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Secreting Peritoneal Mesothelioma

Report of a Case with Cytological, Ultrastructural, Morphometric and Histological Studies

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Summary. A 29 year old woman, living in an area with a high level of asbestos exposure, developed the clinical features of peritoneal mesothelioma. The quantitative cytological features differed from those of other mesotheliomas described in the literature in that the tumor cells had a large amount of vacuolated cytoplasm and an extremely low N/C ratio, resulting in a "benign" appearance.

The ultrastructural study provided evidence for the production and accumulation of secretory products (mucolipids) by the tumor cells. Treatment with chemotherapy and radiation resulted in temporary remission, lasting for 20 months. However the patient then developed pulmonary involvement of the carcinomatose a form and pleural tumors. The cytological pattern and the morphometric features of the metastatic floating malignant mesothelial cells in the pleural fluid closely resembled those of the primary peritoneal tumor.

This case appears to be an example of secretory peritoneal mesothelioma with a bad prognosis, not withstanding the well-differentiated appearance of the tumor cells.

Key words: Morphometry – Secretory peritoneal mesothelioma – Transcoelomic metastasis – TEM of malignant mesothelial cells

Introduction

In those areas of the Netherlands where there is shipbuilding, such as the Rotterdam region, malignant mesothelioma is relatively frequent with an incidence ten times as high as that in surrounding cities (Planteydt 1972).

In such areas of increased asbestos exposure which may be either occupational, environmental or both (Churg and Warnock 1979), both pleural and peritoneal mesothelioma are associated with asbestos (Mann et al. 1966; Waridel and

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Lanitis 1976). In our laboratory (Stichting Samenwerking Delftse Ziekenhuizen, Delft) with a large number of patients from the Rotterdam area, we detect approximately ten mesothelioma cases per year of which the great majority are of primary pleural origin. The cases detected cytologically are predominantly epithelial mesotheliomas, because fibrous mesotheliomas exfoliate few, if any, tumor cells into effusions (Liang-Che Tao 1979). However, even with extensive cytological experience the diagnosis remains a difficult one, the problem being first to recognize the cells as malignant and second to identify them as mesothelial (Berge and Gronthoff 1965; Klempman 1972; Spriggs 1968). Of the malignant mesotheliomas those of peritoneal origin are uncommon (Godwin 1957; Gutman et al. 1976; Kannerstein et al. 1977).

We report here the cytomophometry, chemistry and transmission electron microscopy of a case of secreting peritoneal mesothelioma which was very difficult to diagnose cytologically. We attempt to elucidate the peculiar cytological pattern found.

Case Report

The patient was a 29 year old woman living in the Rotterdam area, whose first complaints were an increase of abdominal size for three months, a vague heavy feeling in the abdomen and vomiting. On examination she was found to have an elevated diaphragm on both sides, and a diffusely swollen abdomen with a flattened navel. The liver and the spleen were not enlarged and no tumors were palpable. Rectal and vaginal examinations were normal. The presence of abdominal fluid was demonstrated by ultrasonic examination, in which "floating intestines" were observed. These clinical features are often observed in primary peritoneal mesotheliomas (Jones and Silver 1979; Moertel 1972).

Cytological material was obtained by paracentesis; laparotomy was decided upon because of the inconclusive nature of the cytological report. A gelatinous fluid occupied the distended abdominal cavity, and the visceral and parietal peritoneum was covered by multiple small (2 cm) tumors. No primary tumor was found in the abdominal organs; the liver and the spleen showed no abnormalities. The possibility of ovarian carcinoma was carefully considered but no evidence of ovarian origin could be found. The right ovary, also covered by numerous tumors, was extirpated and 5000 cc ascitic fluid was removed. Postoperative chemotherapy (Vincristine and Adriamycin) and abdominal irradiation (3200 Rad) were administered. Four months later an additional 4500 cc ascitic fluid was removed, and two months later an additional 400 cc. Chemotherapy was terminated after 12 months. She remained clinically well and free of ascites over a period of 20 months after the operation. Then she developed pulmonary involvement of the lymphangitis carcinomatosa type and later new tumor deposits were evident in the peritoneum and pleurae. Notwithstanding irradiation and chemotherapy she died 6 months later with wide spread metastasized cancer. Permission for autopsy was not obtained.

