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Case report

Small cell neuroendocrine (oat cell) carcinoma of the male breast

Immunocytochemical and ultrastructural investigations*

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Summary. A case of small cell neuroendocrine (oat cell) carcinoma of the breast in a 52-year old male is presented. Oat cell carcinomas have been reported in various extrapulmonary sites, but this is the second case of a primary oat cell carcinoma of the breast and the first one to have been documented in a male. The tumor was investigated histologically, immunocytochemically and ultrastructurally. The relationship to so-called "carcinoid" mammary tumors is discussed.

Key words: Oat cell carcinoma – Male breast – Immunocytochemistry – Electron microscopy

Small cell neuroendocrine (oat cell) carcinomas occur almost exclusively in the lung, but in 4–6% of the cases they are also found in extrapulmonary sites (Fer 1980, 1981; Levenson 1981). So far, only one case involving the breast has been reported (Wade 1983). We observed a further case in a male patient.

Case report

The patient was a 52-year-old man who noticed a swelling in the right axilla. A lymph node was extirpated, and histological examination revealed the metastasis of a poorly differentiated carcinoma. With regard to differential diagnosis an amelanotic melanoma was also considered. Since intensive diagnosis efforts failed to detect a primary tumor, cytostatic and radiation therapy were instituted under the tentative diagnosis of melanoma. Despite this therapy, renewed swelling occurred in the right axilla and also in the region of the right breast six months later with retraction of the nipple and palpable enlargement of the underlying mammary

* Dedicated to Prof. Dr. J. Kracht on the occasion of his 60th birthday

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gland. Mammography presented findings of a mammary carcinoma showing a dense area with an irregular outline. Another primary tumor, in particular a pulmonary one, could be excluded by subsequent clinical and radiological examinations and computerized tomography. Sputum cytology was negative. In the further course the patient's condition deteriorated rapidly. He complained of increasing pains in the spinal column. Computerized tomography revealed multiple skeletal metastases. The pancreatic lodge was unremarkable. In addition, lymph node metastases developed at the hepatic porta leading to obstructive jaundice. Despite irradiation and chemotherapy the patient's condition continued to deteriorate, and he died 14 months after the appearance of the first symptoms. An autopsy could not be performed.

Material and methods

The histologic studies were performed on material fixed in 4% buffered formalin and subsequently embedded in paraffin. Using the peroxidase-antiperoxidase (PAP) method according to Sternberger (for details see van Noorden and Polak 1983), the biopsy taken six months before as well as the recently extirpated tumors were studied for the presence of neuron specific enolase (NSE), calcitonin and carcinoembryonic antigen (CEA). Part of the material from the second biopsy (axillary and mammary tumor) was fixed in 100% ethanol for 48 hours (Altmannsberger 1981) and examined for intermediate filament content by indirect immunofluorescence. Moreover, tumor portions were fixed in 2% buffered glutaraldehyde for two hours and post-fixed in osmium tetraoxide for electron microscopy.

Results

Histologic examination revealed a malignant tumor consisting of densely arranged cells with scanty cytoplasm, moderately hyperchromatic nuclei and numerous mitoses. The tumor infiltrated broad areas of the surrounding tissue. Nucleic acid deposits were seen perivascularly (Figs. 1a and b). Immunocytochemistry showed identical findings in all three biopsies examined. The tumor cell cytoplasm displayed a distinctly positive reaction for NSE, especially along the cellular membrane (Fig. 1c). Calcitonin and CEA could not be demonstrated. Immunofluorescence microscopy showed a distinctly positive reaction for the surrounding connective tissue, adipose tissue and musculature, but no reaction to any of the tested markers (cytokeratin, vimentin, neurofilament and desmin) in the tumor cells.

The ultrastructural findings in the axillary lymph node and in the mammary tumor were identical. Cell complexes were seen whose membranes were connected with one another by "primitive" desmosomes. Occasionally, the cells had small cavities into which filopodia-like cytoplasmic processes were projecting. Mucin granules could not be detected. The cell nuclei showed poorly densified marginal chromatin and small nucleoles (Fig. 2). Besides free ribosomes, occasional mitochondria, rough endoplasmic reticulum and Golgi fields, the cytoplasm contained granules of diverse configuration. In addition to small round granules limited by a halo and having a diameter of approximately 90–120 nm there were also oval pleomorphic granules with a faintly discernible inner structure (Fig. 3a and b).

