10.1053.paor.1999.0211 available online at http://www.idealibrary.com on IDEAL

CASE REPORT

Amphicrine Tumor

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The term amphicrine refers to cells, and tumors, which show both exocrine and endocrine features. Author's aim was to analyse the characteristics of these neoplasms. 40 suspicious cases were reviewed. Mucin-stains (PAS, diastase-PAS, Stains-all, Alcian-blue), immunohistochemistry (antibodies against Neuron-Specific Enolase (NSE), and Chromogranin A (CGA), and electronmicroscopic studies were performed to demonstrate exocrine and/or endocrine features of the tumor cells. By means of these methods, 16 cases turned out to be amphicrine tumors. Among them, there were 4 sinonasal, 1 bronchial, 1 mediastinal, 8 gastrointestinal and 2 suprarenal gland neoplasms. In connection to the subject, a brief review is given of amphicrine tumor, regarding its etiological and pathological aspects. These tumors form a distinct clinicopathological entity and should be separated from both neuroendocrine tumors and adenocarcinomas. (Pathology Oncology Research Vol 5, No 3, 239–244, 1999)

Keywords: amphicrine, adenocarcinoid, neuroendocrine, mucus granules, dense-core granules

Introduction

In the 1930s, Feyrter put forward the concept of *diffuse endocrine system (DES)*. The cells, that contain both exocrine and endocrine secretory granules were first described by him in 1938.[15] However, the term "amphicrine" was advocated first in 1977 by Ratzenhofer for cells synchronously displaying exocrine and endocrine differentiation.[32] Amphicrine cells are divided into two subgroups:[33,5] one is where the cells contain exocrine and endocrine activities separately in the cytoplasm (apical mucus-granules, and basal dense core-granules are characteristic) and the second where the different types of granules are mixed in the cytoplasm. Similarly, neoplasms are distinguishable according to the product of the tumor. Beside pure adenocarcinomas and carcinoid tumors exist the amalgamation of the former ones; the amphicrine tumors. Lewin[25] proposed a simple nomenclature for these neoplasms as follows: a) mixed or composite tumors with an admixture of glandular and endocrine components; b) collision tumors, where these two components are distinct and juxtaposed; c) amphicrine cell tumors, in which mucigen and endosecretory granules are present in the same cell. Tumors with mixed exocrine/endocrine differentiation have been observed in numerous neoplasms in various organs. Amphicrine tumors of sinonasal cavities,[36,23] larynx,[29] lung,[27,37] gastrointestinal tract,[19,45,1] gallbladder,[46] pancreas,[24,28] thyroid,[17] breast,[9,10] middle ear,[44] skin,[35] uterine cervix,[3] vulva[20] and prostate[30] are well described.

From the practical point of view, adenocarcinoids merit special attention, since these tumors are one of the most frequent representatives of the amphicrine tumors. Adenocarcinoids are similar to carcinoid tumors in localization and in appearance, but they are composed of tubular structures in a significant proportion. Many of the cells (the "goblet-cells") contain a large mucinous vacuole. It is very important to make a distinction between adenocarcinoma, adenocarcinoid and typical carcinoid, because the prognosis and the therapy in the different types of tumors are not the same. The purpose of this investigation is the verification of mixed exocrine/endocrine characteristic of neoplasms originated from various locations, by means of histochemical, immunocytochemical and ultrastructural techniques.

Materials and Methods

We have reviewed 25 cases from the files of the Department of Pathology of the Uzsoki Municipal Hospital, Budapest, Hungary, and 15 electronmicrographs from the

Received: Jun 30, 1999; *accepted:* August 21, 1999
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 1219-4956/99/030239+06 $ 12.00/0

files of the Electron microscopic laboratory of Department of Pathology of Postgraduate Medical School. From these latter ones, we have the possibility to make light microscopic investigations in 8 cases.

Paraffin-embedded blocks and slides from 33 cases were available for conventional light microscopic examination. 3 μm sections were stained with hematoxylin and eosin. To demonstrate mucus-production, PAS, diastase-PAS, Stains-All, and Alcian Blue stains were performed. All cases were also studied by immunohistochemistry, using the DAKO LSAB 2 KIT, with AEC substrate for the following antigens: neurone specific enolase (NSE) (monoclonal, DAKO), chromogranin A (CGA) (monoclonal, BioGenex).

