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Neurohormonal Peptide Immunoreactive Cells in Mucinous Cystadenomas and Cystadenocarcinomas of the Ovary*

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Summary. In 144 benign mucinous cystadenomas of the ovary, 33 mucinous cystadenomas of borderline malignancy and 64 mucinous cystadenocarcinomas, the incidence of tumours containing argyrophil (and probably endocrine) cells was 18%, 33%, and 53%, respectively. The results of a semiquantitative assessment of the number of argyrophil cells in each individual tumour indicates that the greatest numbers occurred in the cystadenocarcinomas. As, however, the tumour cell density was larger in the cystadenocarcinomas than in the cystadenomas, and as the argyrophil cells often had a patchy distribution in the tumour epithelium, the incidence figures are unreliable. In addition, visualization of the argyrophil cells depends on an adequate fixation which is difficult to achieve in the routine processing of large tumour specimens.

Many argyrophil cells in the cystadenocarcinomas displayed immunoreactivity with antisera raised against gastro-entero-pancreatic (GEP) neurohormonal peptides. In ten such tumours immunohistochemical evidence was obtained for the presence of the following neurohormonal peptides in the tumour cells: somatostatin, glucagon, gastrin/CCK, neurotensin, and enkephalin. Four of these ten cystadenocarcinomas were multihormonal, in that three contained two cell populations storing GEP neurohormonal peptides, and one tumour even three such populations. In the benign cystadenomas, however, no immunoreactive tumour cells were found. In those of borderline type, only two harboured immunoreactive cells. In both cases the tumour cells stored gastrin/CCK.

The general appearance of the epithelium in the mucinous tumours – a continuous single-cell layer of mucin-producing cells intermingled with

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argyrophil cells of open type – and the spectrum of neurohormonal peptides observed, indicate an origin from the foregut endoderm.

Key words: Gastro-entero-pancreatic (GEP) neuroendocrine system – Neurohormonal peptides – Ovarian mucinous cystadenomas/cystadenocarcinomas – Immunohistochemistry – Argyrophil endocrine cells

Introduction

Both argyrophil and argentaffin cells have been demonstrated in the epithelium of mucinous cystadenomas and cystadenocarcinomas of the human ovary (Fox et al. 1964; Klemi 1978). Ultrastructurally, these cells are characterized by the presence of small secretory granules (Schmid 1977; Klemi and Nevalainen 1978). In the gastro-entero-pancreatic (GEP) region such cell types are known to produce neurohormonal peptides (cf. Creutzfeldt 1980). Tumours arising from these cells (insulomas; carcinoids) (Solcia 1980) may evoke symptoms of endocrine disorders, for instance the insulinoma syndrome, the Zollinger-Ellison syndrome, and the carcinoid syndrome (Friesen and Bolinger 1978; Grahame-Smith 1979). Despite the fact that primary ovarian mucinous tumours contain cells with a peptide hormone producing potential, they are usually not associated with endocrine symptoms (Scully 1980). In two histopathologically documented cases, however, a Zollinger-Ellison syndrome was found to be associated with a mucinous cystadenocarcinoma (Cocco and Conway 1975) and a mucinous cystadenoma (Long et al. 1980), and both tumours were found to produce gastrin. Carcinoid tumours may also arise in the ovary. Recently, it was shown that such tumours contain cells reacting with antisera against a variety of neurohormonal peptides, though usually not associated with endocrine symptoms (Sporrong et al. 1981a, b; Dayal et al. 1980). These observations prompted a more systematic search for neurohormonal peptides in ovarian mucinous tumours.

Material and Methods

A re-examination was made of all the ovarian mucinous cystadenomas and cystadenocarcinomas available from the 1970–1979 files of the Department of Pathology at the Malmö General Hospital, using the Grimelius (1968) silver nitrate procedure for detecting argyrophil tumour cells. Of the 241 tumours examined (paraffin sections from formalin-fixed specimens), 71 contained argyrophil cells. These 241 tumours were grouped according to the World Health Organization classification of ovarian tumours (Serov and Scully, 1973) into three categories: benign cystadenomas (IIa); cystadenomas of borderline type (IIb); and cystadenocarcinomas (IIc); the corresponding number of tumours was 144, 33, and 64, respectively.

