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Ultrastructure of Clear Cell Carcinoma of the Ovary

Case Report and Review of the Literature

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Summary. The fine structure of an ovarian clear cell carcinoma in a 65 year old woman was analysed. The tumor cells were of both clear and "hobnail" types. Both were characterized by the presence of short microvilli, abundant glycogen granules, a well-developed granular endoplasmic reticulum and Golgi apparatus, scanty lysosomes and very few lipid bodies. The tubules and gland-like spaces were always separated from the stroma by a basement membrane. At ultrastructural level the tumor cells do not resemble at all those of clear cell renal carcinomas. On the other hand, their submicroscopic features are strongly similar to those of the clear cell tumors found elsewhere in the female genital tract, emphasizing therewith their very probable müllerian origin. It is recommended to eliminate the term "mesonephroma ovarii" to designate the clear cell carcinomas of the ovary.

Key words: Ultrastructure – Ovary – Clear cell carcinoma.

Introduction

Ovarian clear cell carcinomas, also called mesonephroid tumors or "mesonephroma ovarii" constitute about 5% of all ovarian carcinomas (Scully, 1977). Since the introduction of the term "mesonephroma" by Schiller in 1939, this group of ovarian neoplasms has been the subject of great controversy, particularly in regard to their histogenesis. The "mesonephroma" of Schiller was so called because the tubular and papillary structures present in these tumors were considered reminiscent of renal tubules and rudimentary glomeruli. In fact the series of Schiller comprised two different types of ovarian neoplasms. The first one was later considered as a specific extra-embryonic form of germ cell tumors (Teilum, 1971). These neoplasms are known to be highly malignant

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and occur in children as well as in young women. The second tumor type comprises the so-called clear cell tumors of the ovary that often show a tubular pattern and an epithelium of a "hobnail" or peg-like character with transition to glycogen-containing cells resembling those of renal carcinoma. This latter type of ovarian tumor occurs chiefly in women over 30 years of age, is much more frequent and has a far better prognosis than the first type (Norris and Robinowitz, 1971; Genton, 1973; Doshi and Tobon, 1977; Eastwood, 1978). A quite interesting aspect of these ovarian tumors is that it is the type that has been reported most frequently in association with the para-endocrine syndrome of hypercalcemia (Ross and Shelley, 1968; Smith et al., 1968; Ferenczy et al., 1971; Scully, 1977). Some controversy still exists concerning the histogenesis of these neoplasms although they are currently considered to be of müllerian nature. There are only very few available ultrastructural studies of ovarian clear cell carcinomas in the literature, and the conclusions drawn by the different authors reveal several discrepancies. The purpose of this study is to carry out an analysis of the ultrastructural characteristics of an ovarian clear cell carcinoma and to compare them with those of similar tumors occurring in the female genital tract.

Material and Methods

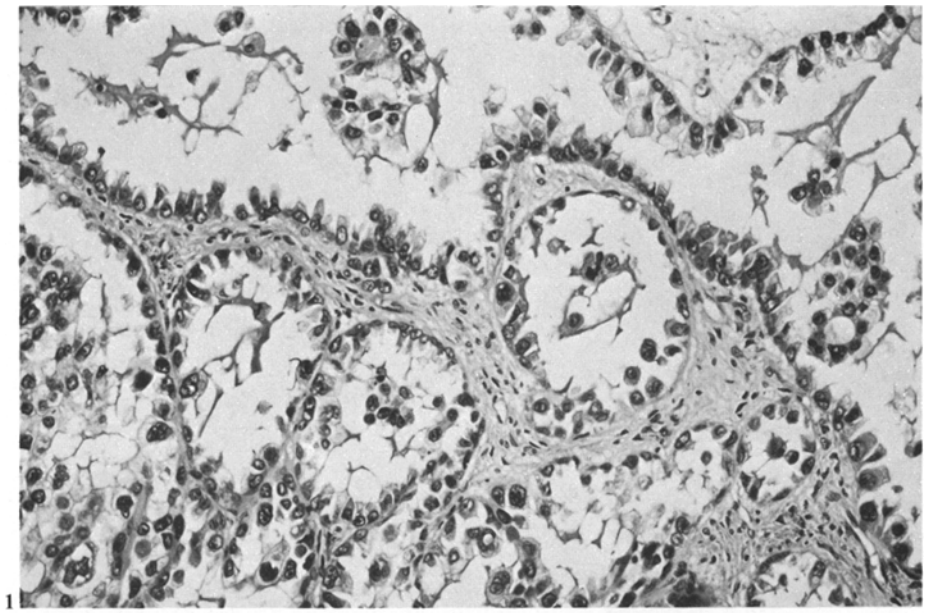
The material studied here was obtained from a 65 year old woman who presented at the Department of Gynecology of the University Women's Hospital in Zürich because of a lower abdominal mass. No other pertinent physical or laboratory abnormalities were noted, in particular no hypercalcemia was present. At laparotomy the right ovary was found to be replaced by a tumor mass. The uterus was small and the left adnexa normal in appearance. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed as well as an omentectomy, the frozen section examination having revealed the malignant character of the neoplasm.