Materials for electron microscopy were fixed overnight in 5% phosphate-buffered glutaraldehyde postfixed in 1% phosphate-buffered osmium tetroxide for 1 hour, dehydrated in graded ethanols, and embedded in Durcupan ACM. Specimens were examined with Philips CM 10 electron microscope.

Results

Among the examined 33 cases, we were able to demonstrate amphicrine features in 16 tumors. Among these tumors, there were 4 sinonasal, 1 bronchial, 1 mediastinal (derived from trachea), 8 gastrointestinal (the mesenterial adenocarcinoid was the metastasis of an ileal adenocarcinoid, which were removed 8 years ago) and 2 suprarenal gland neoplasms (*Table 1*).

Light microscopy

The sinonasal carcinomas were composed of solid nests of basaloid cells, embedded in mucinous pools. The cells were often arranged in a glandular fashion, accompanied by extracellular, intraluminar mucus (*Figure 1a).* Granular intracytoplasmic mucin-positivity was also present in the 80–90% of the cells. A number of mucin-containing cells were recognizable. The tumor-cells were moderately differentiated, mitotic activity was approx. 12–15/10 HPF. CGA immunoreactivity showed diffuse positivity throughout the sections *(Figure 1b).* The intestinal type adenocarcinoma of the sphenoid sinus showed a well-differentiated tubulopapillary architecture. Its structure somewhat resembled small intestine mucosa with goblet cells. Cytoplasms were vacuolated, the vacuoles were filled with mucus-like substrate. CGA staining showed the presence of endocrine cells in 10–15%. Atrophic gastritis, intestinal metaplasia, and – in one case – endocrine hyperplasia were seen in the vicinity of gastric adenocarcinoids. Tumors showed the typical features of carcinoids, however glandular structures and goblet-cells were recognizable in 10–40%. Tumors were well differentiated, with minimal nuclear pleomorphism and mitotic activity, but stromal invasion could be seen in all of the cases. In the ileal adenocarcinoid (case 11), most of the CGA positive tumor cells formed glandular lumens. The lumens contained mucoid substance *(Figure 1c).* The structure of the ”malignant” adenocarcinoids was basically similar to their less malignant counterparts. These tumors were moderately differentiated, showed glandular growth pattern

Table 1. **The main characteristics of 16 amphicrine tumors**

No.	*Sex*	*Age*	*Localisation*	*Histology*	*Mucus-production- or glandular structure**	*Chromo-granin positive cells**	*EM***
1.	m	71	nasal cavity	basaloid adenocarcinoma	+++	+	–
2.	m	50	sphenoid sinus	basaloid adenocarcinoma	+++	++	–
3.	f	74	maxillary sinus	basaloid adenocarcinoma	+++	+	–
4.	f	75	sphenoid sinus	adenocarcinoma of enteric type	+++	+	+
5.	f	76	mediastinum	malignant adenocarcinoid	++	+	+
6.	m	30	bronchial tube	adenocarcinoid	+	++	–
7.	f	59	stomach	adenocarcinoid	++	+++	–
8.	f	66	stomach	adenocarcinoid	+++	+++	–
9.	f	58	stomach	adenocarcinoid	+++	++	–
10.	m	59	duodenum	adenocarcinoid	+	++	+
11.	m	58	ileum	adenocarcinoid	+++	+++	+
12.	m	66	mesenterium	adenocarcinoid	+++	+++	+
13.	f	67	caecum	malignant adenocarcinoid	++	+++	+
14.	m	42	caecum	poorly differenciated adenocc.	++	+	–
15.	m	65	suprarenal gland	phaeochromocytoma	±	+++	+
16.	m	51	suprarenal gland	phaeochromocytoma	±	+++	+

* + 10–40%, ++ 40-70%, +++ more than 70%.
** + performed, – not performed

in approx. 50% and had definite nuclear pleomorphism with prominent nucleoli. Mitotic activity was approx. 8–11/10 HPF. Stromal, vascular and perineural invasion was evident. Adenocarcinoma of the colon (case 14), contained CGA positive cells in about 10–15% *(Figure 1d)*. The tumor was of a very agressive type, with great pleomorphism, extensive lymphatic vessel invasion. The mucus production was scanty. The mucus proved to be PAS positive, but Alcian blue and Stains-all negative. Consequently, the mucus produced by the tumor was of neutral type. This finding also supports the fact, that this tumor was poorly differentiated. We were unable to demonstrate unequivocal mucus production in the phaeochromocytomas by light microscopic techniques. The amphicrine features of these tumors (case no. 15 and no. 16) were electron microscopic findings.