For immunohistochemistry, sections of 5 μm thickness, were deparaffinized, hydrated, and washed over night. The antisera against neurohormonal peptides were applied for 3 h at room temperature when the immunofluorescence procedure was used. The antisera used and their source and dilutions are listed in Table 1. The antiserum against gastrin reacts equally well with cholecystokinin (CCK), and that against glucagon reacts with both gut type and pancreatic type glucagon. Fluoresceinated or unlabelled sheep anti-rabbit IgG (or anti-guinea-pig IgG) was applied as the second antibody, diluted 1:20. For immunofluorescence, the sections were rinsed and mounted in buffered glycerine. Alternatively, the peroxidase-antiperoxidase (PAP) procedure (Sternberger 1979) was applied, using the same antisera at the dilutions given in Table 1. Incubation time

Table 1. Specification of the GEP neurohormonal peptide antisera used and their source of origin and working dilutions.

Antisera, raised against	Working dilution		Code	Source
	IF[a]	PAP[b]		
Pure bovine insulin	1/80	1/5120	LAI	L.G. Heding, Novo Res. Inst., Bagsvaerd, Denmark
Synthetic ovine somatostatin (SOM)		1/2560	19578	M.P. Dubois, Station Physiol. Reprod., INRA, Nouzilly, France
Pure porcine glucagon		1/640	7811	J.E. Thorell, Dept. Nucl. Med., Malmö Gen. Hospital, Malmö, Sweden
Pure bovine pancreatic polypeptide (PP)	1/320	1/2560	7823	J.E. Thorell, Dept. Nucl. Med., Malmö Gen. Hospital, Malmö, Sweden
Pure porcine secretin	1/80	1/2560	5585	O.B. Schaffalitzky de Muckadell, Bispebjerg Hospital, Copenhagen, Denmark
Pure porcine vasoactive intestinal polypeptide (VIP)		1/5120	5603	J. Fahrenkrug, Dept. Clin. Chem., Copenhagen County Hospital, Glostrup, Denmark
		1/5120	7852	J.E. Thorell, Dept. Nucl. Med., Malmö Gen. Hospital, Malmö, Sweden
Synthetic human gastrin 2–17		1/5120	4562	J.F. Rehfeld, Dept. Med. Biochem., University of Aarhus, Aarhus, Denmark
Synthetic bovine substance P (SP)	1/20		K 16	G. Nilsson, Dept. Pharmacol., Karolinska Inst. Stockholm, Sweden
	1/80		SP-8	P.C. Emson, Med. Res. Council, Cambridge, England
Synthetic bovine neurotensin (NT)		1/640	HC-8	R.E. Carraway, Lab. Hum. Reprod., Dept. Physiol., Harvard Med. Sch., Boston, MA, USA
Synthetic leu- or met-enkephalin (Enk)	1/240	1/240 1/640	Leu-enk Met-enk	R.J. Miller and K.J. Chang, Burroughs Wellcome Res. Lab., Triangle Park, NC, USA
Synthetic human β-endorphin (β-End) (β-lipotropin 61–91)		1/640	7763	J.E. Thorell, Dept. Nucl. Med., Malmö Gen. Hospital, Malmö, Sweden
Synthetic porcine motilin		1/640	MBR-1105	N. Yanaihara, Shizuoka Coll. Pharm. Shizuoka, Japan
Synthetic human calcitonin (CT)		1/160	AS292/5	I. MacIntyre, Endocr. Unit. Royal Postgrad Med. Sch., London, England
Pure porcine adrenocorticotropic hormone (ACTH)	1/80	1/640	No 1	Own

[a] IF = Immunofluorescence
[b] PAP = Peroxidase-Anti-Peroxidase procedure

Table 2. Relative incidence of argyrophil epithelial cells in the parenchyma of ovarian cystadenomas and cystadenocarcinomas (Grimelius' procedure)

	Total number	0	+	++	+++	%[a]
Benign Cystadenoma	144	118	17	8	1	18
Cystadenoma of Borderline Type	33	22	6	2	3	33
Cystadenocarcinoma	64	30	4	16	14	53
Total	241	170	27	26	18	29

+ = Occasional argyrophil cells; ++ = Moderate numbers of argyrophil cells; +++ = Numerous argyrophil cells

[a] Per cent of tumours with at least "+" incidence of argyrophil tumour cells

was 24 h at +4° C. Control sections were exposed to antiserum inactivated with excess amount of antigen (10–100 μg of synthetic and/or highly purified natural peptide per ml diluted antiserum). Details concerning antisera and antigens have previously been reported (Sporrong et al. 1981b).