Results

Cytological Findings

In cytological preparations of the ascitic fluid mesothelial cells and numerous histiocytes were observed. Almost all mesothelial cells lay isolated, and few cell clumps were found. One percent of the mesothelial cells contained more than two nuclei, 12% two nuclei and 87% were mononucleated. The cells differed greatly in nuclear and cytoplasmic area, and all mesothelial cells had abundant cytoplasm. Many had a prominent nucleolus. The nuclear shape was regular and round, the histiocytes had finely vacuolated, ill defined cytoplasm.

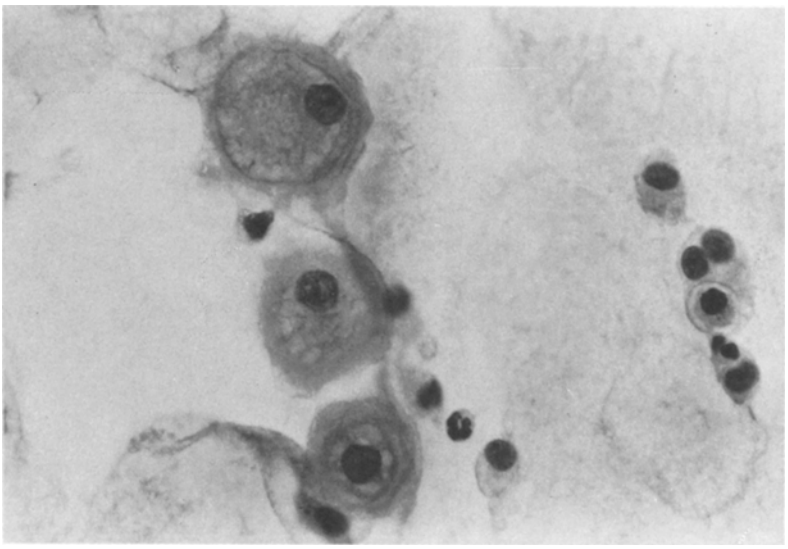

Fig. 1. Cytological specimen of mesothelioma cells. Note the marked cytoplasmic vacuolization and the relatively fine chromatin. (PAP, ×500)

In the alcohol-fixed Papanicolaou-stained smears the cytoplasmic staining of the mesothelial cells was striking; the central perinuclear area stained light blue or pink and was often vacuolated. In many cells the vacuolization involved the cytoplasm almost completely, with a remaining narrow dense outer zone. Often vacuoles were making little "holes" in the nuclei. The nuclei were slightly hyperchromatic with a fine chromatin pattern (Fig. 1).

In the air-dried Giemsa-stained smears almost all mesothelial cells displayed a brush border. The cyptoplasmic vacuolization and dense outer zone, which stained blue, were also visible in these smears (Fig. 2). The cytological pattern of the pleural fluid was similar.

Electron Microscopy

Five ml of ascitic fluid was fixed immediately in 5 ml of cacodylate buffered 1.5% glutaraldehyde for four hours and centrifugated at 1200 rpm for 15 min. The pellet was rinsed with buffer and processed for transmission electron microscopy. From two blocks ultrathin sections were cut and stained with uranyl acetate and lead citrate. From the electron micrograph negatives membrane thickness was measured at multiple sites where the membranes were well defined using a light microscope equipped with an ocular micrometer.