Electron microscopy

The examined tumors were found to contain cells with variable numbers of dense-core membrane-bound granules of neurosecretory (NS) type. These granules were mainly peripherally located with vascular pole condensation *(Figure 2a)*. A few types of NS granules were identified. Round, uniform electrone-dense granules, of the same size, clear vesicles, and ovoid, or irregular NS granules *(Figure 2a)* were observed. Cells with secretory exocrine granules of mucin type were identified as well *(Figure 2b)*. The mucin granules were located mainly toward glandular or intracytoplasmic lumina. These were membrane-bound structures, with an electron-lucent, reticulated content. In some cases so-called "Bull's eye"-structure – an osmiophilic core within the granule – was recognizable. A number of amphicrine cells were recognizable. In case no. 13 intracytoplasmic vacuoles surrounded by microvilli could be seen *(Figure 2c)*. Accordingly, the examined neoplasms were adenocarcinoids of composite type, as well as amphicrine tumors. Several cases did not react with CGA monoclonal antibodies, although NS granules were identified.

Discussion

It is well known, that tumors from a variety of organs may consist of more than one cell line. A controversy still exists as to the origin of the different cells. The question

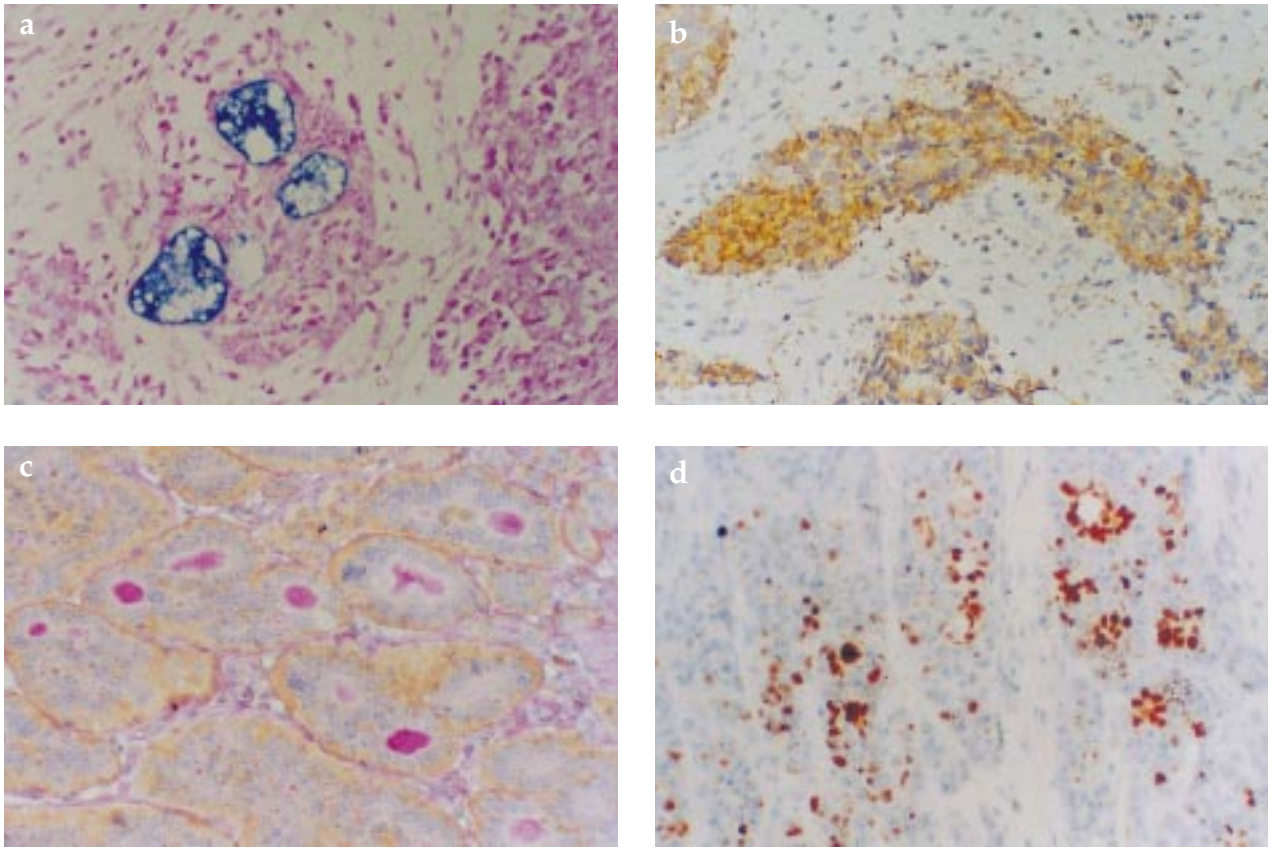

Figure 1. (a) *Case 2. Extracellular mucin-pools, surrounded by solid nests of basaloid cells. (Stains-all staining, x200).* ***(b)*** *Case 1. Solid nest of CGA-positive tumor cells. (chromogranin-A x200).* ***(c)*** *Case 11. Histological structure of the tumor showing glandular pattern. Note the intraluminal mucus, and the chromogranin-positivity at the basal pole of tumor cells. (Diastase-PAS staining and chromogranin-A x200).* ***(d)*** *Case 14. Small clusters of CGA-positive cells. (chromogranin-A x200)*

