

Argyrophilia in ovarian serous tumors. A comparative study in 127 epithelial ovarian tumors

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Summary. The distribution of argyrophil cells in epithelial ovarian tumors was studied in 127 cases. The results showed that not only mucinous tumors and endometrioid tumors contained argyrophil cells, but also some serous tumors expressed argyrophilia. 31% of serous tumors including 40% of serous adenocarcinomas contained variable numbers of argyrophil cells. Argyrophilia has been demonstrated in mucinous tumors, endometrioid tumors and Brenner tumors before. However, this is the first time the presence of argyrophilia in serous tumors has been noticed. Moreover, the argyrophil cells in 5 serous carcinomas showed reactivity with Neuroendocrine (chromogranin A) antibody but not with serotonin. The expression pattern of argyrophilia in the serous tumors was different from that of the mucinous tumors; in the former, argyrophil granules appeared in apical portions or throughout the cytoplasm of single or clustered cells. In addition, the argyrophilia in some serous tumors and endometrioid tumors decreased after diastase digestion. Ultrastructurally, no typical neurosecretory granule was found in the argyrophilic serous tumors. The findings in this study suggest that argyrophilia could be quite frequently found in ovarian epithelial tumors and in itself is not a very specific differential characteristic of carcinoid tumors. The argyrophilia found in a variety of epithelial ovarian tumors might lend additional support to the histogenesis and close relationship between the common epithelial tumors of the ovary.

Key words: Argyrophilia, Chromogranin A, Ovarian serous tumors

Introduction

As early as in 1938 Masson noted the presence of

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argentaffin cells in ovarian mucinous tumors (Saksela, 1989). This observation has subsequently been confirmed by numerous other investigations (Fox et al., 1964; Klemi, 1978; Sporrang et al., 1981), and the studies became more and more intensive and extensive. The variety of ovarian tumors with argyrophilia and neuroendocrine cells has been enlarged, including teratomas with endodermal components, mucinous tumors, endometrioid carcinomas, Brenner tumors, carcinoids, small cell carcinomas and Sertoli-Leydig cell tumors with heterologous elements of endodermal type. An excellent review was published about this by Scully (1980).

Considering the common origin of most epithelial ovarian tumors, which are believed to be derived from the surface epithelium covering the ovary (Cramer et al., 1983; Czernobilsky, 1987), together with the findings that histological elements from various epithelial ovarian tumors are commonly found as admixtures within a given tumor, we speculated about the presence of argyrophilia in every type of the common epithelial ovarian tumors, including serous tumors, in which argyrophilia has never been mentioned. In order to prove this hypothesis, the present study was undertaken. The investigation has been directed towards whether argyrophil cells are present in every type of common epithelial ovarian tumor and, whether all the argyrophil cell tumors have a neuroendocrine nature by using immunohistochemical demonstration of Neuroendocrine (chromogranin A) and serotonin. In relation to the embryogenesis and histogenesis, the characteristics and significance of the argyrophilia in common epithelial tumors of the ovary are discussed.

Materials and methods

127 cases of epithelial ovarian tumors were studied. They were classified and grouped into benign, borderline and malignant forms according to the criteria of the World Health Organization (Serov et al., 1973). The

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tumors consisted of serous tumors (64), mucinous tumors (27), serous & mucinous mixed tumors (13), endometrioid carcinomas (7), clear cell carcinomas (8), Brenner tumors (3), malignant mesodermal mixed tumor (1), and metastatic carcinomas (4).

The World Health Organization has made a practical criterium for classification of ovarian tumors based on morphology. All the tumors studied were classified according to the criteria. It was recognized to be important an exact classification because any mistake could bias the final conclusion. Therefore, by combining morphology, histochemistry and immunohistochemistry, the characters of usual common epithelial tumors of the ovary are listed in Table 1 (Rosai, 1981; Charpin et al., 1982; Kabawat et al., 1983; Russell, 1987; Czernobilsky, 1987), which was often helpful for making the diagnosis in problematical cases. The diagnosis was made based on the predominant cell elements in every tumor.

