorylase, succinic dehydrogenase, a moderate activity of β-glucuronidase and a slight activity for acid phosphatase, indicating the diagnosis of eccrine porocarcinoma. In case 1, the tumour cells showed positive immunoreaction for anti-high-molecular-weight cytokeratin antibody (MA903) in their cytoplasm and intracytoplasmic globular inclusions. No tumour cells, however, immunoreacted with anti-low-molecular-weight cytokeratin antibody (MA902).

On electron microscopy of cases 1 and 3, most tumour cells had polygonal-shaped cytoplasm and an irregularly shaped, frequently indented oval nucleus with prominent nucleoli (Figs. 2A, 3A). They contained relatively abundant tonofilaments, a well-developed Golgi apparatus, and some endoplasmic reticulum (Figs. 2A, 3A). They showed variable numbers of desmosomes (Figs. 2A, 3A). Several cells in cases 1 and 3 exhibited the formation of one or more intracytoplasmic lumina that were lined with numerous microvilli and which frequently contained amorphous material (Figs. 2A, 3A). The tumour cells in these two cases occasionally contained keratohyalin granules in the cytoplasm (Fig. 3B). In case 3, clear vesicles and dense matrix were frequently seen in the mitochondria (Fig. 3B). In case 1, aggregations of glycogen granules were observed in the cytoplasm. In case 3, many membrane-bound vacuoles containing vesicles, which were probably secretory and mucous in nature, were observed in the cytoplasm close to the lumen (Fig. 3C).

In case 1, two types of tumour cells were identified according to the features of mitochondria. Most of the cells in the intradermal islands contained numerous tightly packed mitochondria which were surrounded by a thick layer of tonofilaments in the cytoplasm (Fig. 2A). These cells also contained massive cytoplasmic materials composed of numerous fine filaments which were randomly arranged and embedded in the amorphous matrix (Fig. 2B). These unique inclusions seemed to correspond to the intracytoplasmic globular inclusion observed under the light microscope. They also appeared to lack a definitive limiting membrane. Most

tumour cells in the intraepidermal islands had a moderate number of mitochondria scattered throughout the cytoplasm.

However, two types of tumour cells were identified in cases 4 and 5 (Fig. 4A); one was a medium-sized polygonal mononuclear cell and the other a bizarre giant cell (Figs. 4A, 5A). The polygonal cells had a narrow rim of cytoplasm and a round or oval nucleus with large prominent nucleoli. Giant cells had abundant cytoplasm and showed a single giant nucleus or multinucleation, giving a bizarre appearance (Figs. 4A, 5A). In multinucleated tumour cells, two to several nuclei were arranged randomly or in a ring-like fashion in the cytoplasm (Fig. 4A). The nucleoli were sometimes giant and multiple. Both types of cells had relatively well-developed cell organelles, numerous free ribosomes and sparsely scattered tonofilaments in the cytoplasm, and some cells in case 5 contained numerous densely packed mitochondria. Scanty desmosomes were observed between the tumour cells. Numerous microvillous projections were observed on the cell surface (Fig. 5A). In case 5, the bizarre giant cells occasionally had a formation of intracellular lumen lined by numerous microvilli. Although there was no distinct lumen formation in the tumour cells of case 4, a lumen-like vacuolar structure with a few microvillous projections was observed in the cytoplasm. Secretory and keratohyalin granules were absent from the cytoplasm of the tumour cells in both cases. In case 4, the tumour cells sometimes contained accumulations of glycogen granules.

In cases 4 and 5, some cells showed a loss of intercellular cohesion with infiltrating neutrophils or lymphocytes (Fig. 5A). Tumour cells in case 4 occasionally contained cellular debris or leucocytes within the cytoplasm (emperipolesis) (Fig. 4B).

A striking finding in case 5 was the presence of virus-like particles both in the nucleus and in the cytoplasm (Fig. 5B). These particles were 160 nm in diameter and bounded by an envelope around the central core structure. In all four cases studied by electron microscopy, most of the tumour cell nests were devoid of a basal lamina (Fig. 5A). In case 1, bundles of elastic elements were entrapped in the intradermal tumour cell nests (Fig. 2C).

Discussion

The five cases in this study showed histological and enzyme histochemical characteristics of eccrine porocarcinoma. Among these characteristics, a striking finding was the presence of a definite intracellular lumen formation (cases 1–3, 5). In case 4, although such lumen formation was not observed, enzyme histochemistry indicated that the tumour cells were of eccrine sweat duct nature (Hashimoto and Lever 1964; Mehregan 1986).

We classified the five cases into two types. The first consisted of almost uniform medium-sized cuboidal cells. This feature has already been described in eccrine porocarcinoma (Pinkus and Mehregan 1963; Turner et al. 1982; Mehregan et al. 1983; Bottles et al. 1984; Puttick et al. 1986). We consider that cases 1–3 correspond to this common type.

