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Case Report

Neurohormonal Peptides and Argyrophil Cells in an Androblastoma of the Ovary *

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Summary. An ovarian epithelial tumour is described with a compound histological structure containing features of an androblastoma with well differentiated Sertoli-Leydig cell structures and features resembling a carcinoid tumour.

Scattered argyrophil cells were demonstrated in both components of the tumour. Neurohormonal peptides were found immunocytochemically in a minor fraction of the argyrophil cells. These included pancreatic polypeptide (PP), glucagon/enteroglucagon and enkephalin.

These findings indicate a high degree of multipotentiality of the progenitor cells of the neoplasm.

Key words: Ovarian androblastoma – Carcinoid structures – Argyrophil cells – Neurohormonal peptides

Androblastoma of the ovary is a rare tumour, composed of Sertoli cells, Leydig cells or their precursors either alone or in any combination (Fox and Langely 1975). The histogenesis of androblastoma is still under debate. There is evidence that certain types might be of teratomatous, stromal or hamartomatous origin. This, together with the prevailing theory of homology between granulosa cells and Sertoli cells may suggest that androblastoma is derived from the general mesenchyme or epithelial sex cords which have a latent bisexual competence (Nordén and Dahlberg 1956; Teilum 1976). In the present investigation we present a hitherto unknown variant of the neoplasm, mainly composed of Sertoli cells but also displaying features of a carcinoid tumour. Since this tumour was found to contain Grimelius positive cells which in other locations are

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known to produce neurohormonal peptides, an immunohistochemical investigation for the demonstration of various neurohormonal peptides was also performed.

Case History

The patient was a married, previously healthy Caucasian woman with 2 normal deliveries 1948 and 1950. In 1972 an asymptomatic tumour as large as a hen's egg egg was noticed to the left of the uterus at routine examination. Since that time the patient was regularly controlled every 6th month until 1978.

Early in 1978 an enlargement of the tumour was noticed, and the patient was admitted to hospital. She underwent a bilateral salpingo-oophorectomy together with a subtotal hysterectomy and resection of the omentum. Preoperative determinations were all within normal range (including FDP, LD, p-oestradiol, p-progesterone, s-prolactin, s-CEA, p-testosterone, FSH and LH). The postoperative course was uneventful and the patient was discharged 6 days after operation. Up to now, all controls have been normal.

Material and Methods

Histology

Paraffin sections from formalin fixed specimens were stained with haematoxylin-eosin and periodic acid – Schiff. Sections were also treated according to the Grimelius (1968) silver nitrate procedure for the demonstration of argyrophil cells. Masson-Hamperl's method was used to demonstrate argentaffin cells (Romeis 1948).

Immunohistochemistry

Sections of 5 μ thickness were deparaffinized, hydrated and washed over night. The antisera (rabbit) against neurohormonal peptides were applied for 3 h at room temperature. Fluoresceinated sheep anti rabbit 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 was 24 h at 4° C. Control sections were exposed to antiserum inactivated with excess antigen (10–100 μg of synthetic and/or highly purified natural peptide per ml diluted antiserum). Antisera against pancreatic polypeptide (PP), gastrin/cholecystokinin, somatostatin (SOM), enkefalin (ENK), glucagon/enteroglucagon, calcitonin, substance-P, β-endorphin, vasoactive intestinal protein (VIP), neurotensin, ACTH, and secretin were used.

Results

Pathological Findings

The left ovary measured 4.5 × 4.5 cm and contained a well defined polycyclic tumour with homogenous yellowish-brown cut-surfaces, covered by a thin rim of ovarian cortex.

The tumour was composed of regular cylindrical cells mostly organized in tubules or cribriform structures (Fig. 1a) or in trabeculae consisting of single rows of palisading cells (Fig. 1b). These cells contained light, eosinophil cyto-

Table 1. Specification of neurohormonal peptide antisera used together with source and working dilutions