All the tissues were fixed in 10% neutral formalin and embedded in paraffin. Sections, 3 to 5 μm in thickness, were stained with hematoxylin and eosin for general studies. In addition, periodic acid-Schiff (PAS), alcian blue, and Masson-Fontana stains were used in about half of the cases for differential diagnosis. Grimelius silver staining (Grimelius and Wilander, 1968) was performed in all cases. Grimelius-positive cases were once more stained by the Grimelius technique after a 1 hr digestion of the section with diastase.

By using the monoclonal antibodies the peroxidase-antiperoxidase (PAP) technique was employed for the demonstration of chromogranin A and serotonin. The sections were deparaffinized in xylene, and hydrated in a graded alcohol series. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide. The slides were subsequently incubated at room temperature with the following reagents (with 0.05 M Tris buffer (pH 7.6) washings in between): blocking serum; first monoclonal antibodies; second biotinylated anti-mouse antibody; peroxidase reagent; chromogen and hematoxylin (the stain kits were from DAKO Corp. U.S.A.). The first monoclonal antibodies were Neuroendocrine monoclonal antiserum, at 1:800 dilution (from Enzo Biochem, Inc. U.S.A.), and serotonin monoclonal antiserum at 1:40 dilution (from Dako Corp. U.S.A.).

All the cases were also immunostained for CA-125, CEA, and S-100 protein, and in poorly differentiated cases, EMA demonstration was performed.

Electron microscopical study was carried out on the tissues retrieved from paraffin blocks. The tissues were cut from paraffin blocks in the place where argyrophil cells were found.

They were then deparaffinized in xylene, and rehydrated in graded ethanol concentration to water. After this, the usual procedure was followed, i.e., refixed with glutaraldehyde and osmium tetroxide, dehydrated in ethanol and embedded in Epon 812. Semithin sections were stained with alkaline toluidine

blue for orientation purposes. Ultra-thin sections of Epon-embedded tissues were stained with uranyl acetate and lead citrate.

Results

1. Argyrophilia in epithelial ovarian tumors

Argyrophil cells were identified by the presence of fine, brown to black granules in the cytoplasm. However, there was considerable variation in the relative numbers of argyrophil cells in the different tumors and in different areas of the same tumor. Argyrophil cells were detected in serous borderline and malignant tumors, mucinous tumors, serous & mucinous mixed tumors and endometrioid carcinomas, as detailed in Table 2. The argyrophilia was expressed in two different patterns by these tumors.

In the serous tumors, serous elements of serous & mucinous mixed tumors and some endometrioid carcinomas, which were positive with Grimelius staining, the argyrophil cells appeared in the tumors singly or in small clusters, and were randomly distributed. The argyrophil granules were found in some cells with uniform distribution throughout the cytoplasm of the positive cells (Figs. 1a,b). However, more often they were most detectable in the apical portions of the cells, sometimes only restricted to the luminal surface (Figs. 2a,b). In a few cells, basal accentuation of the granules was observed, but this was not a common feature in these tumors.

Mucinous tumors, which were composed of mucinous epithelium, showed scattered and conspicuous argyrophil cells with closely packed coarse dense granules, readily seen under low-power examination. These argyrophil cells were irregular or triangular, and often lay on the basement membrane of the glands; reminiscent of those seen in the intestinal mucosa. In mucinous elements of two serous & mucinous mixed tumors, as well as in two cases of the endometrioid carcinomas, the argyrophil cells were arranged in the same way (Fig. 3).

One metastatic adenocarcinoma from the stomach contained predominant argyrophil cells.

Except for mucinous tumors, the argyrophilia in some tumors showed certain changes after diastase digestion; 5 cases of argyrophilic serous adenocarcinomas and 1 case of argyrophilic endometrioid carcinomas exhibited a decrease of the Grimelius reactivity, and the argyrophilia in 1 serous adenocarcinoma disappeared after diastase digestion. Among the 6 diastase-sensitive cases of argyrophil cell tumors, 2 cases were still positive for Neuroendocrine staining.

2. Immunoreactivity for chromogranin A and serotonin in the tumors with argyrophilia

The expression of chromogranin A and serotonin by the argyrophil cell tumors was quite different (Table 3).

