Virchows Arch. A Path. Anat. and Histol. 371, 283—294 (1976)

Argyrophil Cell Carcinoma (Apudoma) of the Esophagus

A Histopathologic Entity *

R. Tateishi, K. Taniguchi, T. Horai, T. Iwanaga, H. Taniguchi, T. Kabuto, M. Sano, S. Ishiguro, and A. Wada

Departments of Pathology, Surgery, and Internal Medicine
The Center for Adult Diseases, Osaka, Japan

Received May 10, 1976

Summary. In a series of 79 cases of primary esophageal carcinoma resected at The Center for Adult Diseases, Osaka, there were six tumors with specific histopathologic features valid for the diagnosis of argyrophil cell carcinoma. Of the 6 tumors, 3 were studied electron microscopically and assay for ACTH content was performed on 4 tumors.

Clinically, the ages of the 6 patients ranged from 56 to 71 years; two were women and four men. Four of the 6 patients died with widespread tumor recurrences within 9 months of operation.

Microscopically, the 6 tumors were composed largely or almost entirely of small, spindle-shaped cells resembling those of oat cell carcinoma of the lung, and were characterized by the arrangement of tumor cells in solid sheets or anastomosing cords, the presence of argyrophil tumor cells, and the deposits of amyloid. Electron microscopically, the three tumors contained neurosecretory-type granules. Using bioassay or radioimmunoassay ACTH activity in the tumor tissues was detected in 3 out of the 4 tumors determined.

From the light and electron microscopic characteristics and the assay evidence, it seems reasonable to conclude that the 6 tumors are endocrine polypeptide producing tumors (apudomas) that arise from argyrophil cells normally found among the basal cells of the esophageal mucosa, and that they represent a distinct histopathologic entity clearly distinguishable from other types of esophageal carcinomas.

Key words: Carcinoma of the esophagus — Apudoma — Oat cell carcinoma — Amyloid — Argyrophil cells.

It has only recently been appreciated that oat cell carcinomas of the lungs are derived from argyrophil cells (APUD cell) distributed throughout the bronchial trees (Bensch et al., 1968; Hattori et al., 1972; Tateishi, 1973; Lauweryns and Goddeeris, 1975), and that they are a type of apudoma, the endocrine polypeptide producing tumors that arise from the cells of the APUD series (Pearse and Polak, 1974; Smith, 1975).

Small cell carcinomas identical in microscopic appearance to pulmonary oat cell carcinomas may occur wherever argyrophil cells are present. Extrapulmonary sites are the salivary glands (Koss et al., 1972), the thyroid glands, the thymus (Cohen et al., 1960), the esophagus (McKeown, 1952), the pancreas (Corrin et al., 1973) and the uterine cervix (Tateishi et al., 1975). Although clinically the majority of small cell carcinomas in these sites are hormonally inactive, we feel that they should be regarded as an endocrine polypeptide producing tumor (apudoma) that arise from the argyrophil cells in these sites.

* Supported in part by a Grant-in Aid for Cancer Research from the Ministry of Education, Science and Culture, and the Ministry of Health and Welfare, Japan

A second type of epithelial cell, the argyrophil cell has been described in the human esophagus (Tateishi et al., 1974). Since argyrophil cells are normally found in the esophageal mucosa, the occurrence of oat celled carcinoma may well be anticipated at that site. In 1952 McKeown first reported two examples of oat cell carcinoma of the esophagus. Since the first description, there have been only sporadic reports of such cases (Taniguchi et al., 1973; Turnbull et al., 1973; Watanabe et al., 1974; Rosen et al., 1975; Matsusaka et al., 1975), and the existence of oat cell carcinoma in the esophagus as a distinct entity has not gained widespread recognition, particularly outside Japan. This paper is concerned with the light and electron microscopic characteristics of a group of esophageal carcinomata that we believe originate from the argyrophil cells of the esophageal mucosa.

Materials and Methods

In the 5-year period between January, 1971 to December, 1975, 79 patients had undergone resections for carcinomas of the esophagus at The Center for Adult Diseases, Osaka. Sixty of the patients were male and nineteen female. For light microscopy three or more blocks of all primary tumors and of metastatic lesions were available. Formalin-fixed, paraffin embedded sections of each block were stained with hematoxylin and eosin, and the Grimelius (1968) silver impregnation method.

Of the 79 tumors 6 were found to have tumor cells with argyrophil granules, and these 6 tumors form the subject of this paper. Two (Cases 2 and 3) of the 6 tumors were previously reported (Taniguchi et al., 1973; Imura et al., 1975). Additional sections were prepared from all 6 tumors and were stained by the periodic acid-Schiff reaction (PAS), and Fontana-Masson argentaffin reaction. Alkalin Congo red stain (Puchtler et al., 1962) with dichroism was employed for demonstrating amyloid.

Electron microscopic study was carried out in three cases (Cases 3, 4 and 5). Tumor tissue obtained at the operation was fixed in 2.5% cold glutaraldehyde (cacodylate buffer, pH 7.4), washed in the buffer, and post-fixed in 1% buffered osmium tetroxide. The tissue was then embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead nitrate. The 6 patients received neither radiotherapy nor chemotherapy prior to the operations.

Four (Cases 1, 2, 3 and 4) of the 6 patients came to necropsy and in these 4 cases the content of ACTH in the tumor tissue was determined by bioassay or radioimmunoassay. The methods for the determinations of ACTH were described in a previous paper (Imura et al., 1975).

Results

The clinical and pathologic features and assay data of the 6 tumors are summarized in Table 1.