Tissue for light microscopy was fixed in 10% buffered formalin, processed by conventional methods and stained with hematoxylin-eosin, PAS and Best's carmine. For electron microscopy small blocks of tumor tissue were immediately fixed by immersion in buffered 2% glutaraldehyde at 4° C. Post-fixation was carried out in s-collidine-buffered 1% osmium tetroxide after washing in phosphate buffer. Following dehydration in series of ethanol the tissue blocks were embedded in Epon. Semithin sections for orientation were stained with toluidine blue. Ultrathin sections were cut with an Ultrotom III and after staining with uranyl acetate and lead citrate, they were examined in a Philips 201 electron microscope.[1]

Observations

Light Microscopy. The tumor tissue consists mostly of typical tubular spaces lined by clear and "hobnail" cells (Fig. 1). In the larger gland-like spaces, the neoplastic cells form papillary structures (Fig. 2), some of them displaying a few microcalcifications (Fig. 3). Solid areas formed by clear cells are sparse. Both tumor cell types contain large and irregular hyperchromatic nuclei often exhibiting a prominent nucleolus. The cytoplasm of the clear cells is abundant,

[1] I express my gratitude to Miss Silvia Heeb for her invaluable technical assistance



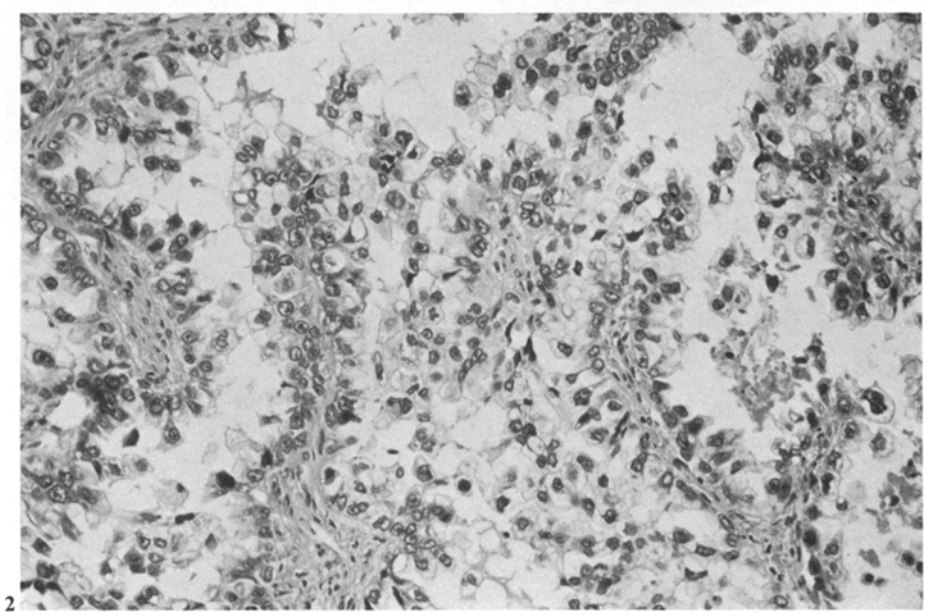


Fig. 1. Typical tubular structures lined by clear and "hobnail" cells. HE, ×160

Fig. 2. Papillary structures covered by one or more layers of both clear and "hobnail" cells. HE, ×160

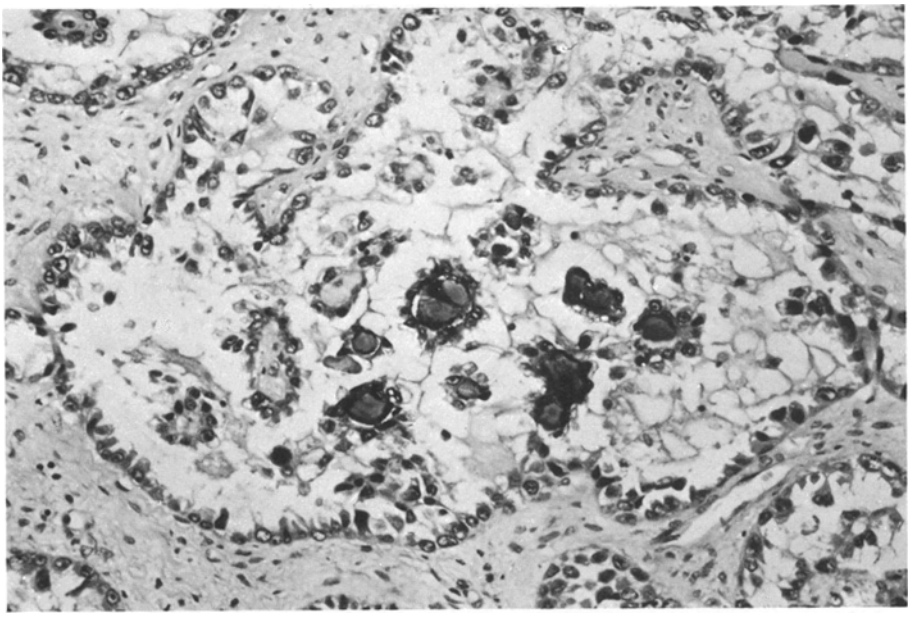


Fig. 3. Tubular structure with some papillary projections displaying a calcified core. HE, ×160