In some instances, sections first examined for the presence of immunofluorescent cells were restained with silver nitrate according to the Grimelius procedure.

Results

Incidence of Argyrophil Tumour Cells. The three categories of tumours differed with regard to their apparent incidence of argyrophil epithelial cells (Table 2). Of the 144 tumours classified as benign cystadenomas, 26 (18%) harboured argyrophil cells. Eleven of the 33 tumours classified as borderline tumours contained argyrophil cells (33%), whereas 34 of the 64 cystadenocarcinomas (53%) contained such cells. When, however, these incidence figure were related to the cell density, it was found that the number of cells in the sections varied considerably; the tumour cells were 10–100 times more numerous in the borderline and malignant tumours than in the benign cystadenomas. The different incidence of argyrophil cells may perhaps partly reflect differences in the tumour cell density. Another source of error in the assessment of the incidence of argyrophil cells was their very patchy distribution. Lastly, all the tumours were large; hence, it might be suspected that the fixation of the deeper parts of the tumour parenchyma was far from optimal. Both the argyrophil reaction and the immunoreaction depend on an adequate fixation. Thus, the incidence figures do not allow any far-reaching conclusions.

In general, the epithelium of the ovarian mucinous tumours formed a continuous single layer of mucin-producing cells, reminiscent of the epithelium seen, for instance, in the gut, in the antrum of the stomach, in the gall bladder, in the bile ducts or in the large pancreatic ducts. This light-microscopical impression was supported by the presence of disseminated argyrophil cells, usually of open type, in the epithelial lining. Some examples of argyrophil cells and

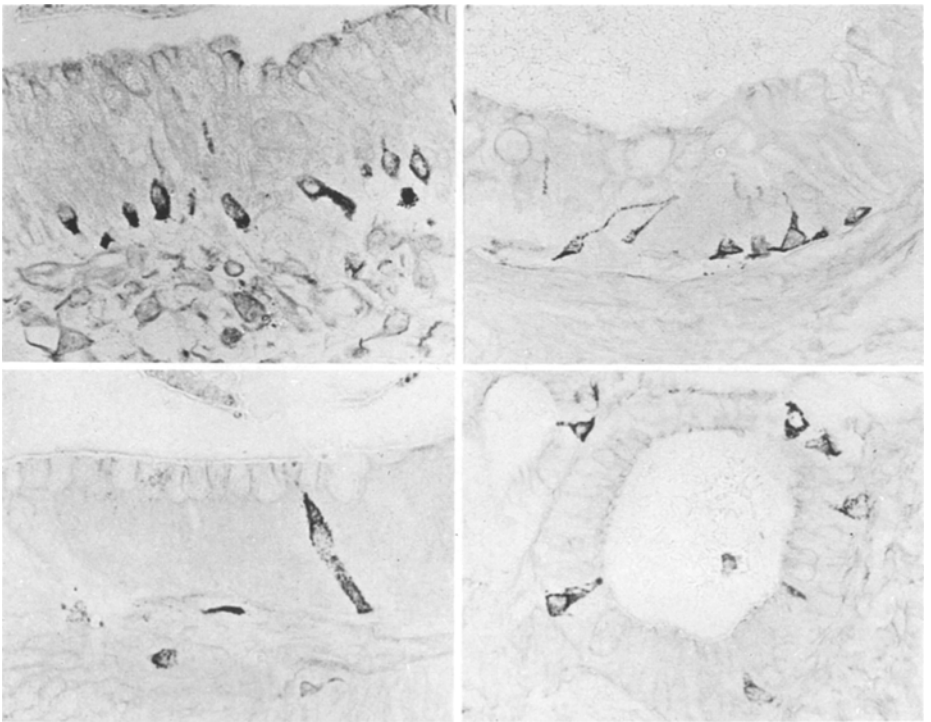

Fig. 1. Medium-power photomicrographs of four ovarian mucinous cystadenocarcinomas, showing the widely varying structure of the argyrophil cells (black) in the tumour epithelium. Grimelius' silver nitrate procedure. × 200