Discussion

Among the neuroendocrine tumors, small cell (oat cell) carcinoma occupies an exceptional position. The tumor is nearly always localized in the lungs

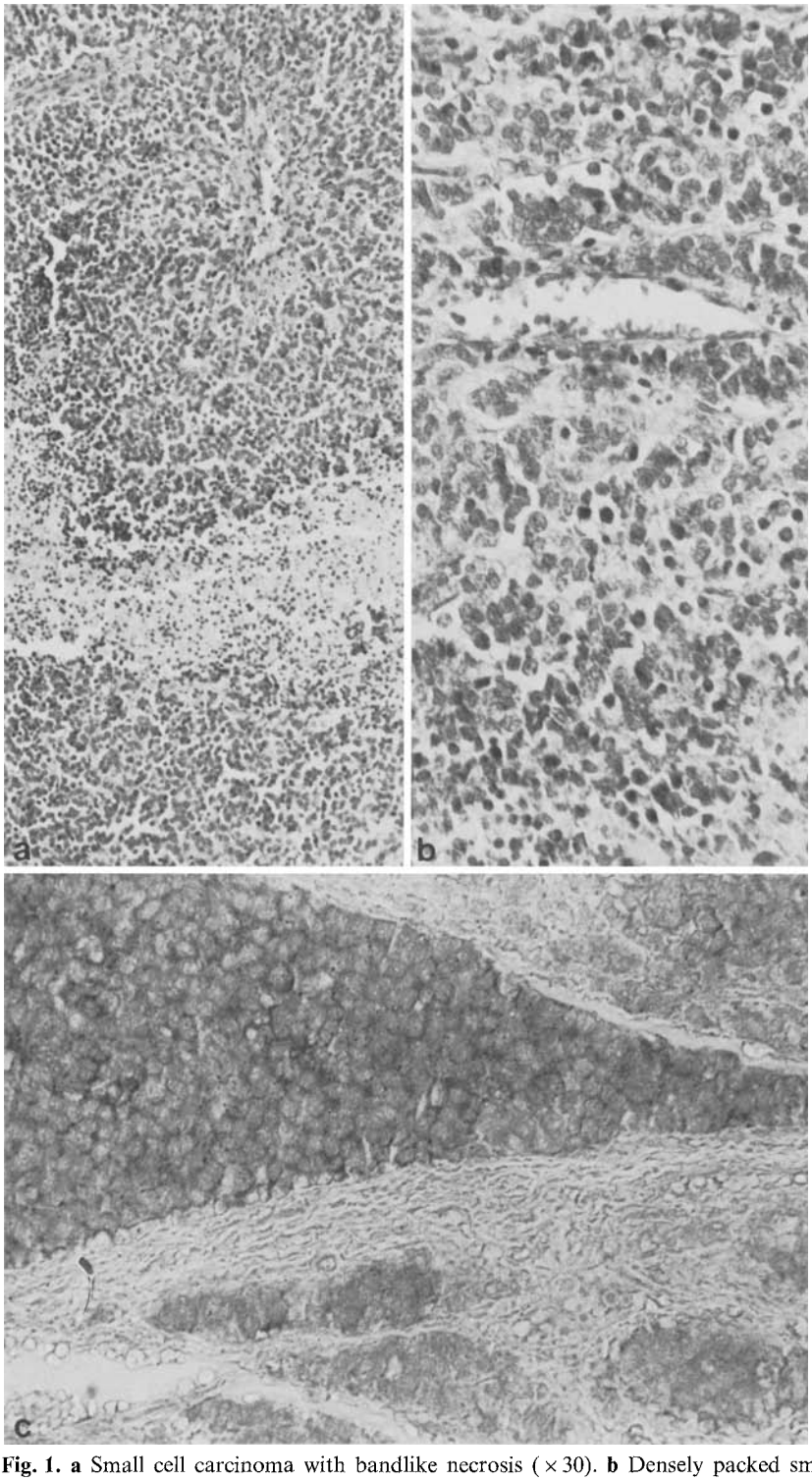

Fig. 1. **a** Small cell carcinoma with bandlike necrosis (× 30). **b** Densely packed small tumor cells with narrow cytoplasmic seam, moderately hyperchromatic nuclei and nuclear pyknosis (× 300). **c** Positive reaction for neuron-specific enolase. Peroxidase-antiperoxidase, no counterstaining (× 300)