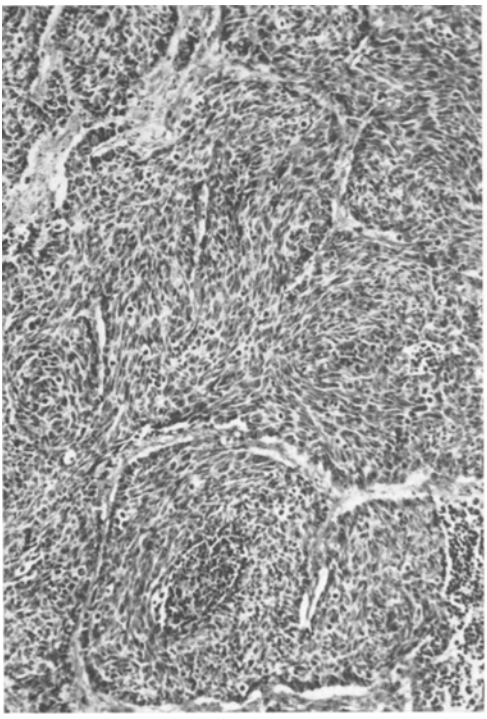
Light microscopic features: The tumor cells in this series of 6 tumors presented a great variation in size, shape and appearance, both within the same and in different tumors. The predominant tumor cell type greatly resembled that of oat cell carcinoma of the lung. It showed small, spindle-shaped nucleus filled with evenly distributed chromatin and scanty, pale cytoplasm with indistinct cellular borders (Fig. 1). Numerous mitotic figures were present. Four of the 6 tumors contained areas composed of tumor cells with larger, less chromatic nuclei and more prominent cytoplasm, with spindle-shaped, oval or polygonal outlines. The cytoplasm varied in amount from scanty to abundant, and in staining characteristics from water-clear to eosinophilic granulated (Fig.s 2 and 3). Cells intermediate in appearance between these two types were readily encountered.

Table 1. Clinical and pathological features and ACTH contents of the six tumors

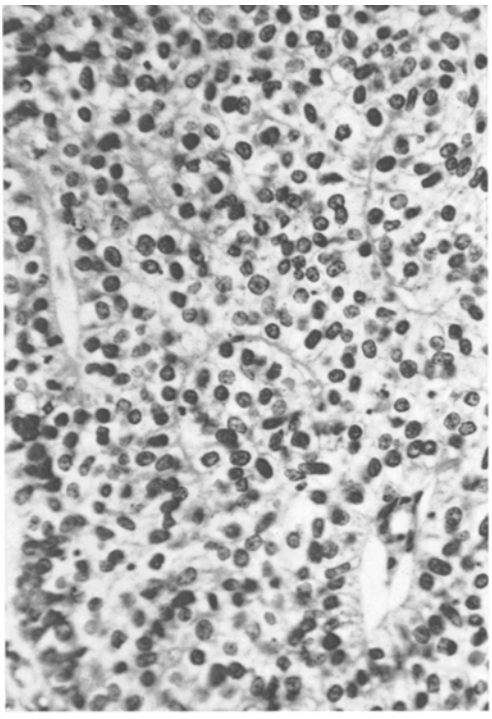
Case No.	Age at onset and sex	Location	Gross findings	Amyloid deposition	Distant metastasis at autopsy	ACTH in tumor tissue	Post-operative course
1.	58, ♀	Middle third	Fungating tumor with an ulcerated surface. 5.5 × 3.0 cm	−	Pleura, liver, left lung	0.83 ng/g (Radio-immuno-assay)	Died, 4 Mo. postop.
2.	57, ♀	Lower third	Slightly raised tumor with a small ulcer in the center. 1 × 1 cm	+	Bilateral supra-clavicular, hilar and mediastinal lymph nodes, vertebral bone	0.08 mU/g (Bioassay)	Died, $8^1/_2$ Mo. postop.
3.	62, ♂	Lower third	Fungating tumor with multiple polypoid excrescences. 1 × 1 cm	+	R-supraclavicular and mediastinal lymph nodes, peritoneum, pleura, liver, 1-lung, 1-kidney	3.2 mU/g (Bioassay)	Died, $3^1/_2$ Mo. postop.
4.	58, ♂	Middle third	Ulcerating tumor with a raised margin. 2.5 × 2.0 cm	+	Hepatic gastric and mediastinal lymph nodes, liver, kidneys, pleura, diaphragma, skin spleen	not detectable	Died, 8 Mo. postop.
5.	71, ♂	Lower third	Fungating tumor. 3.0 × 2.0 cm	−			Alive, 24 Mo. postop.
6.	56, ♂	Lower third	Fungating tumor with an ulcerated surface. 3.5 × 3.0 cm	−			Alive with tumor recurrence, 14 Mo. postop.

The histologic patterns of the tumors also varied greatly. The basic pattern of growth was that the tumor cells were arranged in irregular sheets or nests with a delicate, fibrovascular stroma (Fig. 1). Within most of the cell nests the spindle-shaped cells were arranged in whorls or in interlacing bundles presenting a streaming pattern. On occasion the tumor cells at the periphery of the nests showed a palisading arrangement. When the nests or sheets were composed predominantly of polygonal cells, microscopic similarities to thyroid medullary carcinomas were striking (Fig. 3). Another structural feature presented by three tumors was the arrangement of the cells in parallel or anastomosing cords (Fig. 4).