Antisera against	Working dilution		Code	Source
	IF[a]	PAP[b]		
Synthetic ovine somatostatin (SOM)		1/2560	19,578	MP Dubois, Station Physiol Reprod, INRA, Nouzilly, France
Pure porcine glucagon		1/640	7,811	JE Thorell, Dept Nucl Med, Malmö Gen Hospital, Malmö, Sweden
Pure bovine pancreatic polypeptide (PP)	1/320	1/2560	7,823	JE Thorell, Dept Nucl Med, Malmö Gen Hospital, Malmö, Sweden
Pure porcine secretin	1/80	1/2560	5,585	OB Schaffalitzky de Muckadell, Bispebjerg Hospital, Copenhagen, Denmark
Pure porcine vasoactive intestinal polypeptide (VIP)		1/5120	7,852	JE Thorell, Dept Nucl Med, Malmö Gen Hospital, Malmö, Sweden
Synthetic human gastrin 2–17		1/5120	4,562	JF Rehfeld, Rigshospitalet, Copenhagen, Denmark
Synthetic bovine substance P (SP)	1/20		K 16	G Nilsson, Dept Pharmacol, Karolinska Inst, Stockholm, Sweden
Synthetic bovine neurotensin (NT)		1/640	HC-8	RE Carraway Lab Hum Reprod Dept Physiol, Harward Med School, Boston MA, USA
Synthetic met-enkephalin (Enk)		1/640	Met-enk	RI Miller and KJ Chang Burroughs Wellcome Res Lab Triangle Park, NC USA
Synthetic human β-endorphin (β-end) (β-lipotropin 61–91)		1/640	7,763	JE Thorell, Dept Nucl Med, Malmö Gen Hospital, Malmö, Sweden
Synthetic human calcitonin (CT)		1/160	AS292/5	I MacIntyre, Endocr Unit, Royal Postgrad Med School, London, England
Pure porcine adrenocorticotropic hormone (ACTH)	1/80	1/640	No 1	Own

[a] IF = Immunofluorescence
[b] PAP = Peroxidase – antiperoxidase procedure

plasm and round or elongated nuclei with small distinct nucleolei. They were reminiscent of Sertoli cells. In some places there was an admixture of smaller cells which resembled Leydig cells, having granular eosinophil cytoplasm and small, chromatin dense nuclei (Fig. 2). The tumour also showed foci with compact nests of rather small and uniform tumour cells with light cytoplasm, surrounded by a single row of palisading darker cells with a granular cytoplasm.