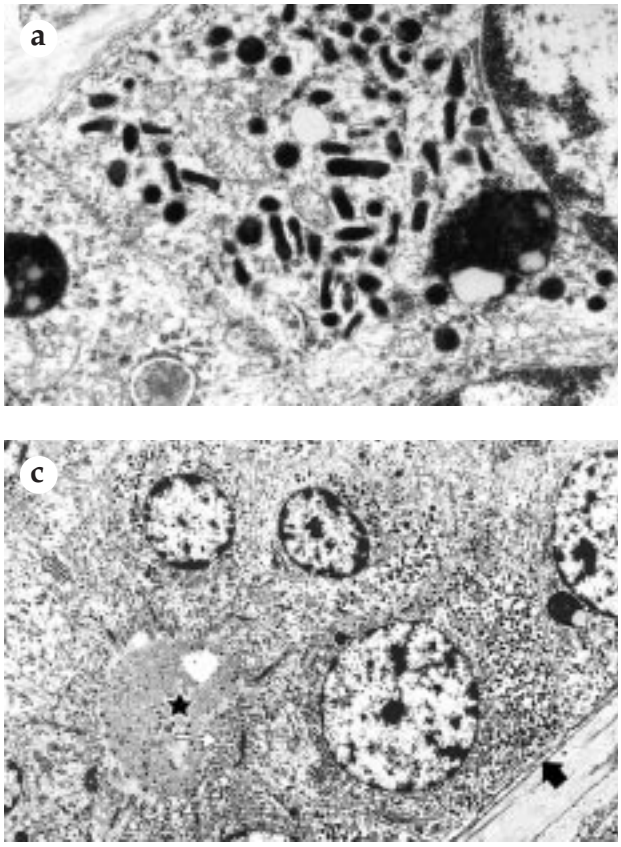

Figure 2. *Ultrastructure of the tumor cells.* ***(a)*** *Case 12. Long, ovoid, irregular shaped dense-core granules.* ***(b)*** *Case 16. Both mucus-granules and NS-granules (arrows) are recognizable in the same cell.* ***(c)*** *Case 12. Glandular lumen is encircled by cells, which contain microvilli, and desmosomes at the apical pole (thin arrow), and dense core granules at the basal pole (thick arrow). The lumen is filled with mucus granules. (asterisk).* ***(a)*** *x6610,* ***(b)*** *x6610* ***(c)*** *x1650,.*

is, where the endocrine cells of the sinonasal and the gastrointestinal mucosa originate from. Are they of ectodermal, neurocrest origin? Are they derived by differentiation from endoderm?[2,16] It is possible, that the neoplastic changes occur independently in two different cell lines, at the same time. The other possibility is, that the tumor derives from one common stem-cell. In accordance with a number of observations, and studies, it is well proved, that the main part of the mucosal endocrine cells are of endodermal origin, and the different cell-types of some composite tumors have a common stem-cell origin.[12,13,38] Some of the tumors of this study contain amphicrine cells. Moreover, one of these cases (case no. 12.) was a metastatic tumor. These findings strongly support the theory of the common stem-cell origin of these neoplasms.