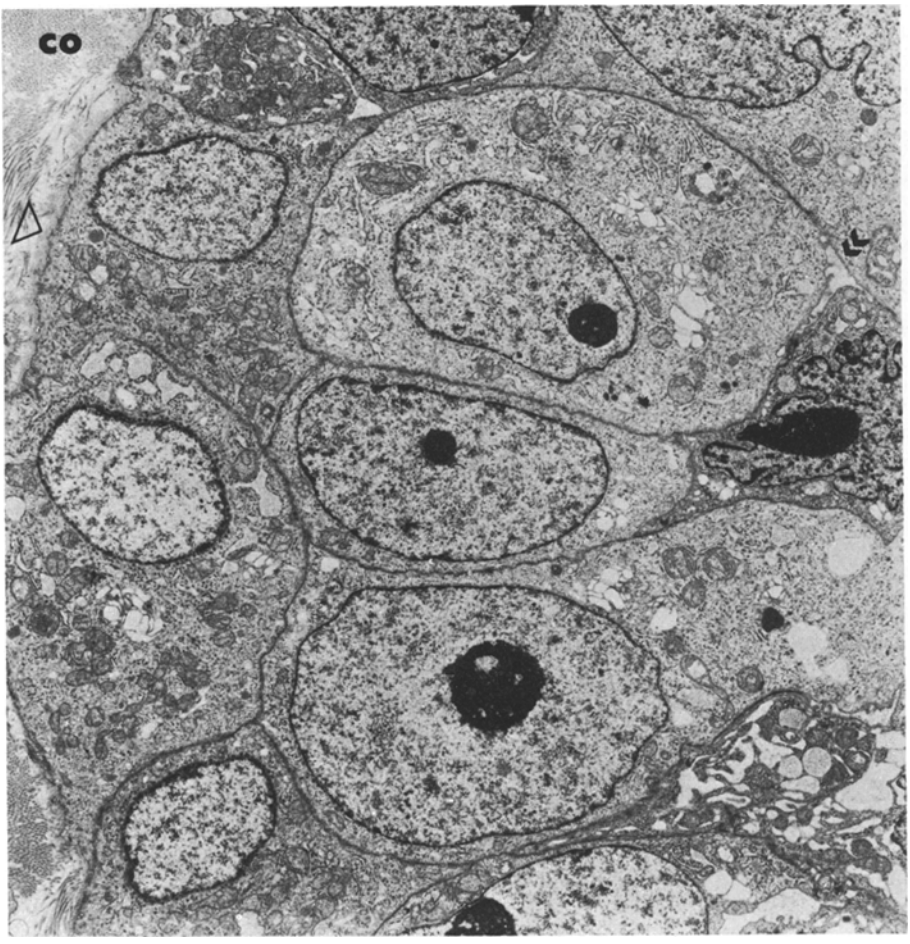


Fig. 4. Low magnification electron micrograph of a tubule lined by several layers of polymorphous tumor cells and surrounded by a basement membrane (▷) and collagen fibers (*co*). Note the small widening of the intercellular space (»). ×4,200

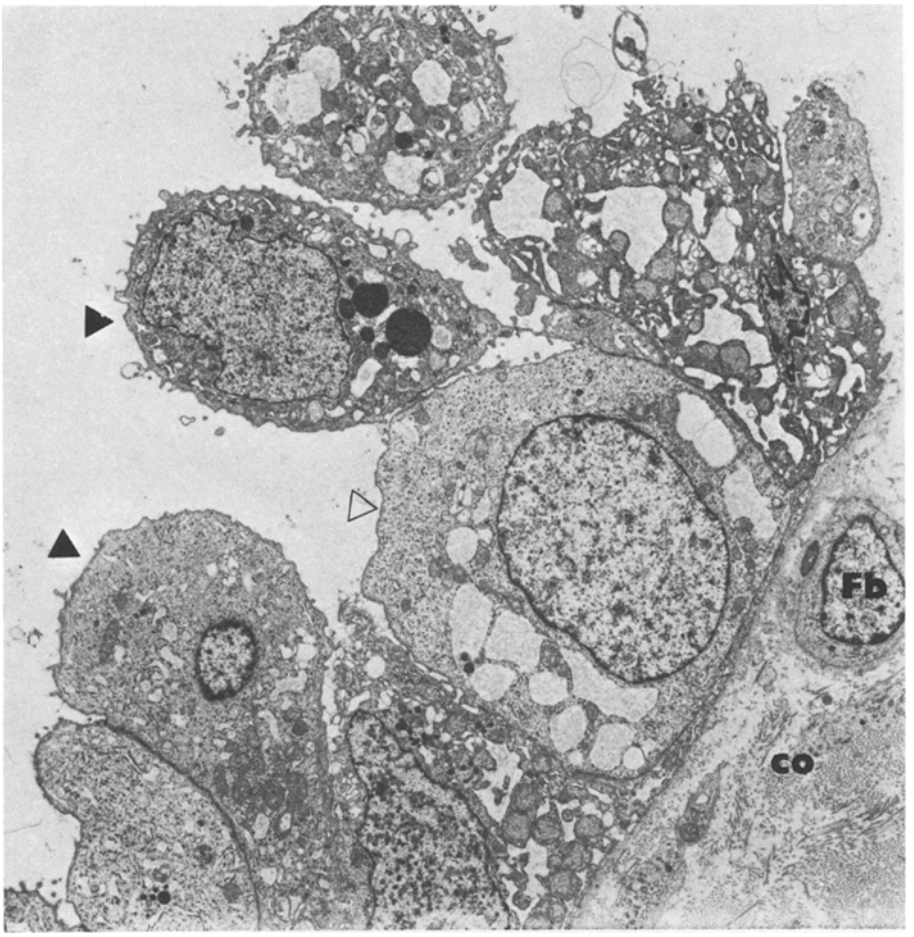


Fig. 5. Low magnification electron micrograph of a tubule lined by a clear cell (▷) and two "hobnail" cells (▶). Outside the tubule, collagen fibers (*co*) and a fibroblast (*Fb*). ×4,200

the cell membranes are distinct. The amount of stored glycogen in the tumor cells as revealed by Best's carmine is quite irregular. Some cells are tightly packed with glycogen granules while others seem almost totally deprived of them. Normal and pathological mitoses are sparse but readily recognizable. Some areas of focal fibrosis are present but no evident necrosis or hemorrhage can be found. The wall of the cyst displays focal ossification.