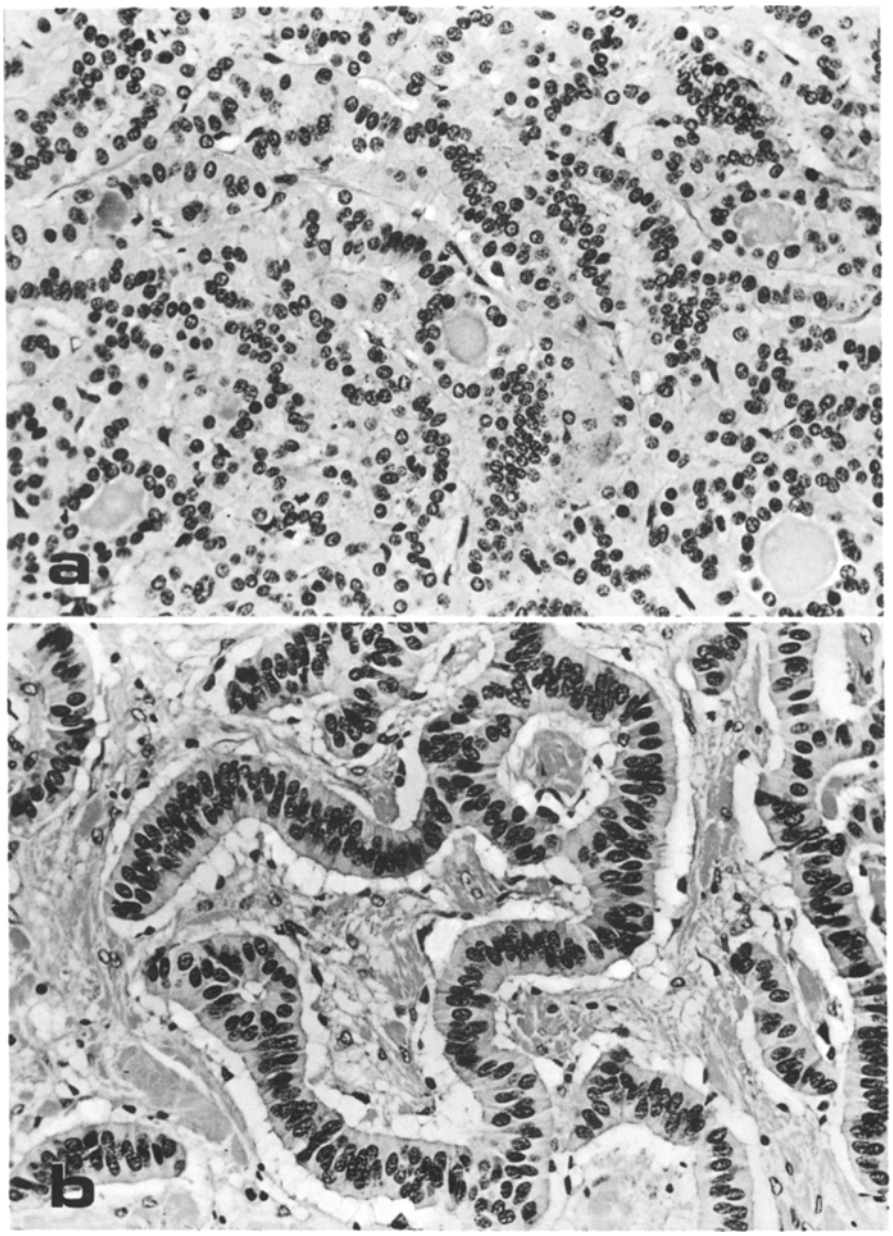

Fig. 1. (**a**) Sertoli cell component of the ovarian tumour, showing tubules and trabeculae of polygonal, often cylindrical cells with little atypia. (**b**) Some trabeculae are formed by a single row of palisading cylindrical tumour cells. Haematoxylin-eosin, × 310