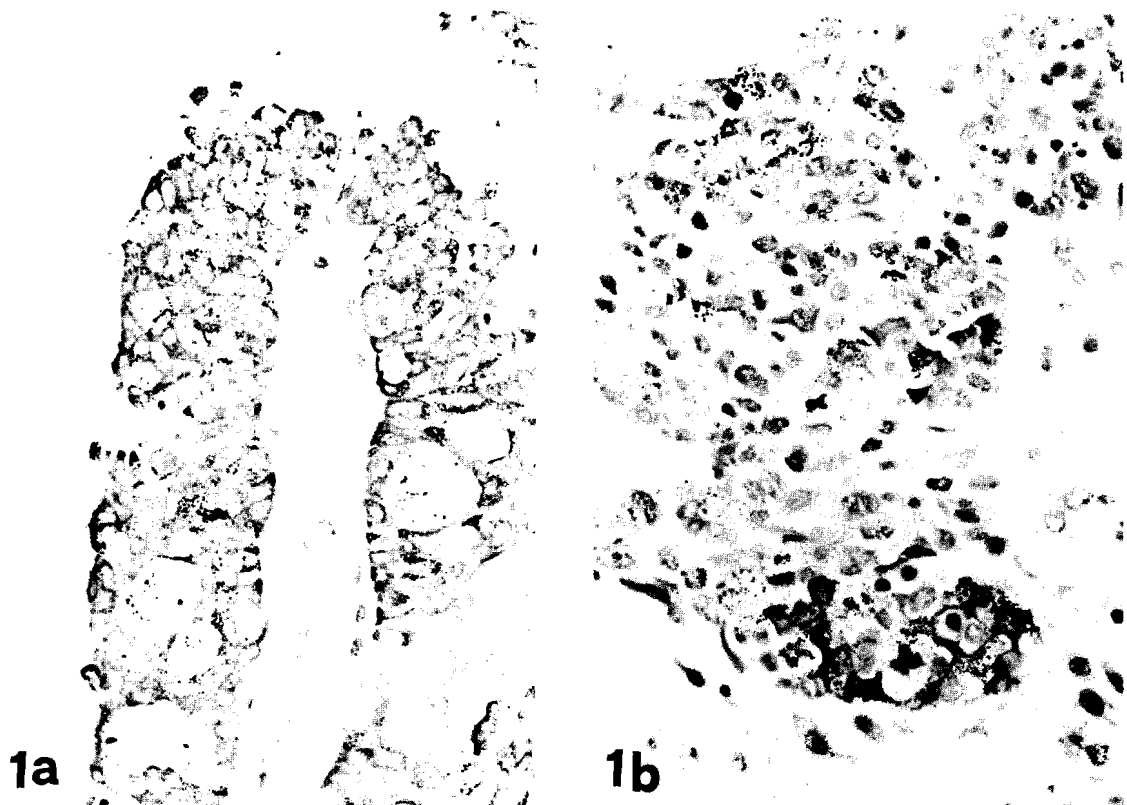


Fig. 1. Argyrophil granules found to be present throughout the cytoplasm in a serous adenocarcinoma (a), and a poorly-differentiated serous adenocarcinoma (b). H&E. $\times 205$



Fig. 2. Argyrophil granules found in apical portion of serous adenocarcinoma (a), and some of them only restricted to the luminal surface (b), H&E. $\times 205$