Many large and (sometimes) small groups of tumor cells were seen together with macrophages. The tumor cells showed many long microvilli around their circumference (Fig. 3) which was covered with a fuzzy material. Sometimes blunt cytoplasmic processes were seen. The cytoplasm possessed numerous large vacuoles, whose diameter varied from 0.5 to 3 micron. These were filled with fuzzy, material and usually lined by a single membrane (Fig. 4). This membrane

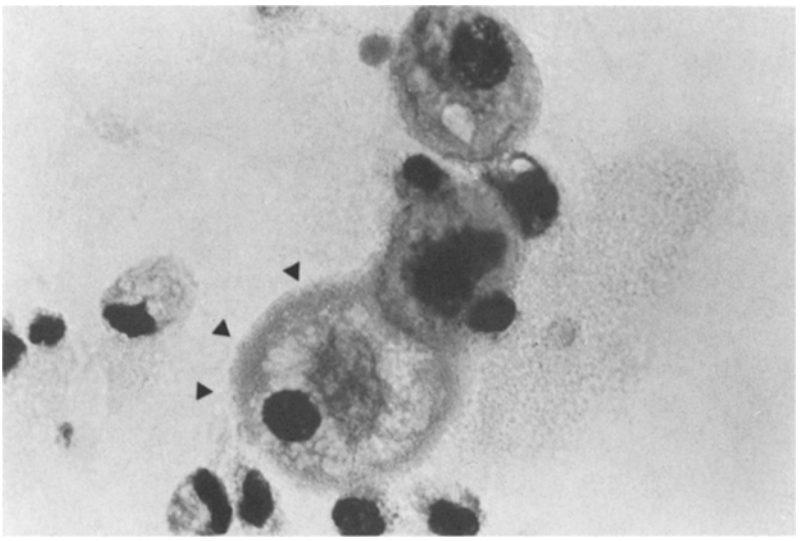

Fig. 2. Cytological specimen of mesothelioma cells, showing a vaguely outlined brush border *(arrowheads)*. (Giemsa, × 500)

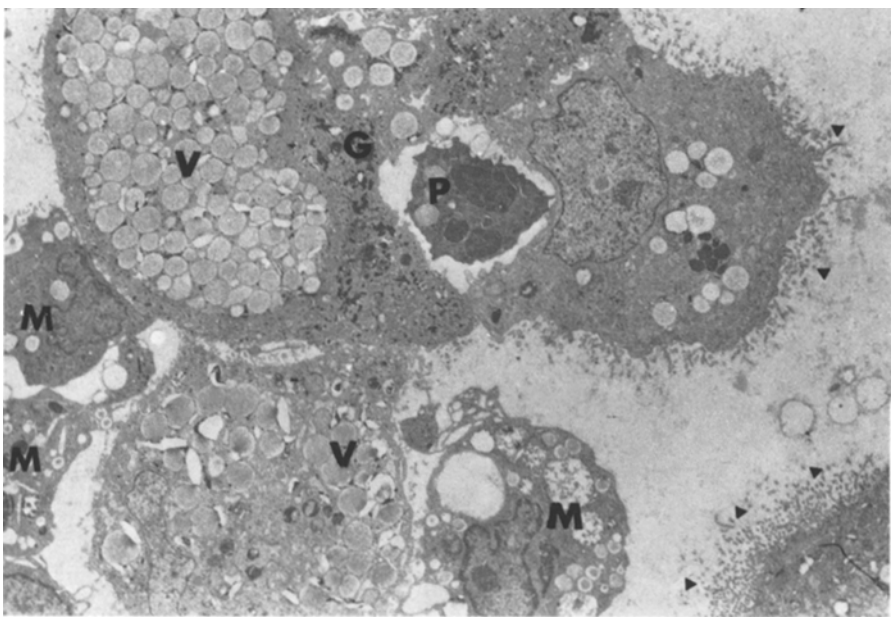

Fig. 3. Electron micrograph of a small group of mesothelioma cells. Note the presence of bush-like microvilli (*arrowheads*) and the abundance of vacuoles (*V*) in the cytoplasm of the tumor cells. *G* glycogen; *M* microphage; *P* polymorphnuclear leucocyte. (Uranyl acetate and lead citrate, × 3,500)