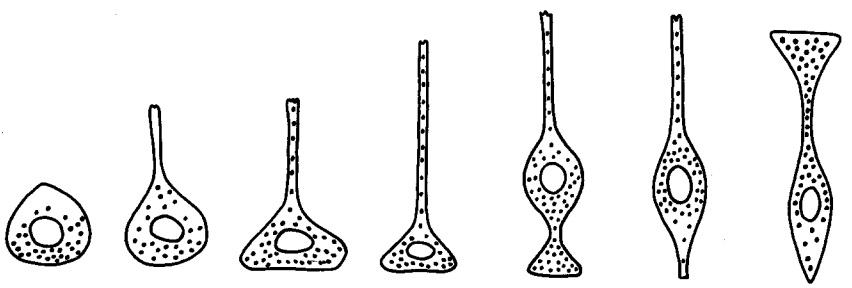

Fig. 2. Schematic outline of the spectrum of argyrophil cell types seen in the tumour epithelium of ovarian mucinous cystadenomas and cystadenocarcinomas. All cells stand on the basal membrane of the epithelium; some are of closed type (left), i.e., they do not seem to reach the luminal surface; others are of open type, being equipped with apical processes of varying shape (middle and right), extending all the way from the basal membrane to the microvillous border at the lumen

a schematic outline of their rather widely varied structure are given in Figs. 1 and 2.

The number of argyrophil cells observed in the individual tumours also seemed to vary in proportion to the degree of malignancy. Thus, in the tumours classified as mucinous cystadenomas and borderline tumours argyrophil cells

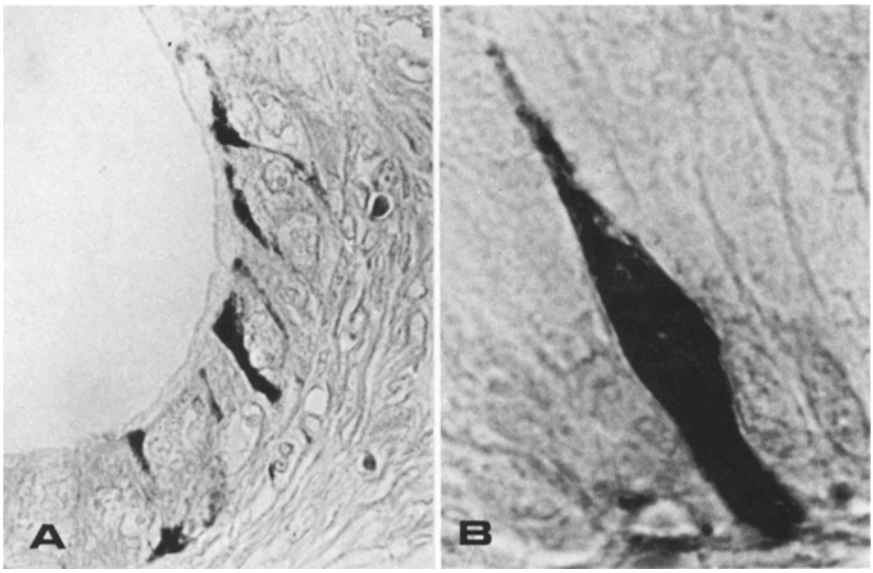

Fig. 3. Medium **A** and high-power **B** photomicrographs of two ovarian mucinous cystadenocarcinomas, showing cells in the tumour epithelium displaying immunoreactivity with antisera against (met)enkephalin **A** and gastrin/CCK (B), respectively. The general structure of the immunoreactive cells conforms to that of the argyrophil cells (Figs. 1 and 2). PAP procedure. ×800 **A** and 2,000 **B**

were few or moderate in number, whereas in the cystadenocarcinomas they were often quite numerous.