Electron Microscopy. The tubules and gland-like spaces are lined by one or more layers of polymorphous tumor cells and surrounded by a basement membrane, collagen and fibroblasts (Figs. 4 and 5). The tumor cells are polygonal, cylindrical or display a typical "hobnail" appearance (Fig. 5). The cell membranes are distinct and run mostly parallel to those of the neighboring cells. A few widenings of the intercellular space are seen, in which protrude some

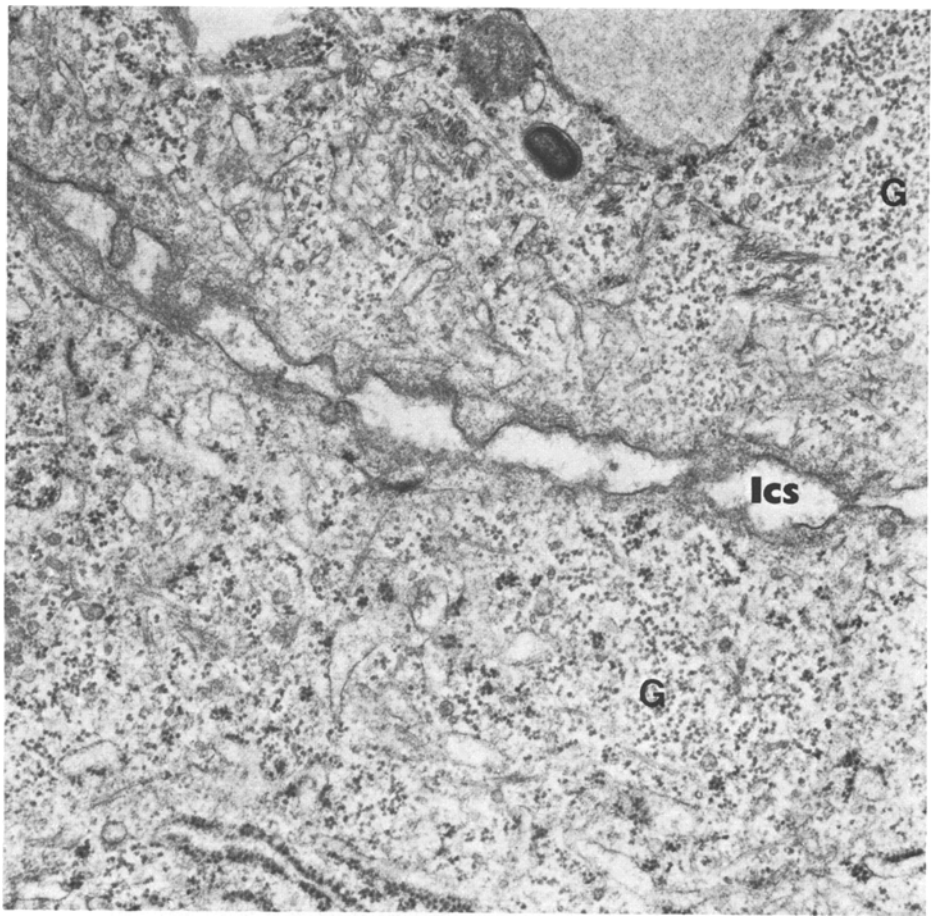


Fig. 6. Focal widening of the intercellular space (*Ics*) in wich project short cytoplasmic processes and stubby microvilli. In both cells abundant glycogen granules (*G*). ×26,100

short and thick cytoplasmic projections (Fig. 6). The microvilli present at the luminal border of some cells are mostly short and stubby although long and slender microvilli are also occasionally found (Fig. 7). Cell attachments are relatively sparse and no well-developed desmosomes can be identified.

The nuclei are irregular in shape, mostly round or oval, but occasionally showing numerous and deep indentations. The heterochromatin is mostly evenly dispersed although some peripheral clumping may be present, especially in the deeply indented nuclei. The predominantly solitary and prominent nucleoli are somewhat irregular, some of them being homogenous and round, others occasionally displaying quite a bizarre appearance (Fig. 8).

The cytoplasm is of moderate electron density. Practically all cells contain glycogen granules, these being more abundant in the clear than in the "hobnail"