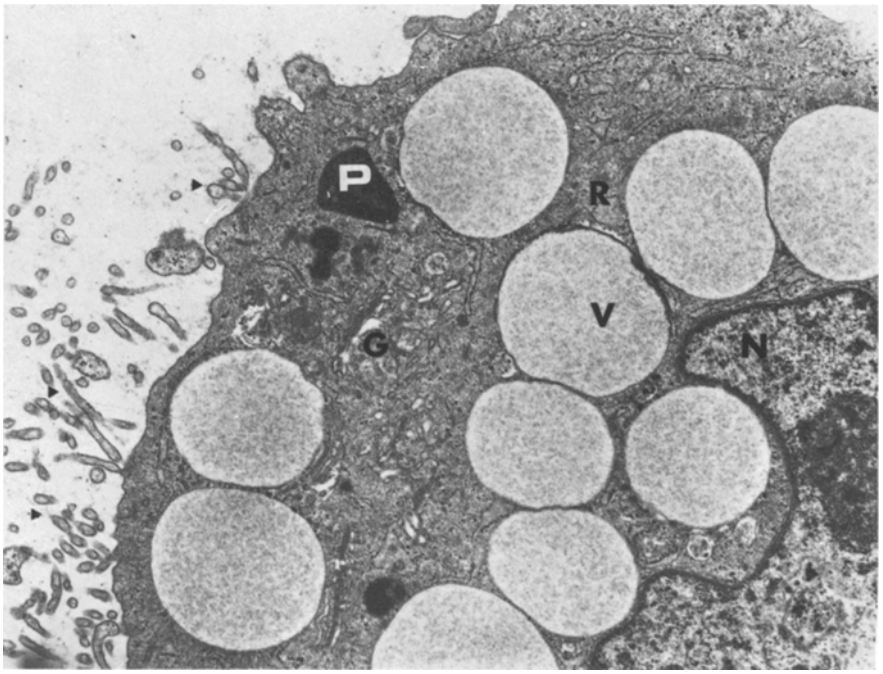

Fig. 4. Electron micrograph of a part of the cytoplasm of a mesothelioma cell. Note the dilated cisternae of rough endoplasmic reticulum (*R*), Golgi apparatus (*G*), vacuoles (*V*) filled with fuzzy material, phagosomes (*P*), and the microvilli (*arrowheads*). (Uranyl acetate and lead citrate, × 12,000)

Table 1. Comparison of membrane thickness of vacuoles, rough endoplasmic reticulum, phagosomes and cell membrane of mesothelioma cells

Membrane	Number of measurements	Thickness (nm)	
		Mean	Standarddeviation
Vacuoles	28	8.15	0.85
Rough endoplasmic reticulum	11	7.88	0.68
Phagosomes	10	10.91	1.00
Cell membrane	10	10.17	1.59

was similar in thickness to the rough endoplasmic reticulum, but significantly ($P < 0.001$) thinner than those of the cell membrane and of phagosomes (Table 1) and possessed the characteristics of a unit membrane (Fig. 5). Surrounding these vacuoles, varying amounts of glycogen were found (Fig. 4). Mitochondria were fairly numerous, sometimes swollen with a loss of cristae, and often surrounded by cisternae of rough endoplasmic reticulum that were usually distended and filled with homogenous material. Occasionally, the Golgi apparatus was very prominent. Some phagosomes were seen. The cytoplasm contained many thin filaments, occasionally arranged in short bundles. Several small pinocytotic vesicles were usually seen. The nucleus was irregular and showed both euchroma-