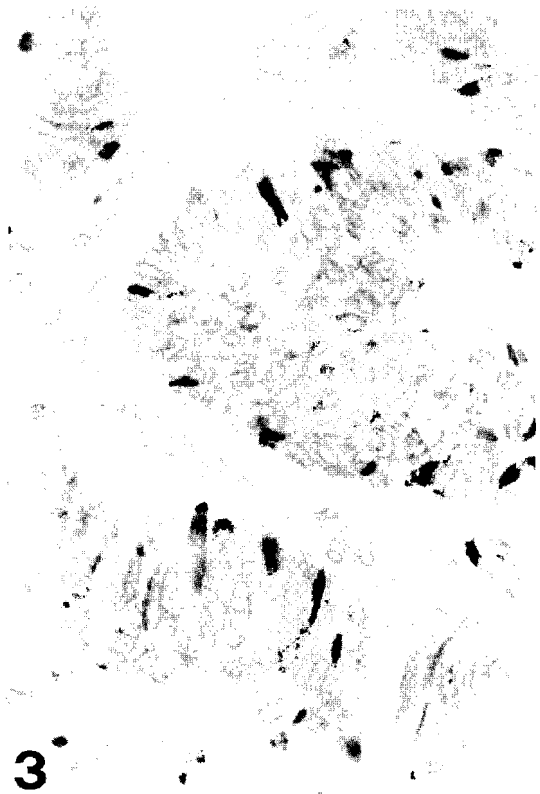


Fig. 3. Argyrophil cells in an adenocarcinoma with intestinal-type arrangement. H&E. $\times 410$

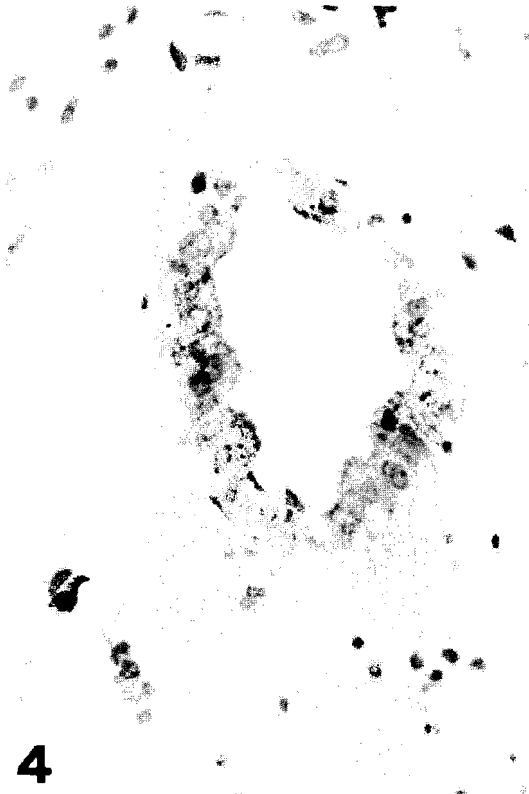


Fig. 4. Positive staining of chromogranin A in a serous adenocarcinoma. Peroxidase-antiperoxidase. $\times 410$