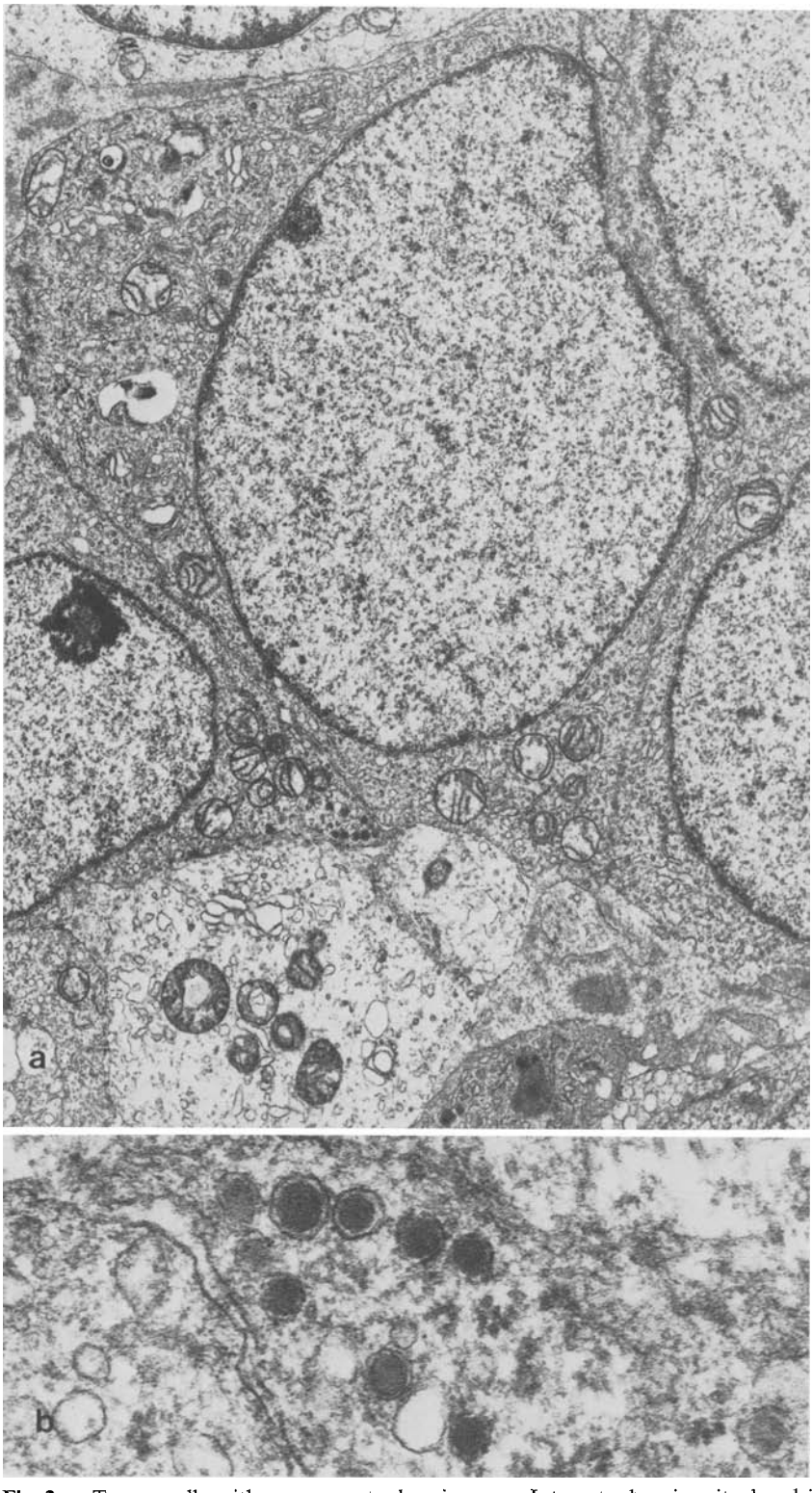

Fig. 2. **a** Tumor cells with narrow cytoplasmic seam. Intracytoplasmic mitochondria, small Golgi fields, rough endoplasmic reticulum, free ribosomes and neuroendocrine granules (90–120 nm in ∅). Nuclei show small nucleoli and moderately densified chromatin (× 10,900). **b** High power magnification (× 92,000): neuroendocrine dense core granules with a distinct halo (ca. 90–120 nm in ∅)