A conspicuous feature observed in each tumor was the focal accumulation of proteinaceous material that occurred in varying quantity between the tumor cells and in the stroma. In Cases 2 and 3, interspersed within the cell nests or between the cell cords, globoid and trabecular masses of the proteinaceous material were observed (Figs. 5 and 6). The material, most prominent in Case 2, appeared eosinophilic, amorphous or fibrillar in hematoxylin and eosin staining and purple in PAS stain. When stained with alkalin Congo red method, most of the protein-



1



2

Fig. 1. Predominant pattern of argyrophil cell carcinoma. Solid sheets are composed of small, spindle-shaped cells arranged in a streaming pattern. Case 4, H.E. stain, ×300

Fig. 2. Broad, anastomosing cords of tumor cells with clear cytoplasm. Case 3, H.E. stain, ×720

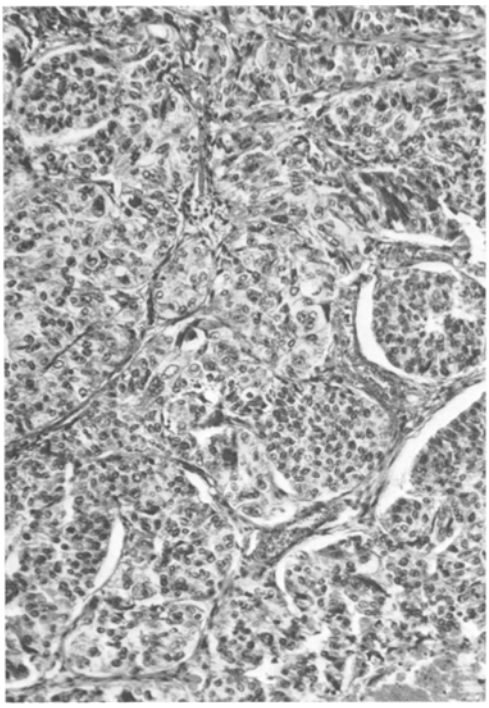
aceous material appeared pale and failed to exhibit dichroism. In Cases 2, 3 and 4, the material contained small, densely stained areas that showed dichroism. In Case 4, some cell nests showed a broad, hyalinized stroma in which small deposits of amyloid were found.

Two tumors showed the formation of intercellular gland-like lumina that contained varying amounts of the proteinaceous material. A gland-like lumen has been defined as a space lined by tumor cells that are not surrounded by a supporting stroma (Tateishi et al., 1975). True rosette formation was detected in none of the 6 cases.

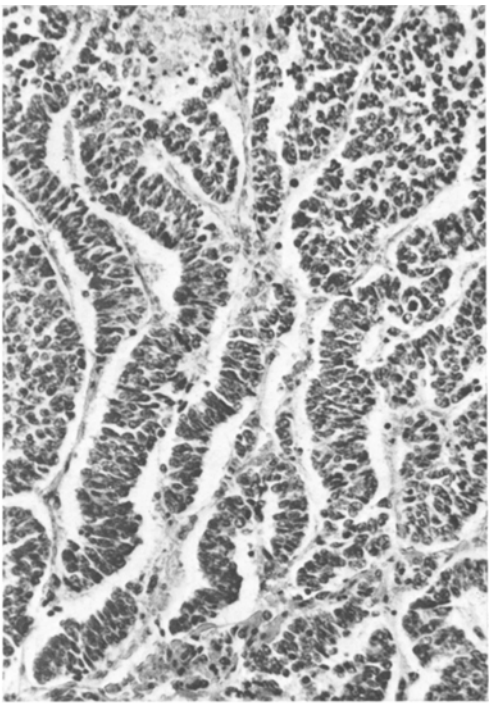
Foci of in situ carcinoma were found in the esophageal mucosa immediately adjacent to the tumors and they could be interpreted as lateral intraepithelial spreads from the main tumors.

The histologic appearances of the metastatic lesions were basically similar to those of the primary tumors.

With the Grimelius silver impregnation method, all the 6 tumors were observed to have tumor cells with intracytoplasmic argyrophil granules. The argyrophil cells occurred only in those areas where the tumor cells were arranged in solid sheets or nest, and they usually appeared with a patchy distribution. The numbers



3



4

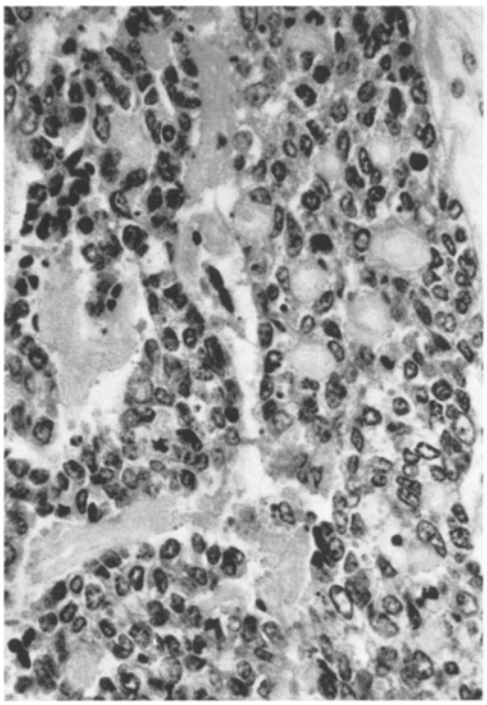
Fig. 3. Tumor cell nests composed of polygonal cells. Fibrous septa divide the masses of tumor cells into irregular cell nests. Multinucleated cells are scattered. Case 1, H.E. stain, ×760