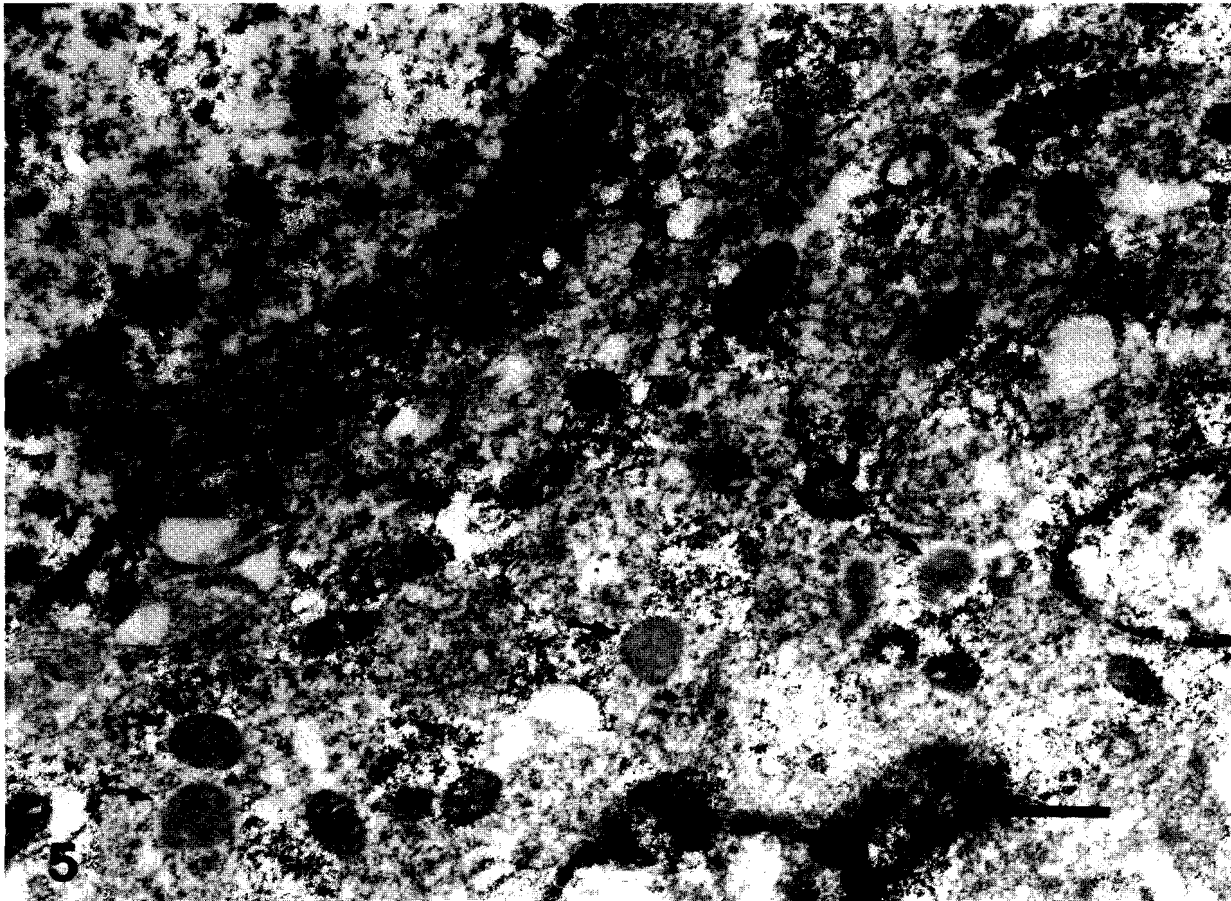


Fig. 5. Electron micrograph of the tissue retrieved from paraffin block of an argyrophilic serous adenocarcinoma. Some spherical and uniformly electron-faint granules are present within the cytoplasm (arrows). (uranyl acetate and lead citrate, $\times 7,000$) Bar indicates $1 \mu\text{m}$

Table 1. Characteristics of common epithelial tumors of the ovary in microscopic, immunohistochemical and histochemical findings

	Serous tumors	Mucinous tumors	Endometrioid carcinomas	Clear cell carcinomas
Epithelium	cuboidal or columnar	columnar	tall columnar	partly hobnail
Nucleus	oval and basally located	basally located	elongated and centrally located	round with prominent nucleoli
Cilia	frequent	absent	rare	rare
Cytoplasm	eosinophilic or with granules	vacuolated	eosinophilic	clear and/or with some granules
Psammoma bodies	present in many cases	exceptional	exceptional	none
Others	presence of syncytial-like giant cells		squamous metaplasia, microglandular pattern in poorly diff. cases	
PAS and alcian blue stain for mucin	luminal border positive	entire cytoplasm positive	luminal border positive	luminal border or intracytoplasmic diastase-sensitive positivity
CEA positivity	none	high	certain percentage	exceptional
CA 125 positivity	high	none	exceptional	exceptional

Table 2. Frequency of argyrophil cells in epithelial ovarian tumors.

Histological types	No. of cases (% of total cases)	No. of cases with argyrophil cells (% of the cases)
Serous tumors	Benign	0
	Borderline	1 (25%)
	Malignant	19 (40%)
		<u>48</u> 64 (50%)
Serous and mucinous mixed tumors	Benign	3 (27%)
	Malignant	0
		<u>2</u> 13 (18%) 3 (23%)
Mucinous tumors	Benign	4 (18%)
	Malignant	3 (60%)
		<u>5</u> 27 (21.4%) 7 (26%)
Endometrioid carcinomas	7 (5.5%)	3 (43%)
Clear cell carcinomas	8 (6.3%)	0
Brenner tumors (benign)	3 (2.4%)	0
Malignant mesodermal mixed tumors	1 (0.8%)	0
Metastatic tumors	4 (3.1%)	1 (25%)*
TOTAL	127	34

* The origin of the carcinoma was the stomach.