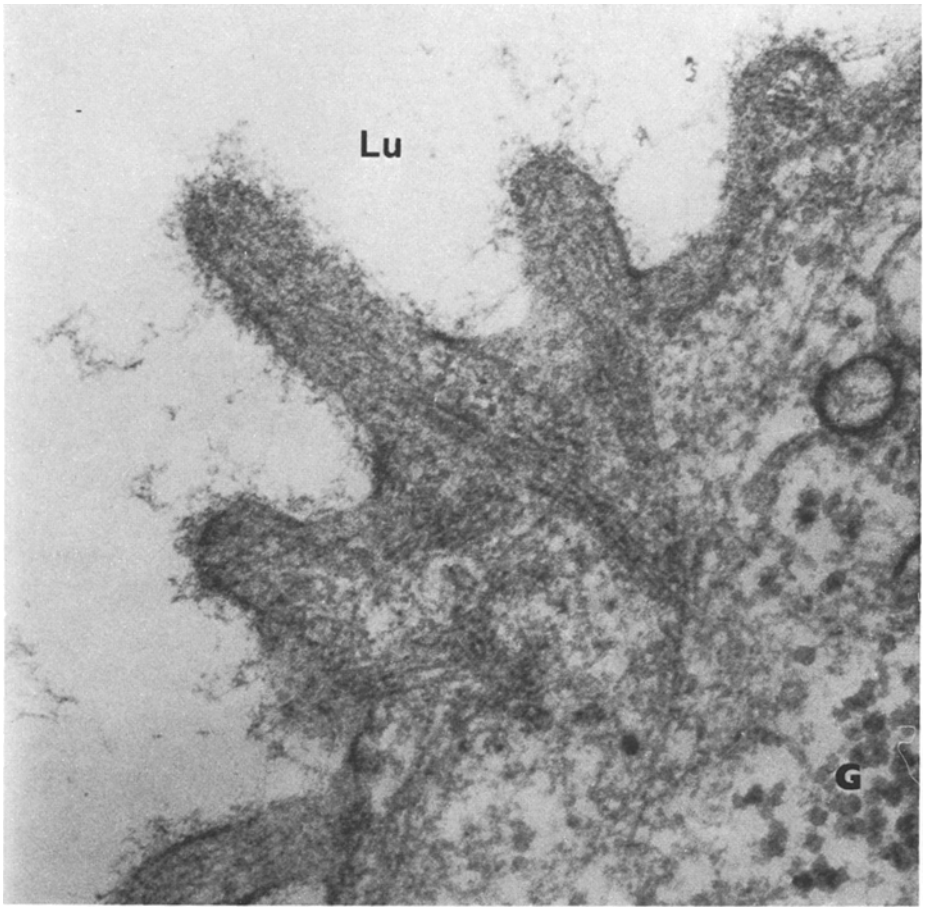


Fig. 7. High magnification electron micrograph of the short and thick microvilli with filamentous core exhibited by some cells and projecting in the lumen (*Lu*). In the cytoplasm, some glycogen granules (*G*). ×88,600

type of cells. The granular endoplasmic reticulum is irregularly developed, often in close relationship to mitochondria. It is rarely stacked in short parallel or concentric strands and in some cells it displays prominent dilated cisternae (Fig. 9). The Golgi complexes are well-developed in most cells, lie predominantly in supranuclear location and are occasionally dilated or associated with groups of microvesicles (Fig. 10). Mitochondria are irregular in number and distribution, mostly round or oval with transverse, oblique or interdigitating plate-like cristae (Fig. 11). Scattered free ribosomes are present in all cells, predominantly as polyribosomes, and are occasionally difficult to distinguish from glycogen granules although the latter appear in the rule somewhat lighter stained as the former. Bundles of microfilaments are present in many cells as well as microtubules, the latter being especially numerous in the apical part of the cytoplasm.

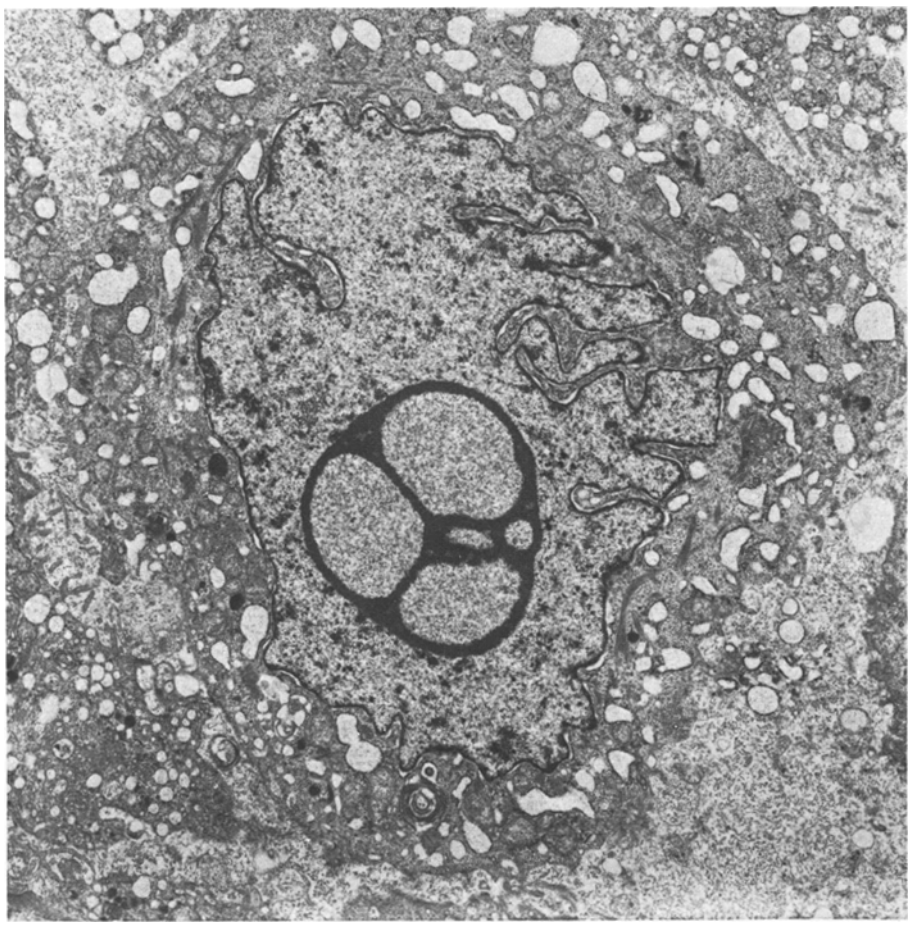


Fig. 8. Tumor cell exhibiting a deeply indented nucleus with focal peripheral clumping of the heterochromatin and bizarre nucleolus. In the cytoplasm numerous dilated cisternae of granular endoplasmic reticulum. × 6,400

Membrane-bound primary and secondary lysosomes as well as very rare lipid droplets are present in some cells (Fig. 12).