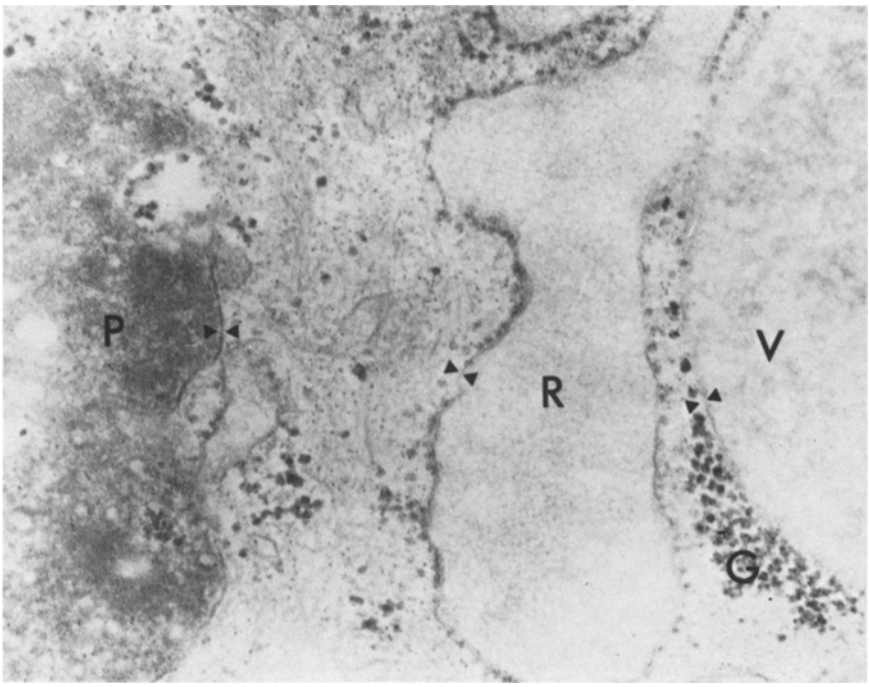

Fig. 5. Electron micrograph of a part of the cytoplasm of a mesothelioma cell. Note the difference in thickness between the single membrane of the vacuoles (*V*) and rough endoplasmatic reticulum (*R*) on one hand, and the unit membrane of the phagosomes (*P*) on the other (*arrowheads*). *G* glycogen. (Uranyl acetate and lead citrate, ×55,000)

tin and heterochromatin, which was dispersed in clusters or as an incomplete rim near the nuclear membrane. Occasionally a compact prominent nucleolus was found. In some tumor cells the cytoplasm showed a few electron dense rod-like structures (length 0.75 μ diameter 0.1 μ), lying in vacuoles filled with fine, granular material and lined by a single membrane.

Between adjacent tumor cells some tight junctions were seen. Mucin granules were not found. Sometimes there was partial engulfment of one vital-looking tumor cell by another. The macrophages showed several irregularly distributed long cell processes, a few very large (diameter about 0.5 μ) vacuoles filled with fuzzy material (Fig. 3). The nuclei were somewhat irregular with a prominent central indentation, a broad rim of heterochromatin and sometimes a rather large compactly structured nucleolus.

Morphometry

The nuclear and cytoplasmic area of 50 Giemsa-Stained mesothelial cells in the peritoneal fluid were measured with a planimeter (ASM. Leitz) and a camera lucida system at 1000× initial magnification. Only cells with a well defined dense blue-staining outer zone, often with central vacuolization were measured. Cells with ill-defined completely vacuolated cytoplasm were classified as histio-

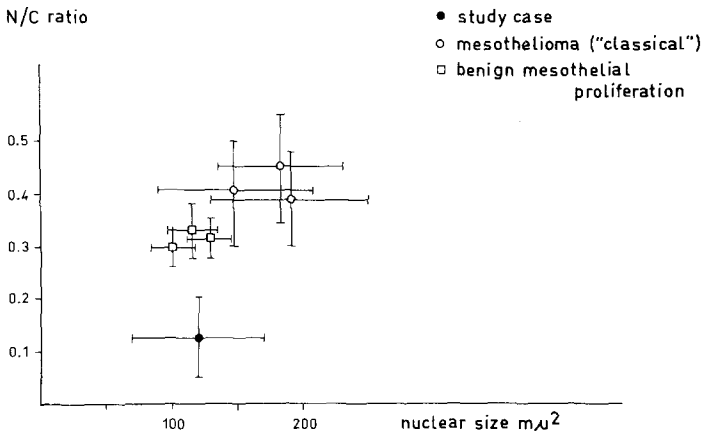

Fig. 6. Relationship between nuclear/cytoplasmic ratio and nuclear size. Because of its large cytoplasmic dimensions the N/C ratio of the study case is remarkably low