25% of serous tumors with argyrophilia showed reactivity with antibodies to chromogranin A (Fig. 4), whereas none of them was positive for serotonin. 2 out of 3 cases of endometrioid carcinoma harbouring argyrophil cells express chromogranin A but no serotonin.

In all the cases of mucinous tumors and serous & mucinous mixed tumors which contained argyrophil cells, chromogranin A was demonstrated, and half of them were positive for serotonin.

Metastatic carcinoma with argyrophilia showed no reaction with these two antibodies.

*Argyrophilia in ovarian serous tumors***Table 3.** Demonstration of chromogranin A and serotonin in the epithelial ovarian tumors with argyrophilia.

Histological types	No. of cases with argyrophilia	Neuroendocrine-(chromogranin A) positive cases	Serotonin-positive cases
Serous tumors	20	5	0
Serous & Mucinous mixed tumors	3	3	0
Mucinous tumors	7	7	5
Endometrioid carcinomas	3	2	0
Metastatic carcinomas	1	0	0
TOTAL	34	17	5

3. Electron microscopical findings

2 serous carcinomas displaying argyrophilia were examined ultrastructurally. The electron-microscopical examination revealed no obvious neurosecretory granules. Some spherical and uniformly electron-faint granules, 430-540 nm in diameter, were observed (Fig. 5), which were bigger than usual Neuroendocrine granules.

Discussion

Argyrophilia was first found in the gastrointestinal mucosa (Lillie and Fullmer, 1976). Subsequently, the presence of argyrophilia has been reported to be a characteristic of APUD cells and APUDomas (Scully et al., 1984; Saksela, 1989). Thus, argentaffin or argyrophil staining method has traditionally been used for identification of Neuroendocrine cells of the APUD system. Recently, the tumors observed with argyrophilia has been continuously increasing, and even in many common carcinomas argyrophilia has also been revealed (Lillie and Glenner, 1960; Azzopardi and Pollock, 1963; Ueda et al., 1977; Clayton et al., 1982; Bannatyne et al., 1983). Furthermore, many studies have indicated that argyrophilia in some carcinomas may be due to the presence of a variety of cellular products including lactalbumin (Clayton et al., 1982), mucins, glycogen (Aguirre et al., 1984), and lipofuscin (Waxman, 1979), which express argyrophilia as a result of a similar chemical reaction to that of sialoglycopeptides with β (1-4)-glycoside bonds in endocrine granules (Solcia et al., 1976; Aguirre et al., 1984). Therefore diastase digestion before Grimelius staining and various immunohistochemical demonstrations of peptide hormones and amines have been recommended.

On the other hand, chromogranins, first isolated from adrenal medullary cell granules and sympathetic nerve vesicles, are considered as a general marker of Neuroendocrine cells (Solcia et al., 1986). They are non-hormone components of Neuroendocrine granules,

but they play a role in hormone storage and release (Cohn et al., 1982). Many authors have confirmed a parallelism between chromogranin A immunoreactivity and positive Grimelius silver reaction in normal and neoplastic Neuroendocrine cells, though no chromogranin immunoreactivity has been found in non-neuroendocrine argyrophil cells and related tumors (Lloyd et al., 1984; Solcia et al., 1986). On both morphological and chemical grounds, a relationship seems to exist between chromogranin A and Grimelius' argyrophilia (Rindi et al., 1986). The present study has also found that the Grimelius technique positivity is identical to Neuroendocrine immunoreactivity in most of the cases except for serous tumors which showed a much higher incidence of argyrophil cells than frequency of positivity for Neuroendocrine. In general, chromogranin antibodies and Grimelius staining were considered to be useful for the light microscopical diagnosis of Neuroendocrine tumors, especially the ones with unknown hormonal products.