Fig. 4. Tumor cell cords separated by connective tissue septa. Cords are composed of small cells closely packed in several layers. Case 1, H.E. stain, ×700

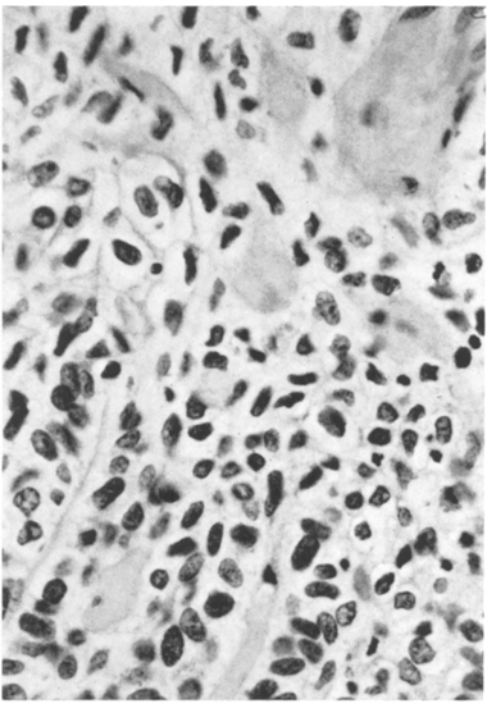
of such cells varied considerably from tumor to tumor and in different areas within the same tumor. Tumors of Cases 1, 3, 4 and 6 contained moderate numbers of the cells, while the remaining 2 tumors contained them in smaller numbers. In Case 2, they were found after a prolonged search in several sections. The argyrophil cells were oval, fusiform or triangular in shape, and frequently exhibited a non-branching, dendrite-like, cytoplasmic process that extended for a considerable distance among other tumor cells (Figs. 7 and 8). With the Fontana-Masson method, no argentaffin tumor cells were detected in the 6 tumors.

Electron microscopic features: The electron microscopic features of the 3 tumors were sufficiently similar to allow a composite description. Tumor cells were usually elongated or polygonal in shape with an irregular outline. Adjacent tumor cells frequently showed interlocking cytoplasmic processes forming an irregular intercellular space (Fig. 9). The spaces on occasion contained finely granular substance, but no fibrillar material was observed in the spaces examined (Fig. 10). Desmosome-like thickenings between adjacent cells were few.

The tumor cell nuclei were fusiform or irregularly shaped with identations of the nuclear membranes and irregular chromation clumpings. Some cells showed oval nuclei with evenly distributed chromatin. The cytoplasm was relatively



5



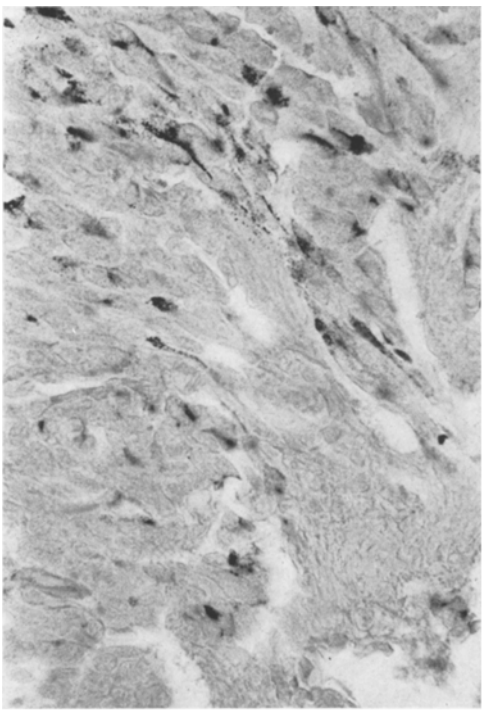
6

Fig. 5. Tumor cell nests in which globoid and trabecular masses of amorphous, proteinoid material are interspersed. Small parts of the material show a positive reaction for amyloid with alkaline Congo red stain. Case 2, H.E. stain, ×1,200

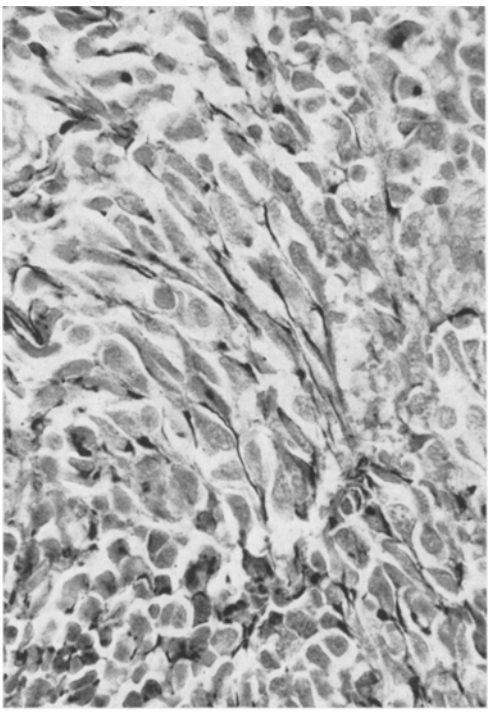
Fig. 6. Solid sheets of tumor cells with clear cytoplasm. Spherules and trabeculae of amyloid are present between the tumor cells. Case 3, H.E. stain, ×1,150

electron-transparent. This could be accounted for by the relative sparsity of rough surfaced endoplasmic reticulum, and moderate numbers of free ribosomes. The rough surfaced endoplasmic reticulum was often dilated. Golgi apparatus was not prominent. Mitochrondria at times were swollen and exhibited dissolution of the cristae. They were oval to elongated, relatively few in number, and irregularly distributed. Microfilaments and microtubules were abundant, the former being particularly numerous adjacent to the plasma membranes.