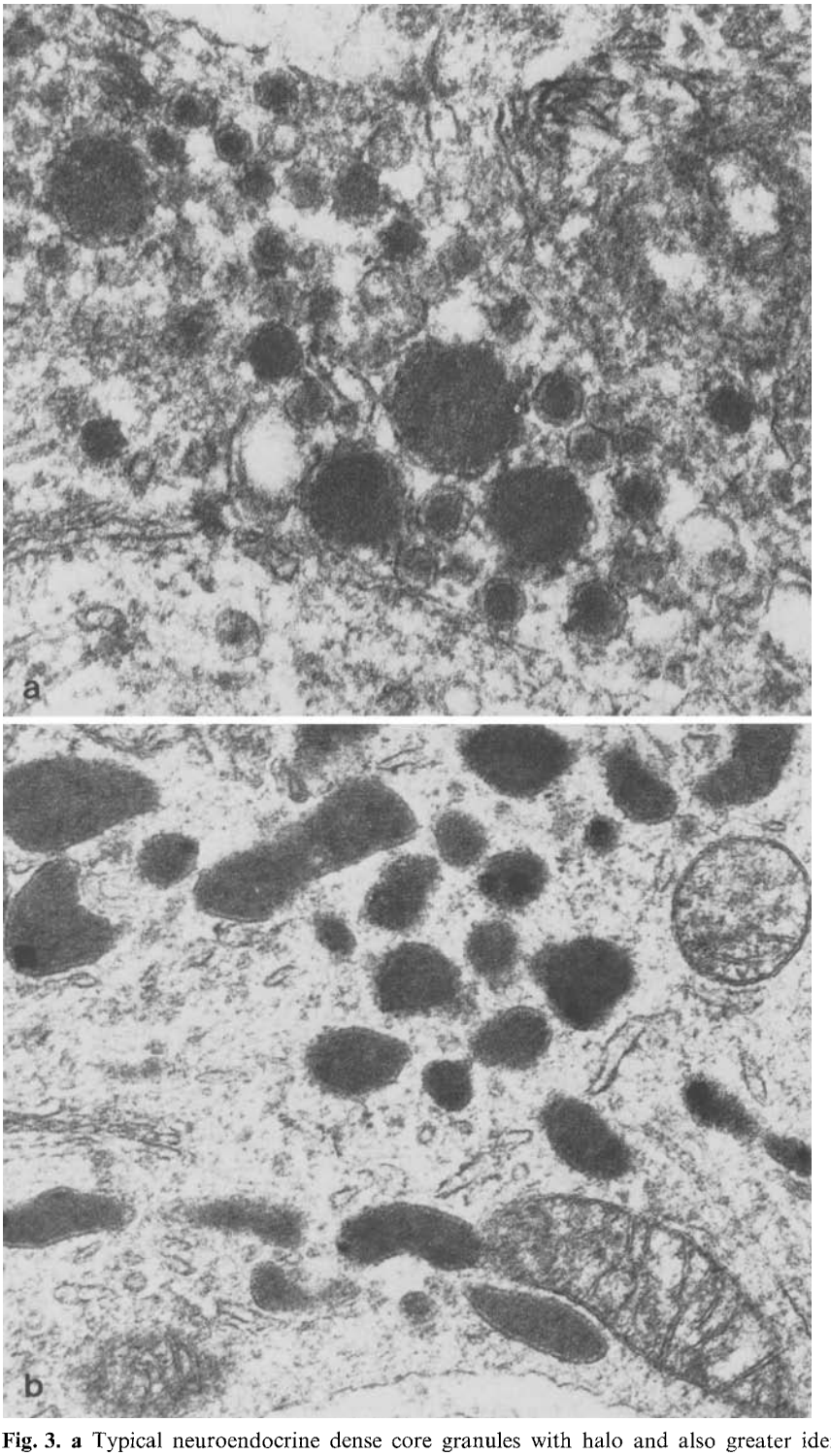

Fig. 3. a Typical neuroendocrine dense core granules with halo and also greater identically configurated granules (220–350 nm in ∅) (× 116,000). **b** Pleomorphic granules with faint halo containing homogenous electron dense material (× 40,000)

and characterized by a rapid progress, which often results in death within a short period of time under the clinical picture of generalized tumor spread. In recent years, tumors with a similar histological and ultrastructural pattern have been described in various extrapulmonary sites, such as the larynx, uterine cervix, prostate and skin (Fer 1980; Levenson 1981). In a study including 20 cases of extrapulmonary small cell carcinoma of his own and 113 cases reported in the literature, Fer (1981) did not find any essential differences with regard to clinical course or response to oncological treatment.

To our knowledge, our case is the second one concerning a small cell neuroendocrine carcinoma of the breast (Wade 1981) and at the same time the first observed in a male patient. All the clinical, radiological and computerized tomography examinations performed suggest that the breast tumor was a primary one, since a pulmonary tumor was excluded by all follow-up studies. The only reservation is that verification by autopsy was not possible.