Discussion

As already mentioned these neoplasms are now generally considered to be of müllerian nature as much evidence has been brought for this modern view of histogenesis. Indeed, ovarian clear cell carcinomas have been relatively often found in close association with endometriosis (Plate, 1966; Aure et al., 1971; Kurman and Craig, 1972; Genton, 1974) as well as with endometrioid carcinomas of the ovary (Scully and Barlow, 1967; Scully, 1970). Clear cell carci-

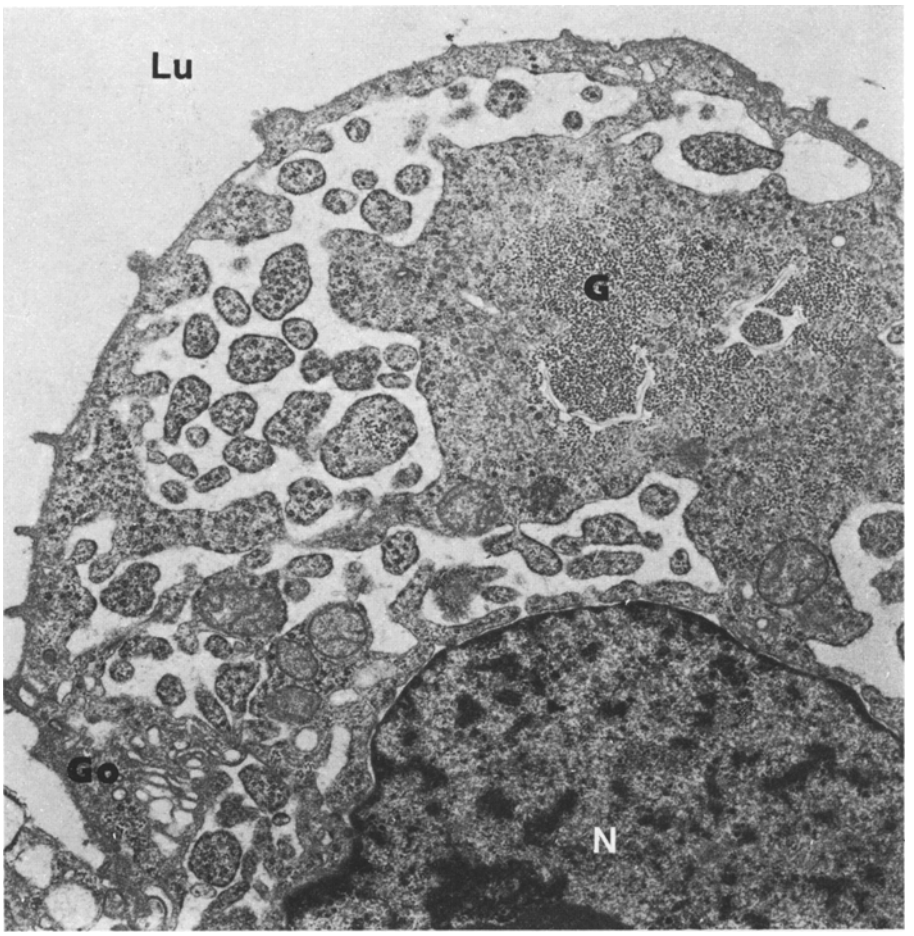


Fig. 9. Apical part of a "hobnail" cell projecting into the lumen (*Lu*). The granular endoplasmic reticulum displays strongly dilated cisternae. In the cytoplasm numerous partially aggregated glycogen granules (*G*). In the lower left a well-developed Golgi complex. ×13,800

nomas are also known to occur in the endometrium (Rutledge et al., 1965; Kurman and Scully, 1976; Photopulos et al., 1979), cervix uteri (Hameed, 1968; Hart and Norris, 1972; Woyke et al., 1972) and vagina (Silverberg and DeGiorgi, 1972). In these two latter locations most of the reported tumors occurred in girls or young women following maternal ingestion of nonsteroid estrogens during pregnancy (Tsukada et al., 1972; Herbst et al., 1974; Nordqvist et al., 1976). No such association is known for the endometrial or ovarian neoplasms. In all locations the clear cell type of adenocarcinoma has been subjected to ultrastructural studies.

The findings of Silverberg and DeGiorgi (1973) who first described the ultrastructure of a clear cell adenocarcinoma of the endometrium are identical to those revealed by studies of clear cell tumors reported in other locations.