A distinguishing feature of the 3 tumors was the occurrence of neurosecretory-type granules that were present in small numbers in about half of the tumor cells of the 3 tumors. They were often found within the cytoplasmic processes (Figs. 9 and 12). The granules were round, oval or pleomorphic and had an electron-dense core which was usually enclosed by a limiting membrane (Figs. 9 through 12). In Cases 3 and 4, the granules showed round or oval dense cores from 90 to 700 mμ in diameter, while in Case 5, the granules showed pleomorphic cores, being round, oval, dumbbell or teardrop in shape, and varying from 70 to 750 mμ in greatest diameter (Fig. 12).



7



8

Fig. 7. Tumor cells with argyrophil granules. Some of them show a long cytoplasmic process. Case 1, Grimelius stain, ×720

Fig. 8. Area of streaming pattern showing spindle-shaped cells tend to lie with their dendrite-like, cytoplasmic processes in a parallel fashion. Case 3, Grimelius stain, ×1,200

Discussion

On the basis of the light and electron microscopic findings and the assay evidence provided, we consider that the 6 tumors presented here are endocrine polypeptide tumors (apudomas) that arise from argyrophil cells normally found among the basal cells of the esophageal mucosa, and that they represent a distinct histopathologic entity clearly distinguishable from other types of esophageal carcinomas. Instead of the term "oat cell carcinoma", we used "argyrophil cell carcinoma" to designate this specific type of esophageal carcinoma, since 4 of the 6 tumors showed a considerable cellular variation, though they were composed predominantly of small cells.

Histologically, the 6 tumors were characterized by the arrangement of the tumor cells in solid sheets and anastomosing cords, the presence of argyrophil secretory granules, and the deposits of amyloid. Deposits of amyloid are consistently associated with calcitonin producing thyroid medullary carcinomas (Hazard et al., 1959; Williams et al., 1966) and also have been reported in other endocrine polypeptide producing tumors that include pancreatic islet cell tumors (Porta et al., 1962), bronchial carcinoid tumors (Štěrba, 1968) and oat cell carcinoma of

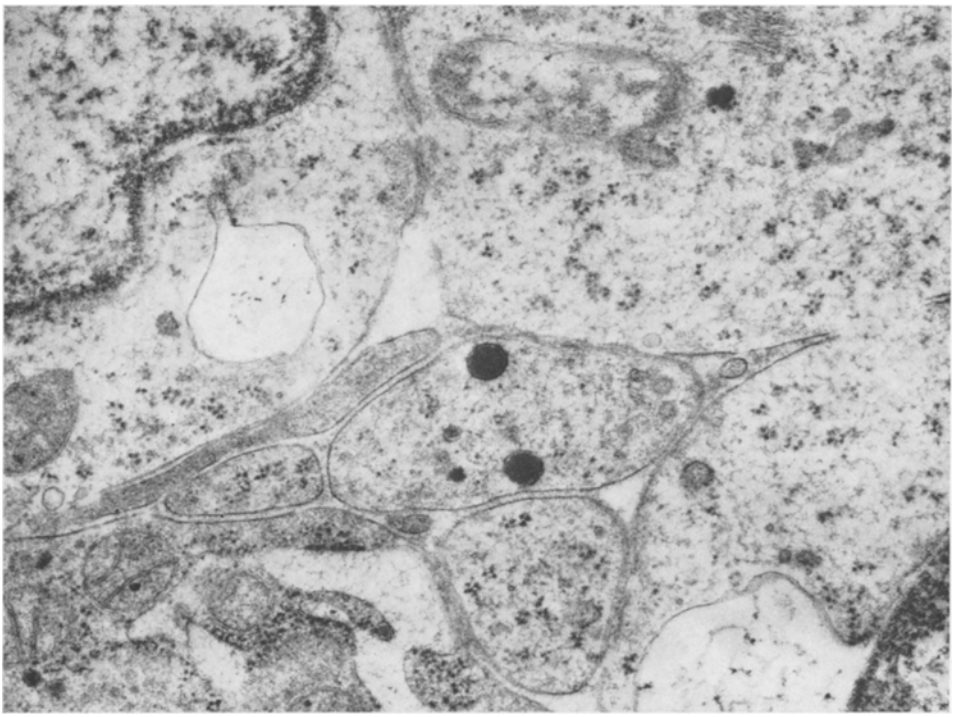


Fig. 9. Electron micrograph showing interlocking cytoplasmic processes of adjacent cells. Two round secretory granules are present. Case 4, ×26,000

the lung (Kozlowsky et al., 1970). Further, an accumulation of amyloid may occur in polypeptide-hormone producing tissues in old ages. It appears likely that the production of polypeptide hormone(s) by neoplastic or non-neoplastic cells may be responsible for the deposits of amyloid. The accumulation of the proteinaceous substance as well as amyloid observed in the tumors presented in this paper might result from the presence of polypeptide hormone(s) secreted by the tumor cells and deposited in the intercellular spaces or in the stroma. In our cases only the concentration of ACTH was determined, but there remains the possibility that the tumors could have been responsible for the production of polypeptide hormone(s) other than ACTH.