Incidence of Peptide Immunoreactive Tumour Cells. Of the tumours classified as benign cystadenomas, none were seen to harbour immunoreactive epithelial cells. Of the borderline tumours, 2 (18%) contained cells reacting with the antiserum against gastrin/CCK (Table 3). Characteristically, the immunoreactive cells were scattered in the epithelium, often two or three together (Fig. 3). Using the restaining technique, it could be shown that these gastrin/CCK-immunoreactive tumour cells were argyrophil. In both these tumours the immunoreactive cells were much fewer than the argyrophil ones.

In the cystadenocarcinoma group, 10 (29%) tumours contained neurohormonal peptide immunoreactive cells (Table 3). Six of these tumours harboured cells reacting with antiserum against only one of the neurohormonal peptides (somatostatin, glucagon/enteroglucagon, gastrin/CCK or enkephalin), whereas 3 tumours contained two immunoreactive cell populations and one tumour even three (Table 3). The immunoreactive peptides most often found were gastrin/CCK and somatostatin, followed by enkephalin. Glucagon immunoreactive cells were found in one tumour only, whereas neurotensin immunoreactive cells occurred in another tumour which also harboured gastrin/CCK cells and enkephalin cells. Of the other cystadenocarcinomas, storing more than one demonstrable peptide, two contained cells reacting with antisera against somatostatin or gastrin/CCK, whereas one tumour harboured cells reacting with antisera

Table 3. Follow up and survey of some histopathological and immunohistochemical data from those 12 patients with ovarian cystadenomas and cystadenocarcinoma where cells immunoreactive with antisera raised against GEP neurohormonal peptides were detected.

Patient		Histo-pathol. tumour type[a]	Relative inci-dence[b] of argy-rophil cells	Relative incidence[c] of cells immunoreactive with antisera raised against					Follow up
Case no.	Age in years at opera-tion			SOM[d]	GLUC[d]	GAST[d] CCK	ENK[d]	NT[d]	
1	52	IIb	++			+			No symptoms after 4 years
2	45	IIb	+++			++			No symptoms after 2 years
3	39	IIc	+++			+	+		No symptoms after 11 years
4	63	IIc	+				+		No follow up
5	66	IIc	+++		+				No symptoms after 2 years No further follow up
6	51	IIc	++			++			No symptoms after 8 years
7	54	IIc	+++	+					No symptoms after 6 years
8	55	IIc	+++	+					No symptoms after 5 years
9	54	IIc	++	++					Dead after 4 years with pulmonary metastases
10	21	IIc	+++			+			No symptoms after 3 years
11	65	IIc	+++	+		++			No symptoms after 3 years
12	48	IIc	+++			+	+	++	No symptoms after 2 years

[a] IIb = Mucinous cystadenomas of borderline malignancy. IIc = Mucinous cystadenocarcinomas
[b] Same semiquantitative grading as in Table 2
[c] + = Occasional immunoreactive epithelial cells in the tumour parenchyma. ++ = Moderate numbers of immunoreactive epithelial cells in the tumour parenchyma
[d] SOM = Somatostatin; GLUC = Glucagon; GAST/CCK = Gastrin/Cholecystokinin; ENK = Enkephalin; NT = Neurotensin

against gastrin/CCK or enkephalin (Table 3). While the somatostatin immunoreactive cells were non-argyrophil, the glucagon and gastrin/CCK immunoreactive cells were argyrophil. As a rule, immunoreactive cells were less numerous than argyrophil cells.

Clinical Aspects. The histopathological analysis of the tumour material was followed by a review of the case histories of 11 of the 12 patients with tumours containing peptide immunoreactive cells. The case history of one patient (case

4) was not available. All patients, except one (case 1; Table 3), presented with rather non-characteristic symptoms, usually abdominal distension, of 3–6 months duration. The patient case 1 presented with symptoms of severe gastritis of 3 months' duration. X-ray examination failed to reveal gastric or duodenal ulcer, but showed a pelvic tumour. All gastric symptoms disappeared after excision of a large cystadenoma of borderline malignancy, rich in gastrin immunoreactive tumour cells (Table 3).