The histological, immunocytochemical and electron microscopic results were consistent with those obtained for primary small cell neuroendocrine carcinomas of the lung. Light microscopy revealed small tumor cells having moderately hyperchromatic nuclei with a narrow cytoplasmic seam. Numerous and in part atypical mitoses were seen. The tumor cells showed a cord-like arrangement. Nucleic acid deposits around smaller vessels were seen in addition to necrotic zones. These findings are in agreement with those described for small cell bronchial carcinoma (Azzopardi 1959; WHO 1981). The Grimelius reaction was negative, but this has also been reported for oat cell carcinomas of the lung (Fisher 1978). On electron microscopy, occasional neurendocrine granules with typical electron-dense osmiophilic nuclei and a narrow halo were demonstrable. Some tumor cells showed pseudopodia-like processes in which the neurosecretory granules seemed more densely packed. Similar findings have been reported by Hattori et al. (1972) in oat cell carcinomas. The observed pleomorphic granules with a vaguely discernible inner structure are difficult to interpret. Because of their often intimate association with Golgi fields and endoplasmic reticulum they may resemble primary lysosomes. However, their rather electron dense inner core and their faint but easily discernible halo seem to favor the interpretation that they are pleomorphic neuroendocrine granules (Henderson and Papadimitriou 1982). The immunocytochemical results likewise strongly advocate the neuroectodermal histogenesis of the tumor. Immunocytochemically (PAP method), NSE was demonstrable in the axillary lymph node as well as in the mammary tumor. Several studies have shown this enzyme to be present not only in neurons but also in the cells of the diffuse neuroendocrine system (Schmechel et al. 1978; Marangos et al. 1982; Wick et al. 1983). Tapia et al. (1981) have demonstrated NSE in pulmonary oat cell carcinomas by immunocytochemical methods.

The expression of intermediate filaments – morphologically similar but immunologically different cytoplasmic proteins 7–11 nm in diameter – has been investigated by several study groups in recent years (Franke et al. 1978; Lazarides 1980; Osborn and Weber 1983; Altmannsberger et al. 1981;

Miettinen et al. 1982). Lung tumor studies by Lehto et al. (1983) have shown that in contrast to all other pulmonary carcinomas, oat cell carcinomas contain only neurofilament. This intermediate filament is specific for all neurons of the central and peripheral nervous system. An unequivocal result, however, was only obtainable with cryostat sections.

Since in our case only ethanol-fixed material was available, the negative reaction of the tumor tissue may mean that some oat cell carcinomas do not contain intermediate filaments, or else that the negative result was caused by the ethanol fixation of the material (Osborn and Weber 1983).

Carcinoma of the male breast is an extremely rare tumor, accounting for only about 1% of all mammary cancers and occurring later (mean age 59 years) than in women (Yogore III 1977; Azzopardi 1979). The three cases of small cell carcinoma of the male breast reported in the literature (Haagensen 1956; Norris and Tylor 1969; Yogore III 1977) exhibited histological and ultrastructural features consistent with those of lobular mammary carcinoma. Neurosecretory granules were not demonstrable in these cases.

According to Wade (1983) small cell neuroendocrine (oat cell) carcinoma of the breast is different from the so-called carcinoid tumors of the mammary gland (Feyrter 1963; Cubilla 1977; Dewitt 1978; Fisher 1979; Capella 1980; Gould 1980; Taxy 1981; Uhl 1983). The latter often show nests and clusters of small cells embedded in a richly vascularized stroma. The tumor cells are argyrophilic and have neuroendocrine granules. Histologically, they have been classified as invasive ductal or invasive lobular carcinomas. Some tumors have been reported to secrete hormonally active substances (Cohle 1979; Coombes 1975; Kaneko 1978). Their histogenesis is still under discussion (Pearse 1977; Eusebi 1980; Govoni 1981; Partanen 1981; Fetissof 1983). Due to the small number of cases, only tentative statements are possible at present, but it appears that these mammary carcinomas occur predominantly in younger women (mean age 45 years) though they do not essentially differ from other mammary carcinomas with regard to prognosis (Cubilla 1977; Taxy 1981; Fetissof 1983). According to some authors (Ghadially 1982) small cell neuroendocrine (oat cell) carcinoma is merely the poorly differentiated variant of a carcinoid (apudoma), thus making a clear-cut distinction between the two tumors seem questionable. Similar immunocytochemical and ultrastructural features found in both tumor types support this opinion (Hattori 1972; Osborn 1983b).

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