At present the function of the argyrophil cells in the esophagus and in the bronchial trees remains undetermined. If the argyrophil cells of the esophageal mucosa secrete a polypeptide hormone that play a significant role in the regulation of the peristalsis of the esophagus, then one might expect to find argyrophil cells in every esophageal mucosa. In a series of 50 esophaguses of Japanese, however, argyrophil cells were found in only 14 (Tateishi et al., 1974). The failure to demonstrate esophageal argyrophil cells in a large proportion of the Japanese suggests that such cells represent vestiges of fetal life.

In general, argyrophil cells in the bronchial tree in the fetus and newborn of mammals (including man) are found more extensively than in adults. Moosavi

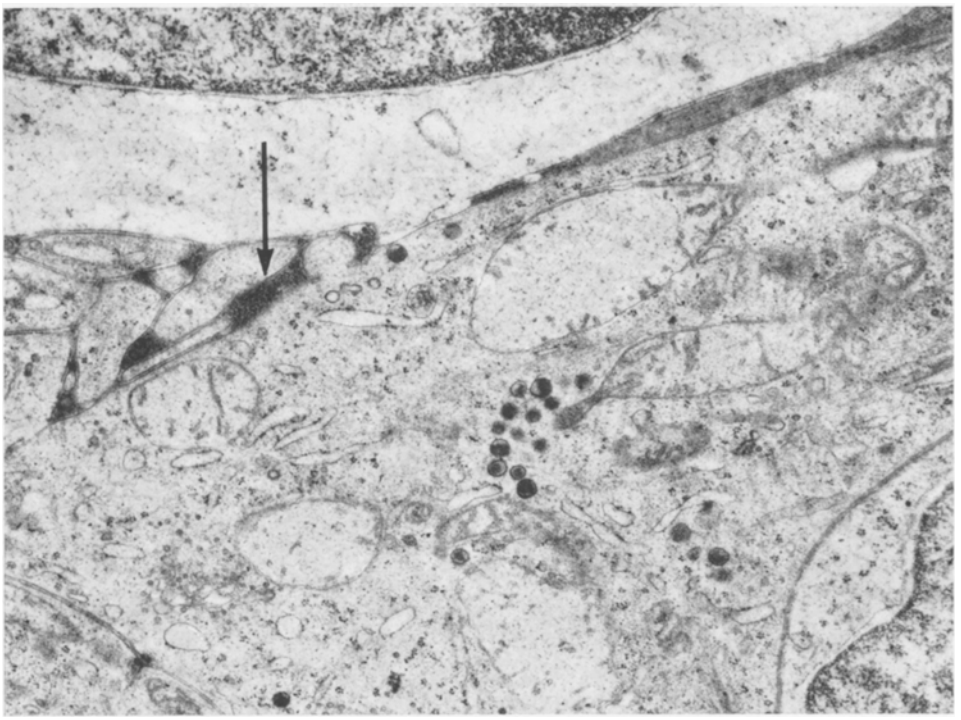


Fig. 10. Electron micrograph showing tumor cell with a cluster of secretory granules. Some granules show eccentric electron-dense cores. Adjacent cells show interlocking cytoplasmic processes forming irregular intercellular spaces filled with finely granular material (arrow). Case 4, ×13,000

and co-workers (1973) have shown in rat lungs, there is a steady decline in the number of argyrophil cells during the first month of postnatal life. Stiller and co-workers (1975) regarded the argyrophil cells of the bronchial trees as rudimentary being important only as the site of origin for bronchial carcinoids and oat cell carcinomas. A similar view can be taken of the histogenesis of argyrophil cell carcinomas of the esophagus. We feel that argyrophil cells of the esophageal mucosa can be regarded as neural crest derivatives that retain their growth potential. They may later form tumors with the possible expression of multiple endocrine functions.

Of interest in this series of esophageal carcinomas is the presence of argyrophil tumor cells with a dendrite-like cytoplasmic process that extends for a long distance among other tumor cells. The demonstration of these dendritic cells and their resemblance to those found in carotid body tumors (Costero and Barroso-Moguel, 1961) or in thyroid medullary carcinomas (Ljungberg, 1970; Tateishi et al., 1972) provide an additional support for the contention that argyrophil cells (APUD cells) are derived from the cells of the neural crest (Pearse, 1969; Pearse and Polak, 1974).

In this study the criterion for the diagnosis of argyrophil cell carcinoma was the presence of argyrophil tumor cells. The diagnosis of argyrophil cell carcinoma