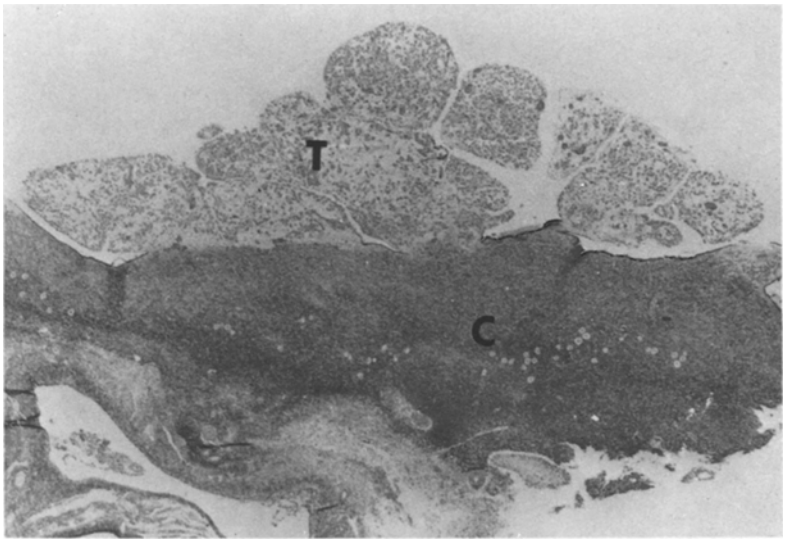

Fig. 7. Photomicrograph of bud-like tumor formations attached to the surface of the ovary. *T* tumor; *C* cortex of the ovary. (H&E, ×15)

cytes, and were not measured. In comparison two cases with benign mesothelial proliferation and two cases of pleural mesothelioma lacking the marked cytoplasmic vacuolization were measured. The benign mesothelial cells had average nuclear and cytoplasmic projected areas of 120 and 440 μm^2 respectively, the malignant pleural mesotheliomas 174 and 400 μm^2 and the peritoneal mesotheliomas 120 and 1000 μm^2 respectively, resulting in a low mean N/C ratio (Fig. 6).

In comparison with the benign cases, the malignant cases showed a higher degree of scattering. In addition, the mesothelial cells in the pleural fluid of

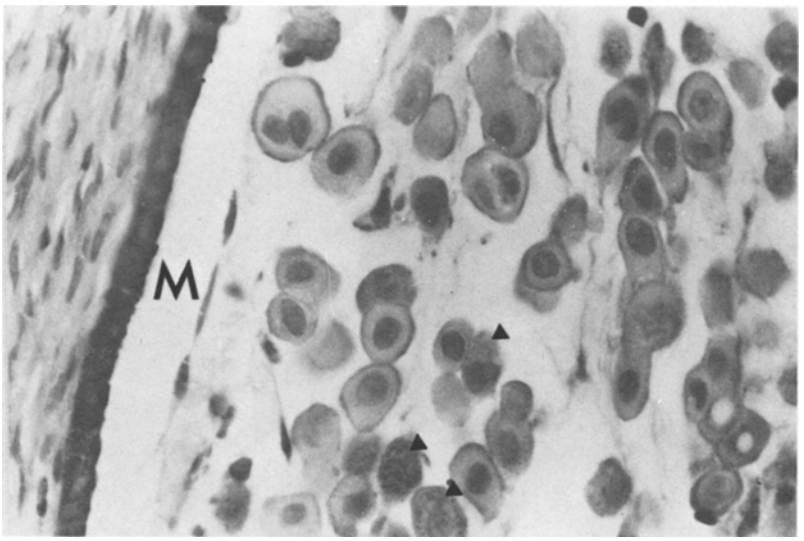

Fig. 8. Photomicrograph of tumor cells with PAS positive brush border and locally glycogen (*arrow heads*). *M* mesothelium of ovary. (PAS, ×400)