Of epithelial ovarian tumors, argyrophilia was first found in mucinous tumors (Fox et al., 1964), and later, in endometrioid carcinomas and Brenner tumors (Klemi, 1977; Klemi and Grönroos, 1979; Ueda et al., 1984). Then Neuroendocrine nature of the argyrophil cells of mucinous tumors has been confirmed by demonstrating a large variety of peptide hormones and amines in these cells (Scully et al., 1984). Among the argyrophil cell population of Brenner tumors only serotonin-immunoreactivity was demonstrated (Aguirre et al., 1986). Few Neuroendocrine peptides or amine were detected in argyrophilic endometrioid carcinomas (Inoue et al., 1985). The present study demonstrates that the argyrophilia is not only present in mucinous tumors and endometrioid carcinomas, but also in serous adenocarcinomas. However, the latter showed no serotonin, and a low percentage of positivity for Neuroendocrine. These new findings observed by us agree with the findings in previous studies and could be quite understandable with regard to the relationship among the common epithelial

tumors of the ovary. Serous tumors, which have a close relation to some other epithelial tumors in histology and histogenesis, frequently have admixtures of the elements of mucinous tumors, endometrioid tumors and/or clear carcinomas, of which mucinous and endometrioid tumors are well known to harbour argyrophil cells. Considering these close relations, it is not surprising to find argyrophilia in serous tumors.

Morphologically, there are two types of argyrophil cell tumors in the common epithelial tumors of the ovary: type I contains "regular nondendritic cells" (Bannatyne et al., 1983), with Grimelius-positive granules in the "apical portion or throughout cytoplasm" (Ueda et al., 1984); and type II harbours "dendritic argyrophil cells" (Bannatyne et al., 1983), as seen in intestinal mucosa. The argyrophilia found in serous tumors and some endometrioid carcinomas was expressed according to type I; and type II tumors were mucinous tumors, Brenner tumors and some endometrioid carcinomas. Diastase digestion was found to diminish Grimelius staining in type I tumors and few neuroendocrine hormones were demonstrated in these tumors. In addition, electron microscopical observation has found no typical neurosecretory granules but some special secretory granules in type I tumors. Therefore, it may be preferable to call type I tumors argyrophilic tumors or carcinomas rather than neuroendocrine tumors.

On the other hand, it is generally accepted that most common epithelial tumors arise from the surface epithelium of the ovary, which could give rise to: a) serous tumors by fallopian tube differentiation; b) mucinous tumors by endocervical change; and c) endometrioid lesions by endometrial development. Because of the common histogenesis of the epithelial ovarian tumors, transitions have often been observed between mucinous, serous and endometrioid tumors (Scully, 1980). This is a well known phenomenon recognized by many authors (Czernobilsky, 1987; Russell, 1987) and is also recognized in this study. Therefore, since argyrophilia was observed in many common epithelial tumors, it is not impossible that the argyrophilia expression is a feature of some common epithelial tumors of the ovary, though the argyrophilia in different types of these tumors has a certain differing nature, which might be related to their differentiated condition. Non-hormonal argyrophilia in serous and some endometrioid tumors could be considered, because diastase digestion had some influence on them, though Neuroendocrine-positivity was still found in some diastase-sensitive cases; and electron microscopical examination did not show any typical neurosecretory granules in these tumors. To explain argyrophilia in ovarian tumors, we take the stand in favour of the opinion of a "neometaplasia", suggested by Young, Kleinman and Scully (1981).

Furthermore, as argyrophil cells have been found to be present in a variety of tumors, the argyrophilia

alone may not be sufficient evidence that a particular carcinoma or tumor represents a neuroendocrine or carcinoid tumor.

In conclusion, the present study shows that several types of the common epithelial tumors of the ovary, including serous tumors, can express argyrophilia, which is mainly expressed in two types. The demonstration of argyrophilia in ovarian serous tumors enlarges the group of argyrophilic tumors in the ovary. The findings suggest that the expression of argyrophilia might be a feature of some common epithelial tumors of the ovary and argyrophilia alone may be not a sufficient evidence for a diagnosis of carcinoid or APUDoma. The argyrophilia in these tumors could probably be explained by neometaplasia of the tumor cells and a close histogenetic relation between the common epithelial tumors of the ovary.

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