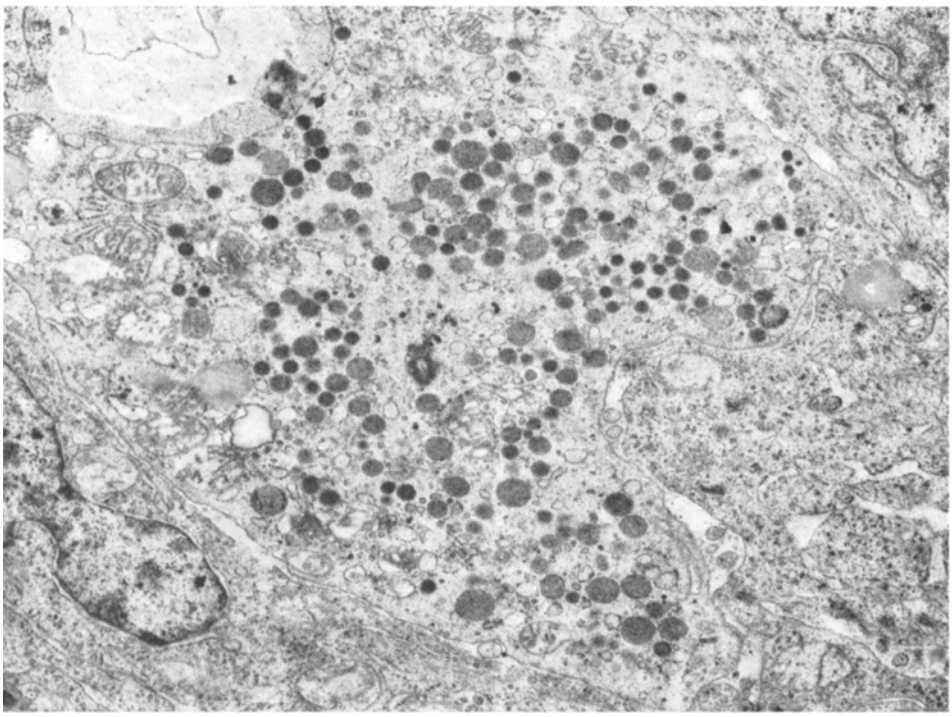


Fig. 11. Electron micrograph shows a tumor cell containing a large number of secretory granules of varying electron density. Case 3, ×8,400

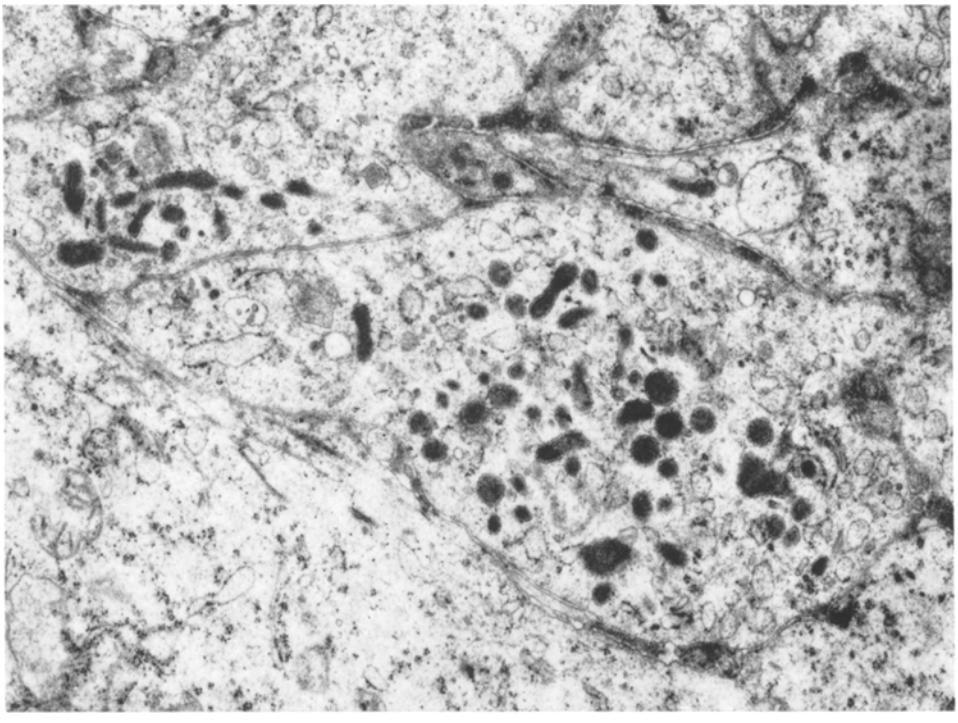


Fig. 12. Electron micrograph shows pleomorphic secretory granules accumulated in the cytoplasmic processes. Intercellular spaces contain finely granular material. Case 5, ×13,000

must be considered when a given tumor of the esophagus is composed largely of small cells. It is then necessary to demonstrate argyrophil granules in tumor cells. Among several argyrophil reactions, the Grimelius method turned out to be especially suitable for detecting argyrophil granules within tumor cells of small cell carcinomas in the lung, the pancreas, the esophagus and the uterine cervix. Clinically, it is also important to consider argyrophil cell carcinoma separately, because it possibly differs from other types of esophageal carcinoma in the natural history and the response to different therapeutic approaches.

The authors are grateful to Prof. H. Imura and Dr. Y. Hirate, Department of Internal Medicine, Kobe University School of Medicine for their interest and performing the assays for ACTH on the tumor tissues.

References

Bensch, K. G., Corrin, B., Pariente, R., Spencer, H.: Oat-cell carcinoma of the lung. Its origin and relationship to bronchial carcinoid. Cancer (Philad.) **22**, 1163–1172 (1968)

Cohen, R. B., Toll, D. G., Castleman, B.: Bronchial adenoma and Cushing's syndrome. Their relation to thymomas and oat cell carcinomas associated with hyperadrenocorticism. Cancer (Philad.) **13**, 812–817 (1960)

Corrin, B., Gilby, E. D., Jones, N. F., Patrick, J.: Oat cell carcinoma of the pancreas with ectopic ACTH secretion. Cancer (Philad.) **31**, 1523–1527 (1973)

Costero, I., Barroso-Moguel, R.: Structure of the carotid body tumor. Amer. J. Path. **38**, 127–141 (1961)

Grimelius, L.: Silver nitrate stain for α_2 cells in human pancreatic islets. Acta Soc. Med. upsalien. **73**, 243–270 (1968)