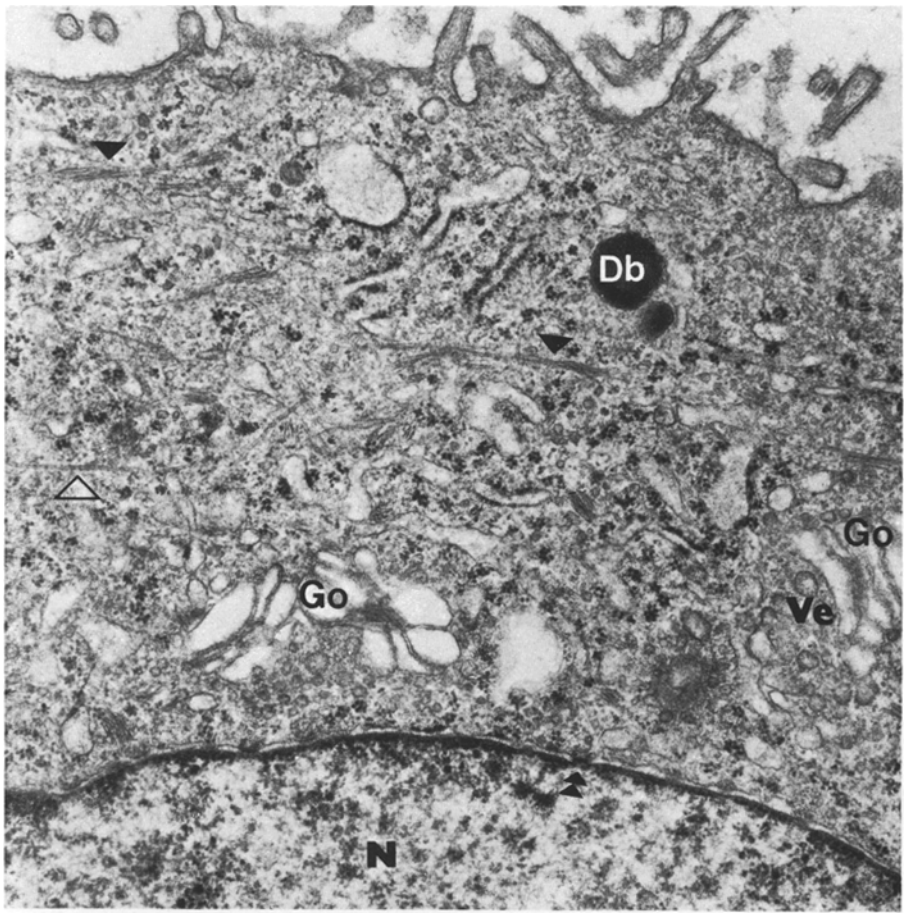


Fig. 10. Apical part of a tumor cell displaying numerous microvilli. The Golgi complexes (*Go*) are somewhat dilated and associated with groups of microvesicles (*Ve*). In the cytoplasm numerous polyribosomes, bundles of microfilaments (▶), some microtubules (▷) and a dense body (*Db*). The membrane of the nucleus (*N*) exhibits a few nucleopores (▶▶). ×26,100

The particular features of the tumor cells include the short and thick microvilli, the expanded intercellular spaces with complicated interdigitating cytoplasmic processes, the prominent intracytoplasmic glycogen granules, the rarity of lipid bodies and lysosomes as well as the stacked lamellar arrangement of granular endoplasmic reticulum.

Rorat et al. (1974) reported that the most striking feature of endometrial clear cell carcinoma at submicroscopic level is the massive accumulation of glycogen particles in close association with prominent membranes of granular endoplasmic reticulum. Similar characteristics have been observed in both hyperplastic and neoplastic endometria after progestin treatment, although, in the latter conditions, the glycogen accumulation is less conspicuous. These authors believe that the massive glycogen storage in the tumor cells is unlikely to be

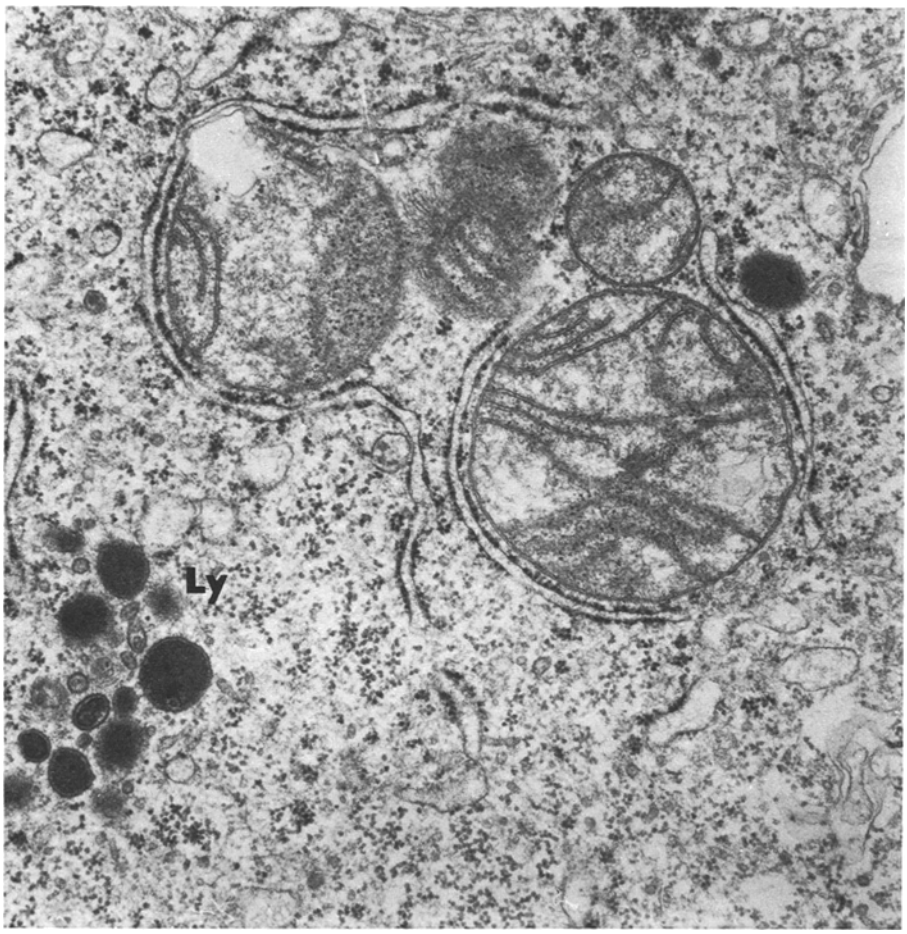


Fig. 11. Cytoplasmic detail of a clear cell containing numerous polyribosomes admixed with glycogen granules and some small membrane-bound lysosomes (*Ly*). A few round mitochondria with irregular plate-like cristae are in close association with some strands of granular endoplasmic reticulum. × 26,100

related to hormonal influence and conclude that the clear cell carcinoma is most likely a variant of the more common endometrial carcinoma.

Although much clinical and pathologic evidence has been brought for a close relationship between the ovarian clear cell and endometrioid carcinomas, this relationship seems not to be so evident at submicroscopic level.