Table 2. Nuclear cytoplasmic ratio of malignant mesothelial cells of illustrated cases published in literature

Author	Case nr.	Staining	*N*	Nuclear cytoplasmic ratio[a]	
				Mean	Standard deviation
WHO	Nr. 162	PAP	10	0.38	0.11
WHO	Nr. 163	PAP	3	0.33	0.06
WHO	Nr. 164	PAP	6	0.55	0.08
Lopes Cardozo	Nr. 271-1	MGG	5	0.38	0.13
Lopes Cardozo	Nr. 272-2	MGG	9	0.14	0.63
Naib	–	PAP	7	0.44	0.09
Berge	–	PAP	13	0.39	0.18
Castor	–	PAP	11	0.28	0.07
Whitacker	–	PAP			

[a] N/C ratio calculated from cell images in photomicrographs

the case under study were measured: the mean nuclear area was 128 ± 33 and the cytoplasmic are 1015 ± 630 μm^2.

Histology

Tissue was obtained from a tumor on the right ovary and fixed in buffered formaldehyde. After paraplast embedding 5 μm thick sections were cut.

The slides were stained with H&E, PAS, PAS after amylase digestion, alcian blue, alcian blue after incubation with hyaluronidase, and with mucicarmine.

The outer rim of the cytoplasm stained atrongly with PAS and alcian blue, which did not disappear after amylase digestion. After hyaluronidase incubation, the alcian blue staining pattern was not weaker. The same staining, though fainter, was present in vacuoles. Mucicarmine staining was negative. Some glycogen was present as small granules in the cytoplasm of the tumor cells and was also diffused through the cytoplasm of the ovarian mesothelium.

Micoscopically budlike formations of tumor tissue were attached to the cortex of the ovary (Fig. 7) with only superficial invasion. These buds consisted of oedematous connective tissue in which a large number of mesothalial cells with an abnormal appearance were present (Fig. 8). The tumor cells were polygonal and possessed a finely-vacuolated eosinophilic cytoplasm, however the degree of vacuolization was less than the floating cells in the cytological specimen. Some nuclei were hyperchromatic and few mitotic figures were found. Only few histiocytes were observed in the tumor tissue.

Chemical Analysis of the Ascitic Fluid

A qualitative test for mucopolysaccharides (o-toluidin blue) was positive. Two dimensional electrophoresis of the cetylpyridinium precipitate had an unrecognizable pattern, pointing to an absence of free mucopolysaccharides. The most probable explanation of these findings is that the ascitic fluid contained large quantities of mucolipids. The fact that the ascitic fluid was less viscous after idurinidase treatment indicates that the enzyme acts on the muco-part of the mucolipids.

Discussion

The described cytological features of malignant mesothelioma include cell aggregates brush borders, apposition of cell borders, peripheral cytoplasmic vacuoles and two-tone staining in the Papanicolaou method (Naib 1976; Liang-Che Tao 1979; Whitaker and Shilkin 1978). The nuclear patterns described include prominence of nucleoli, abnormal chromatin textures and hyperchromasia (Klima et al. 1976; Naylor 1973) multinucleation was often encountered (Castor and Naylor 1969); an unfavorable N/C ratio often noted (Berge and Gronthoff 1965). In contrast, in our case the cytoplasm of the malignant cells was abundant with N/C ratios that were lower than in benign mesothelial cells (Fig. 6) Also in most published photomicrographs of exfoliated malignant mesothelial cells the N/C ratio is high (Table 2), the only exception being one case published by Lopes Cardozo with a mean N/C ratio of 0.14 of the photographed cells. Klima et. al. (1976) mentioned a case with a marked vacuolization, however, we were not able to assess the N/C ratio because the case was not illustrated.