Hattori, S., Matsuda, M., Tateishi, R., Nishihara, H., Horai, T.: Oat-cell carcinoma of the lung. Clinical and morphological studies in relation to its histogenesis. Cancer (Philad.) **30**, 1014–1024 (1972)

Hazard, J. B., Hawk, W. A., Crile, G., Jr.: Medullary (Solid) carcinoma of the thyroid. A clinicopathologic entity. J. clin. Endocr. **37**, 205–209 (1959)

Imura, H., Matsukura, S., Yamamoto, H., Hirata, Y., Nakaki, Y., Endo, J., Tanaka, A., Nakamura, M.: Studies on ectopic ACTH-producing tumors. II. Clinical and biochemical features of 30 cases. Cancer (Philad.) **35**, 1430–1437 (1975)

Koss, L. G., Spiro, R. H., Hajdu, S.: Small cell (oat cell) carcinoma of the minor salivary gland origin. Cancer (Philad.) **30**, 737–741 (1972)

Kozlowski, H., Hrabowska, M., Polonski, R.: Amyloid-ähnliche Ablagerungen in Lungenkarzinom und Bronchialadenomfällen. Arch. Geschwulstforsch. **36**, 370–384 (1970)

Lauweryns, L. M., Goddeeris, P.: Neuroepithelial bodies in the human child and adult lung. Amer. Rev. Resp. Dis. **111**, 469–476 (1975)

Ljungberg, O.: Two cell types in familial medullary thyroid carcinoma. A histochemical study. Virchows Arch. Abt. A **349**, 312–322 (1970)

Matsusaka, T., Watanabe, H., Enjoji, M.: Anaplastic carcinoma of the esophagus. Report of three cases and their histogenetic consideration. Cancer (Philad.) **37**, 1352–1358 (1976)

McKeown, F.: Oat-cell carcinoma of the esophagus. J. Path. Bact. **64**, 889–891 (1952)

Moosavi, H., Smith, P., Heath, D.: The Feyrter cell in hypoxia. Thorax **28**, 729–741 (1973)

Pearse, A. G. E.: The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. J. Histochem. Cytochem. **17**, 303–313 (1969)

Pearse, A. G. E., Polak, J. M.: Endocrine tumours of neural crest origin: Neurolophomas, apudomas and the APUD concept. Med. Biol. **52**, 3–18 (1974)

Porta, A. E., Yerry, R., Scott, R. F.: Amyloidosis of functioning islet cell adenomas of the pancreas. Amer. J. Path. **41**, 623–627 (1962)

Puchtler, H., Sweat, F., Levine, M.: On the binding of Congo red by amyloid. J. Histochem. Cytochem. **10**, 355–364 (1962)

Rosen, Y., Moon, S., Kim, B.: Small cell epidermoid carcinoma of the esophagus. An oat-cell-like carcinoma. Cancer (Philad.) **36**, 1042–1049 (1975)

Smith, L. H.: Oat cell carcinoma as a malignant apudoma. J. thorac. cardiovasc. Surg. **70**, 147–151 (1975)

Štěrba, J.: Metastasierendes Bronchialkarzinoid mit amyloid in Stroma. Zbl. allg. Path. path. Anat. **111**, 555–561 (1968)

Stiller, D., Katenkamp, D., Kuttner, K.: Jugular body tumors: Hyperplasia or true neoplasm ? Light and electron microscopic investigations. Virchows Arch. Abt. A **365**, 163–177 (1975)

Taniguchi, K., Iwanaga, T., Kosaki, G., Horai, T., Sano, M., Tateishi, R., Taniguchi, H.: Oat-cell carcinoma of the esophagus producing ACTH. Report of two cases. [In Japanese.] Saishin-Igaku **28**, 1834–1837 (1973)

Tateishi, R.: Distribution of argyrophil cells in adult human lungs. Arch. Path. **96**, 198–202 (1973)

Tateishi, R., Takahashi, Y., Noguchi, A.: Histologic and ultracytochemical studies on thyroid medullary carcinoma. Diagnostic significance of argyrophil secretory granules. Cancer (Philad.) **30**, 755–763 (1972)

Tateishi, R., Taniguchi, H., Wada, A., Horai, T., Taniguchi, K.: Argyrophil cell and melanocytes in esophageal mucosa. Arch. Path. **98**, 87–89 (1974)

Tateishi, R., Wada, A., Hayakawa, K., Hongo, J., Ishii, S., Terakawa, N.: Argyrophil cell carcinomas (apudomas) of the uterine cervix. Light and electron microscopic observations of 5 cases. Virchows Arch. Abt. A **366**, 257–274 (1975)

Turnbull, A. D., Rosen, P., Goodner, J. T., Beatie, E. J.: Primary malignant tumors of the esophagus other than epidermoid carcinoma. Ann. thorac. Surg. **15**, 463–473 (1973)

Watanabe, H., Karasawa, K., Okada, Y., Akamine, Y., Kobayashi, S., Ariyoshi, H., Sato, T., Suchi, T., Hosoda, S., Suzuki, H., Kito, H.: Carcinoid and oat-cell carcinoma of the esophagus. With emphasis on close relationship between both tumors (in Japanese). Jap. J. Cancer Clin. **20**, 181–190 (1974)

Williams, E. D., Brown, C. L., Doniach, I.: Pathological and clinical findings in a series of 67 cases of medullary carcinoma of the thyroid. J. clin. Path. **19**, 103–113 (1966)

Ryuhei Tateishi, MD
Department of Pathology
The Center for Adult Diseases, Osaka
Nakamichi 1-3-3, Higashinari
Osaka, 537 Japan