Okagaki and Richart (1970) as well as Ferenczy and Richart (1974) reported ultrastructural observations showing that ovarian endometrioid carcinomas are essentially identical with the endometrial carcinomas of the uterus, the tumor cells being particularly characterized by "basket-form nucleoli" as described in endometrial epithelial cells. These authors deny the existence of a close relationship between ovarian endometrioid and clear cell carcinomas. Cummins et al. (1974) also analysed the ultrastructure of four ovarian endometrioid carci-

Fig. 12. Cytoplasmic detail of a tumor cell displaying numerous strands of granular endoplasmic reticulum partially stacked in short parallel or concentric rows. Numerous polyribosomes are admixed with glycogen granules, mitochondria as well as a prominent lysosome (*Ly*) are present. × 18,800

nomas and found no obvious sub-microscopic differences between these neoplasms and the common endometrial carcinomas. The tumor cells were found to display numerous long and slender microvilli as well as some rare cilia, well-developed desmosomes with bundles of tonofibrils, many prominent Golgi bodies with associated microvesicles, an abundant granular endoplasmic reticulum, cytoplasmic microfibrils and a few microtubules, some lysosomes and very sparse lipid droplets. Okagaki and Richart (1970) suggested that the clear cell ovarian carcinoma is epithelial or mesothelial in origin, the only similarity existing with renal carcinoma being the abundance of glycogen in the cytoplasm of the tumor cells. Their observations did not support the theories of mesonephric, metanephric or endometrioid origins and these authors postulated that these tumors develop from the pluripotent coelomic epithelium. The ultrastructural findings of Silverberg (1973) brought some more evidence that the ovarian

clear cell carcinoma is of müllerian rather than mesonephric origin and this author believes that it is probably related to secretory changes in endometrium-type glands. Salazar et al. (1974) described ultrastructural characteristics strongly similar to those of normal and neoplastic structures of müllerian nature in other organs of the female genital system and concluded from their observations that these neoplasms originate from the ovarian surface epithelium and are therefore closely related to the specialized müllerian structures. In addition, these authors observed the presence of intracellular canaliculi and described these structures in various stages of development. Ohkawa et al. (1977) who studied the fine structure of four ovarian clear cell carcinomas found in opposition to the findings of Rorat et al. (1974) that their ultrastructural features resemble those of the Arias-Stella reaction of endometrium as observed in their own study as well as in that of Thrasher and Richart (1972). Submicroscopic similarities also exist with the clear cell carcinoma of the cervix, suggesting in that way the müllerian origin of the ovarian neoplasms. These authors also found honeycomb structures in the cytoplasm of some tumor cells and compared them with the alveolate structures described by Ferenczy and Richart (1974) in the late secretory phase endometrium. They further compared the ultrastructure of the ovarian clear cell carcinomas with that of mesonephroi of human fetuses whereby no similarities could be observed.

The ultrastructural findings in our case of ovarian clear cell carcinoma resemble in many ways those of similar previously reported tumors, although some obvious differences are noteworthy. Numerous widenings of the intercellular spaces with slender interdigitating cytoplasmic processes were observed in most of the published cases as well as numerous and well-developed desmosomes. Such specialization of the cell membrane and intercellular relations were very sparse in our material and no desmosomes could be surely identified. Most authors observed a great abundance of glycogen granules being sometimes aggregated in large pools. In our case the amount of glycogen is quite variable from one cell to another and the granules are very irregularly dispersed throughout the cytoplasm. In all cases the tumor cells beared short and thick microvilli in various number that are quite different from those exhibited by the cells of renal carcinoma. The various amount of small and round mitochondria, the well-developed granular endoplasmic reticulum and Golgi apparatus, the sparse lysosomes and lipid bodies represent common findings in all reported cases. Klemi and Grönroos (1979) who described the ultrastructure of two ovarian "mesonephromas" are the only authors who reported nucleoli having a meshbasket appearance and being therefore reminiscent of those seen in ovarian endometrioid carcinomas, but they did not express any opinion concerning the histogenesis of these neoplasms.

The reported ultrastructural features of clear cell carcinomas of the uterine cervix (Woyke et al., 1972) and vagina (Silverberg and DeGiorgi, 1972) are also very similar to those observed in ovarian and endometrial clear cell tumors.

On the contrary, all published ultrastructural studies of ovarian clear cell carcinomas (Okagaki and Richart, 1970; Silverberg, 1973; Salazar et al., 1974; Ohkawa et al., 1977; Klemi and Grönroos, 1979) have shown that their submicroscopic features do not resemble those of renal carcinoma. The most striking ultrastructural characteristics of the renal tumor cells is the presence of many

large lipid bodies in the cytoplasm and a brush-like structure formed by numerous, long and slender microvilli with a filamentous core. In addition, the cell membranes present pits and invaginations associated with vesicle formation and deep infoldings of the plasmalemma in relation to the basement membrane, resembling those of renal tubules (Oberling et al., 1960; Seljelid and Ericsson, 1965; Ericsson et al., 1966). In fact the only similarity between the cells of ovarian and renal clear cell carcinomas is the abundance of cytoplasmic glycogen granules.

In conclusion, all ultrastructural studies of ovarian clear cell carcinomas have revealed the striking similarities existing between these neoplasms and the clear cell tumors occurring elsewhere in the female genital system, emphasizing therewith their very probable müllerian origin. On the contrary, there exist many important ultrastructural differences between these neoplastic cells and those observed in carcinoma of the kidney or mesonephric structures. Therefore, the terms "mesonephroma", "mesonephroid tumor" or "mesonephroid carcinoma" to designate the ovarian clear cell carcinomas should be consequently eliminated.

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