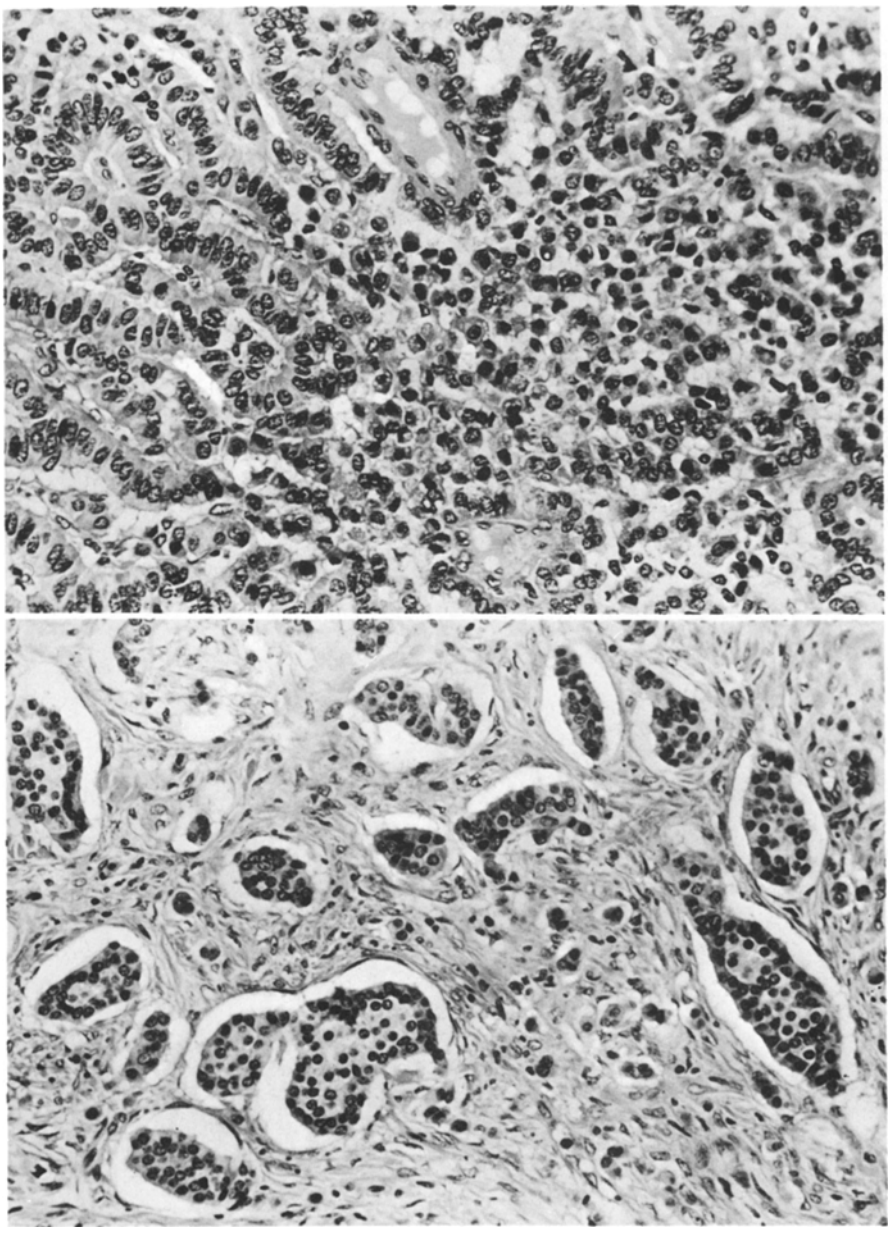

Fig. 2. Part of the tumour with an admixture of irregularly distributed smaller tumour cells with granular cytoplasm and smaller, rather polymorphic and chromatin dense nuclei. These cells may resemble Leydig cells. Haematoxylin-eosin, × 310

Fig. 3. Part of the tumour resembling a carcinoid tumour, showing solid nests and trabeculae built up of small, uniform cells. Some of the nests contain two types of cells, i.e. light cells with clear cytoplasm and dark cells with granular cytoplasm occupying the central and the marginal parts of the nests respectively. Haematoxylin-eosin, × 240