According to this study – in agreement with the literature – these rare tumors can be found in numerous organs of the human body with the predilection of the respiratory passages and the gastrointestinal tract – due to the multipotent mucosal stem-cells of these organs. A small portion of the adenocarcinoids of the gastrointestinal system, mostly of the stomach, possibly originates from endocrine hyperplasia.[31,42,6] In this series, atrophic gastritis, intestinal metaplasia and (in case 8) endocrine hyperplasia were seen in the vicinity of the gastric adenocarcinoids. Endocrine hyperplasia has recently been recognised in chronic antral atrophic gastritis with intestinal metaplasia.[26] The gastritis is usually of type A (autoimmune) with a low incidence of H. pylori colonisation.[22,43] Although it is unusual to find H. pylori in an advanced state of type B gastritis as well, there was no trace of H. pylori colonisation in the present cases. These hyperplasias have also been seen in pernicious anaemia,[39] in chronic hypergastrinemic states,[4] during long-term high doses of antisecretory drugs[21,34] and are currently regarded as carcinoid precursor changes.[11,41]

Although most of the typical carcinoids may show some glandular structure (less than 5–10%), the term adenocarcinoid refers to neoplasms, in which evident mucus-production is recognisable in a greater proportion.[40] The appearance of mucus production could influence the behaviour of these lesions. Adenocarcinoids (above all the goblet-cell type) are generally regarded as being more aggressive tumors than carcinoids, notwithstanding their prognosis is better than adenocarcinomas.[18] It is due to the presence of endogen growing factors as well as the relative immaturity of tumor stem cells (which have retained their capacity for endocrine differentiation) that some of the exocrine neoplasms (first of all the adenocarcinomas of the colon) which contain endocrine cells in a considerable portion, have a worse prognosis than tumors with pure mucus-production.[7,8]

Table 2. **Diagnostic characteristics of the carcinoid-adenocarcinomas**

1. major component of the tumor: exocrine, endocrine, (amphicrine)
2. percentage of minor component (at least 10%)
3. localisation of minor component: mixed, juxtaposed
4. histologic grading, growth pattern
insular, trabecular, glandular, undifferentiated, mixed necrosis
evidence of stromal, vascular, or perineural invasion
5. nuclear grading
6. mitotic activity.

When the possibility of amphicrine nature of a tumor arise, it must be proved by means of special stains, immunohistochemical and (if needed) ultrastuctural techniques. These techniques not just support, but complete each other. As for the differential-diagnosis, it is very important to fit the primary tumor into the carcinoid-adenocarcinoma spectrum on the basis of the criteria listed on *Table 2*. The order of prognosis of the carcinoid-adenocarcinoma spectrum: typical carcinoid tumor > adenocarcinoid tumor > atypical or "malignant" carcinoid tumor (endocrine carcinoma) > "malignant adenocarcinoid tumor" > adenocarcinoma > adenocarcinoma, containing endocrine cells. It is an accepted fact, that the outcome of phaeocromocytomas is unpredictible. This study includes two phaeocromocytomas (cases no. 15 and 16), with amphicrine cells. There is no trace in the reviewed literature of a finding like this. The amphicrine feature of these tumors is important, because this finding might be in connection with the prognosis of the tumors. This supposition needs, of course, much more evidence.

Since it is almost impossible to give the correct preoperative (core biopsy, fine needle aspiration) or intraoperative (frozen section) diagnosis, the careful histological examination is essential in case of these types of tumors and, consequently, there is a possibility of a more radical second operation – e.g. ileocolectomy or right colectomy rather than appendectomy.

Acknowledgements

The author expresses his gratitude to Prof Dr. Sz. Virágh for the opportunity of the electron-microscopic examinations, and for the enthusiastic support. He also grateful for the assistance of all the employees of the Electron Microscopic Laboratory of Department of Pathology of Postgraduate Medical School, Budapest, Hungary.

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