Discussion

A characteristic feature of many cell types producing neurohormonal peptides is their argyrophilia by the Grimelius procedure. Consequently, the presence of argyrophil cells in ovarian mucinous cystadenomas and cystadenocarcinomas suggests the ability of these types of tumours to produce such peptides. The results of the present study confirm that they can produce numerous neurohormonal peptides. As a rule, the existence of argyrophil cells in the tumour did not seem to be correlated with the age of the patients or to have any bearing on their symptoms or survival rate, as found by Fox et al. (1964) and Klemi (1978).

There are several possible explanations why such tumours usually do not give rise to clinical symptoms. The number of peptide producing cells may be so low that the serum concentration of the peptide remains within the normal range, or the rise is too small or too brief to produce overt symptoms; the peptide, although actively secreted, might be metabolized so efficiently that normal serum concentrations are maintained; or the released peptide might be immunoreactive but functionally inactive. Another intriguing possibility that might explain the paucity of symptoms is the not infrequent occurrence of tumour cells with somatostatin-like immunoreactivity together with other neurohormonal immunoreactive substances, notably gastrin/CCK-like activity. Somatostatin is a well known inhibitor of, for instance, the release of gastrin (Efendić 1980; McCann et al. 1980). It is by no means unlikely that it would be possible to find an elevated concentration of a neurohormonal peptide in serum if a blood sample could be drawn from the ovarian vein in a patient with a mucinous cystadenocarcinoma of the ovary. Some support for this suggestion comes from the case history of patient case 1 (Table 3), where there seemed to be a correlation between the sudden disappearance of severe gastritis symptoms and the removal of a gastrin/CCK-producing tumour.

It is also worth noting that the spectrum of the immunoreactive peptides observed in these mucinous cystadenomas differs from that observed by immunohistochemistry in ovarian carcinoids (Sporrong et al. 1981a, b). In the latter group of tumours, pancreatic polypeptide (PP) was found to be the most common neurohormonal peptide, followed by glucagon/enteroglucagon and enkephalin. In an analogous study of rectal carcinoids (Alumets et al. 1981), tumour cells, displaying immunoreactivity with antisera against PP, glucagon, somatostatin, insulin, substance P, enkephalin, or β-endorphin, were observed (in decreasing order of frequency). The reason for these discrepancies is unknown, but they might be due to differences in technique. Rectal carcinoids are usually

small and easily accessible for immediate microscopical investigations (Alumets et al. 1981), whereas both ovarian carcinoids (Sporrong et al. 1981b) and, in particular, mucinous tumours are more difficult to preserve adequately for immunohistochemical investigation, because of their size.

The epithelium which makes up the main part of ovarian tumours is not found in the normal ovary. It is said to resemble colonic epithelium (Klemi, 1978) or that of the uterine cervix, and the prevalent hypotheses are that it arises either as a metaplasia of the ovarian germinal epithelium or as a monophyletic teratoma (Fox et al. 1964). The general appearance of the epithelial lining with its disseminated argyrophil cells of open type is rather that of an endodermally derived mucosa of foregut type, often seen in benign cystic teratomas ("dermoid cysts") of the ovary. It is becoming increasingly realized that epithelial tumours of foregut type may contain argyrophil cells, probably of endocrine nature, as shown for carcinoma of the stomach (Tahara et al. 1975), of the pancreas (Klöppel et al. 1980) and of the gall bladder (Azadeh and Parai 1980). Whether these argyrophil cells are actual tumour cells or represent the result of concomitant metaplasia (Tahara et al. 1975) is still an open question. The present findings suggest that peptide hormone producing cells and mucin producing cells arise from a common stem cell. Some kind of histogenetic relationship between endocrine cells and mucin producing cells is suggested by previous phylogenetical studies (cf. Falkmer et al. 1973) and from observations on several kinds of human tumours and hyperplasias, such as so-called amphicrine cell proliferations and adenocarcinoid tumours of the vermiform appendix and colon (Ratzenhofer 1977; Ratzenhofer and Auböck 1980; Olsson and Ljungberg 1980) and mucoid carcinoma of the breast (Capella et al. 1980).

The immunohistochemical observations made in the present study of argyrophil cells in mucinous cystadenomas and cystadenocarcinomas of the ovary indicate a spectrum of neurohormonal peptides similar to that seen in carcinoids of foregut type rather than in those of midgut or hindgut type (Alumets et al. 1980).

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