In order to explain the peculiar cytological pattern of this case, transmission electron microscopy (TEM) of the effusion was done. The abundance of long cytoplasmic villi, the combination of glycogen, fine filaments, many mitochondria surrounded by rough endoplasmic reticulum and the absence of mucin granules were in agreement with the TEM criteria for malignant mesothelioma in tissue (Davis 1974; Whitaker 1977) and effusions (Kannerstein and Churg 1977; Legrand and Pariente 1974; Murad 1973). Cells of metastastic carcinoma

in effusion may also show several long microvilli as well (Domgala and Woyka 1975; Letho and Virtanen 1978) and the diagnosis of malignant mesothelioma has to be further established by macroscopic appearance, histology and by the exclusion of an adenocarcinoma (McCaughey 1965). In our case the parietal peritoneum was covered by multiple small papillary tumors and after extensive surgical exploration no primary adenocarcinoma could be detected, making the diagnosis of malignant mesothelioma probable. The negative mucicarmine stain and the total staining pattern supported the diagnosis of mesothelioma. However, hyaluronic acid could not be demonstrated in the tumor cells in contrast to the cases of Winslow and Taylor (1960), but its absence does not exclude mesothelioma (Wang 1973).

The conspicious cytoplasmic vacuoles seen by electron microscopy were filled with the same fuzzy material as was found at the surface of the cells. The hyaluronidase resistent staining with alcian blue and PAS of the brush border and vacuoles indicates that the tumor cells produce mucolipids, which is supported by the chemical analysis of the ascitic fluid. This is in agreement with the colloidal iron staining between the bush-like microvilli described by Wang (1973). The vacuoles can, as well as representing an accumulation of secretory material, be the result of reabsorption. The presence of markedly dilated rough endoplasmic reticulum and the conspicious Golgi apparatus in parts of the tumor cells point to secretory activity of the tumor cells (De Duve 1972); reabsorption is not likely because only slight pinocytosis was seen in the TEM. This evidence for production by the tumor cells is supported by the finding of single thin membrane surrounding the vacuoles with a similar thickness of that of the rough endoplasmic reticulum (see Table 2) indicating that they belong to the endoplasmic space.

The many localizations of malignant mesothelioma on the peritoneal surface resulted in marked ascites due to fluid production by the tumor cells. As a result, an equilibrium may be reached between the secretory material in which the cells are floating and that within the cells. Probably this is only established when the cytoplasm has become maximally extended resulting in very large cells with relatively small nuclei, such as seen in epithelial cells in Nabothian cysts of the uterine cervix (Boon and Tabbers-Boumeester 1980) and in mammary cysts (Zajicek 1974). Extreme vacuolization was found in the floating tumor cells, and not in the histological sections of the tumor. Interestingly enough, the cytological pattern and the morphometric data of the malignant mesothelial cells in the pleural fluid closely resembled those of the primary peritoneal tumor.

The prognosis of primary peritoneal mesothelioma is poor (Elmes and Simpson 1976; Hofner 1979) and the average survival time in a relatively large series of cases recently reported was less than one year (Kannerstein and Churg 1977) although also several succesfully treated patients with pleural and peritoneal mesothelioma have been described (Hellstroem et al. 1977; Kucuksu et al. 1976). Our patient eventually deteriorated after a temporary remission, and the tumor proved to have metastastic properties.

Even in publications with extensive illustration of the various cytological presentations of mesotheliomas we could not find a case with a pattern such as occurred in our patient. The cytological diagnosis was extremely difficult

due to the extraordinary low N/C ratio. However, reviewing a large patient material from Vienna, we found that cytological pattern described here is characteristic for peritoneal mesothelioma (Boon et al. 1980). In that study was shown that the pleural metastases of peritoneal mesothelioma have a cytological pattern similar to the peritoneal mesotheliomas and different from primary pleural mesotheliomas.

Also in the case presented in this paper there was a striking similarity of the malignant mesothelial cells in the pleural and ascitic fluids.

Finally, it should be mentioned that, as long as most cytologists are not aware of the fact that primary peritoneal mesotheliomas often present with the pecular cytological pattern, described in this paper, this diagnosis will usually be made in the post mortem room.

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