The second type (cases 4 and 5) was characterized by proliferation of the mononuclear polygonal cells and bizarre giant cells. The development of intracytoplasmic lumina was not conspicuous, as in the common type. We call this lesion the giant cell type of eccrine porocarcinoma which has some morphological characteristics in common with the giant cell carcinoma that arises in other organs (Nash and Stout 1958; Wang et al. 1976; Tschang et al. 1977; Tateishi and Hattori 1982). These common features are: proliferation of both polygonal cells and bizarre giant cells, loss of intercellular cohesion of the tumour cells with inflammatory cell infiltration, and phagocytic inclusion of leucocytes within tumour cells (emperipolesis). The diagnosis of eccrine porocarcinoma, however, is definite, because the tumour showed the typical histochemical patterns of eccrine enzyme (Hashimoto and Lever 1964; Mehregan 1986). Bizarre giant cells made up more than 30% of the tumour mass examined. We suggest that this type is poorly differentiated when compared with the common type because the giant cells lacked keratohyalin granules and secretory granules. Keratinization is absent in the cytoplasm and development of attachment devices and tonofilaments is very poor. Although the prognosis of giant cell carcinoma arising in other organs is usually poor, our two cases are still alive 55 and 28 months after removal. We cannot conclude, however, that the prognosis of this subtype of eccrine porocarcinoma is relatively favourable, since the cases studied here are very few.

Although the common type showed the typical morphological characteristics of eccrine porocarcinoma, considerable diversities were also noted. Keratohyalin granules were commonly observed in all three cases and focal keratinization was seen in two of them. Although the development of keratinization in eccrine porocarcinoma is controversial (Shaw et al. 1982; Mehregan et al. 1983; Bottles et al. 1984), our results indicate that the tumour cells are capable of keratinization. Mucous secretory granules were also observed in the tumour cells of case 3, although it is unclear whether this means that there is a differentiation toward glandular cell. It has been reported that eccrine porocarcinoma is a malignant neoplasm, probably with eccrine acrosyringeal differentiation (Mehregan et al. 1983; Abenoza and Ackerman 1990). From the present findings, however, it could be concluded that the cells of eccrine porocarcinoma can show a wide range of capabilities, from keratinization to mucous secretion.

Some metastatic foci in case 3 showed a ductal structure lined by only one or two layers of tumour cells, a feature that has never been observed in the skin. Such a ductal struture is known to occur in eccrine ductal carcinoma or syringoid eccrine carcinoma (Lipper and Peiper 1979; Mehregan et al. 1983; Santa Cruz 1987). It is suggested that the eccrine porocarcinoma is able to show phenotypic change with overlapping morphological features with other types of eccrine carcinoma.

In some of the tumour cells in cases 1 and 5, a considerable number of mitochondria were observed. Such an increase of mitochondria is similar to that seen in onco-

cytes in various normal tissues (Munger and Roth 1963; Bogart 1970) and in oncocytic tumour cells (Tandler et al. 1970; Feldman et al. 1972; Sun et al. 1975). Although the biological or pathological meanings of mitochondrial hyperplasia are not known (Tandler et al. 1970; Sun et al. 1975), we suggest that it represents a tendency to transform into oncocytes. In case 3, abnormal mitochondria containing clear vesicles and dense matrix were observed in the tumour cells, probably indicating some degenerative process (Ghadially 1988).

Globular filamentous inclusions as observed in the tumour cells of case 1 have not been described in eccrine porocarcinoma but have been reported in various tumours (Keeley et al. 1972; Wang et al. 1976; Horvath and Kovacs 1978; Johannessen et al. 1978). The close relationship between these bodies and intermediate filaments has been demonstrated by several immunohistochemical studies (French 1983; Neumann et al. 1985). Although the functional significance of globular inclusions in our case is not clear, immunohistochemistry indicated that these inclusions are also closely associated with high-molecular-weight keratin filaments.

The occurrence of entrapped elastic fibres in the tumour cell nests (cases 1–3) is also of interest. This has been observed particularly in aggressive lesions of cutaneous squamous cell carcinoma (Hashimoto et al. 1973; King and Barr 1980). We conclude that eccrine porocarcinoma is also aggressive in nature.

Virus-like particles were observed in the tumour cells of case 5. This is the first report of such particles in eccrine porocarcinoma, which are morphologically similar to herpes virions (180 nm in mean diameter with an outer envelope and an inner core; Wildy et al. 1960). However, the implication of this finding is not clear.

We propose that eccrine porocarcinomas should be classified into two types: the common and the giant cell type. The tumours showed diverse histopathological and ultrastructural patterns.

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