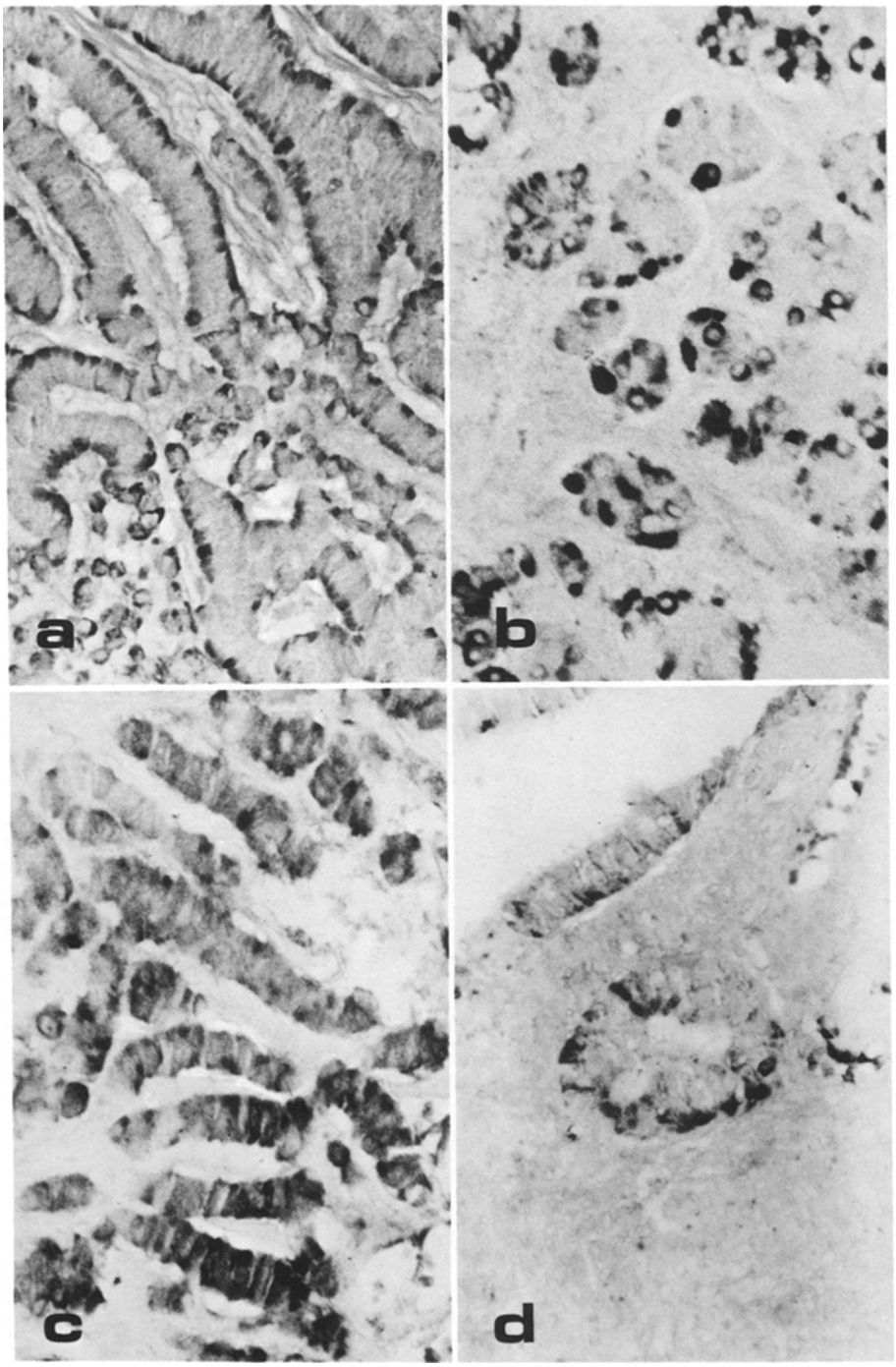

Fig. 4. (**a**) Argyrophil cells in Sertoli-Leydig cell component of the tumour. Argyrophil material is accumulated in the basal parts of triangular cells, interposed between non-argyrophil cylindrical cells, forming anastomosing trabecules. Argyrophil cells are also scattered in the stroma (to the lower left). Grimelius' silver nitrate procedure, × 320. (**b–d**) Immunoreactive neurohormonal peptides in the tumour, demonstrated by the PAP procedure. Cells showing pancreatic polypeptide immunoreactivity are rather evenly distributed within solid clusters and tubular formations of tumour cells (**b**), whereas cells harbouring immunoreactive glucagon/enteroglucagon (**c**) and enkephalin (**d**) have a more pachy distribution. Peroxidase-anti-peroxidase procedure, × 320

This pattern was reminiscent of a carcinoid tumour (Fig. 3). PAS positive material was found within lumina of the tubular and cribriform structures.

Within areas with trabeculae and tubules, many cells were argyrophil (Fig. 4a). Characteristically, the argyrophil cells appeared triangular in shape with their base on the basement membrane and the apex extending between cylindrical, non-argyrophil tumour cells, sometimes forming a long slender process. Generally, however, the apex was rather blunt giving the cells a resemblance to the argyrophil cells of closed type seen in the gastrointestinal canal or the pancreas. Argyrophil granules were also observed in some of the cells mimicking Leydig cells as well as in some of the cells forming the carcinoid-like structures.

No argentaffin material was detected in the tumour. Of the peptides listed in Table 1, cells storing immunoreactive PP were the most common, followed by glucagon/enteroglucagon and enkephalin storing cells. Characteristically the PP cells had a uniform distribution, whereas cells reacting with antisera against glucagon/enteroglucagon or enkephalin had a more patchy distribution (Fig. 4b–d). In either case the immunoreactive cells constituted only a minor fraction of the argyrophil cells.

Discussion

The presence of well differentiated Sertoli and Leydig cells suggests that this androblastoma belongs to the comparatively rare type originally described by Pick (1905) and usually referred to as "well differentiated Sertoli – Leydig cell tumour" (Fox et al. 1975). In this tumour the Sertoli component usually forms tubular structures with Leydig cells scattered between the tubules. The tumour described here however, differed from this tumour type in that it also showed histological features reminding of a primary ovarian carcinoid of mixed trabecular and insular type (Robboy et al. 1977). The carcinoid character of the present tumour is further stressed by the appearance of argyrophil cells.

In both primary ovarian carcinoids and mucinous cystadenocarcinomas many tumour cells producing neurohormonal peptides have been found to be argyrophil with the Grimelius procedure (Sporrong et al. 1981a, b). The immunohistochemical study showed that this particular androblastoma contained cells with the ability to produce several neurohormonal peptides. Moreover, the spectrum of the immunoreactive peptides was similar to that found in primary ovarian carcinoids where pancreatic polypeptide (PP) was found to be the most common peptide, followed by glucagon/enteroglucagon and enkephalin (Sporrong et al. 1981a), lending this androblastoma further similarity to ovarian carcinoids.

It is commonly believed that androblastoma is derived from non-germinal structures, i.e. the undifferentiated mesenchyme of the ovary (Teilum 1976). It has, however, been shown that a minor part of these tumours may contain heterotopic elements such as epithelial cysts of gastrointestinal type with even argentaffin cells, which has been put forward as evidence for a teratomatous nature of the tumour (Hayes et al. 1973; Waxman et al. 1981). In the present case, peptide producing endocrine cells constituted an integral part of the tumour

containing a spectrum of peptides also found in entodermally derived tissues such as the gastro-entero-pancreatic system. This may indicate a high degree of multipotentiality of the progenitor cells of the neoplasm.

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