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Ultrastructure of Gastric Leiomyosarcoma

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Summary. Samples of gastric leiomyosarcomas from two male patients (69 years and 57 years of age) were studied by electron microscopy. The tumour cells contained abundant 50–90 Å thick microfilaments and microtubules. Another cell type, regarded as immature leiomyosarcoma cell, contained numerous profiles of granular endoplasmic reticulum, free ribosomes and a well developed Golgi apparatus. There were intercellular junctions of zonula adherens-type between adjacent tumour cells. It was concluded that electron microscopy offers a valuable aid in the diagnosis of gastric neoplasms of smooth muscle origin.

Key words: Electron microscopy – Microfilaments – Microtubules – Nuclear pockets – Smooth muscle tumours.

Introduction

Gastric leiomyosarcomas are rare tumours (McNeer and Pack, 1967; Stout, 1953). Although their light microscopical appearance and histogenetic origin are well documented, knowledge of their ultrastructure and cellular differentiation is still fragmentary (Kay and Still, 1969). In the present study some characteristic ultrastructural features of gastric leiomyosarcoma cells are described.

Material and Methods

The tissues were obtained from resected stomachs from two patients whose case reports are given below. Samples for light microscopy were fixed in 10% neutral formalin, embedded in paraffin and stained with hematoxylineosin, van Gieson, PAS, PAS-Alcian blue, and Masson's trichrome technique.

The samples for electron microscopy were fixed in 3% glutaraldehyde in cacodylate buffer at pH 7.4 for 24 h and postfixed in 1% osmium tetroxide in the same buffer for 1 h. Ultrathin

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sections of Epon-embedded tissues were stained with uranyl acetate and lead citrate and studied with a JEOL JEM-100C electron microscope.

Case Reports

Patient 1 was a 69-year-old transport manager, whose health had been good. During 1973 he had had two periods of anemia; these were not investigated and the anemia was improved by medication with iron. Early in the year 1974 he was admitted to the hospital with dizziness and dyspnoea and it was then observed that the haemoglobin concentration had decreased from 140 g to 60 g per litre within a fortnight. The anemia was found to be caused by bleeding. In a physical examination, a tumour of about the size of a fist was found on the upper stomach, apparently attached to the liver. No significant deviation from the normal was observed in X-ray examinations of the gastrointestinal tract or stomach. Gastroscopy offered no explanation of the bleeding. Another bleeding episode followed, during which the patient suffered from both hematemesis and melena; 3200 ml blood was transfused to cover bleeding. In this situation laparotomy was considered necessary and at operation a tubular fluctuating tumour, about 17 cm in diameter, was found dorsally between stomach and mesocolon. The tumour was easily detached from mesocolon; however its wall broke and 1000 ml old blood was extracted from it. The base of the tumour, 6 cm in diameter, was attached to the posterior wall of the stomach. In a 50% resection of the body of the stomach the tumour was removed with a margin of 7 cm of healthy tissue. The tumour displayed quite a definite capsule the inner surface of which was covered with a 2–3 cm thick layer of friable tumour tissue, resembling cauliflower. There was a communication ca. 1.5 cm in diameter, between the tumour and the stomach. When the X-ray pictures were examined after the operation, an impression caused by the tumour was recognizable in the wall of stomach and a slender sinus containing contrast-material was seen leading into the tumour. The patient recovered well and after two and a half years, has no gastric symptoms.

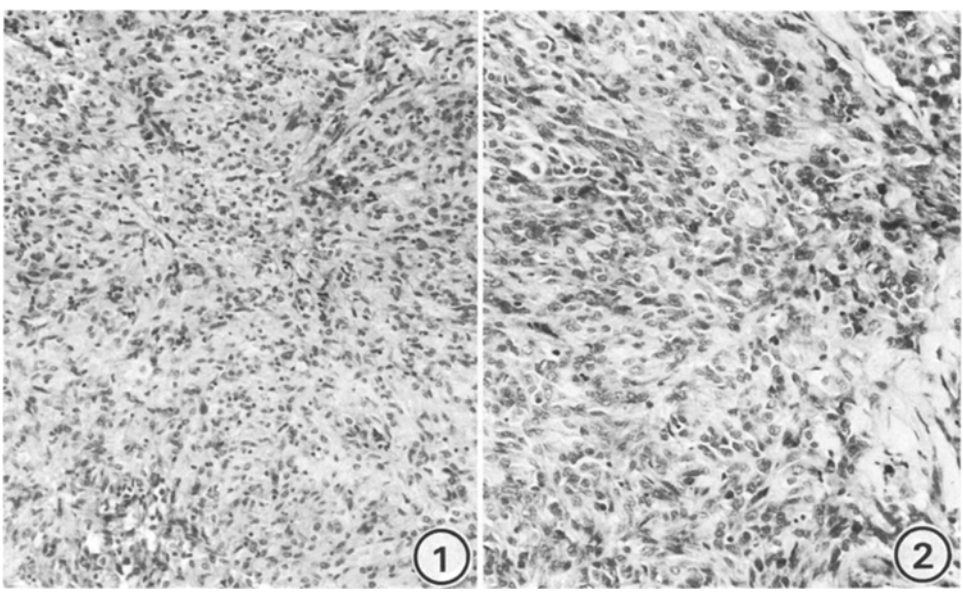

Fig. 1. Light micrograph of the tumour in case 1. The tumour consists of solid sheets of slightly elongated cells. H-E. Mag. ×100

Fig. 2. Light micrograph of the tumour in case 2. The tumour structure is similar to that of case 1. H-E. Mag. ×100

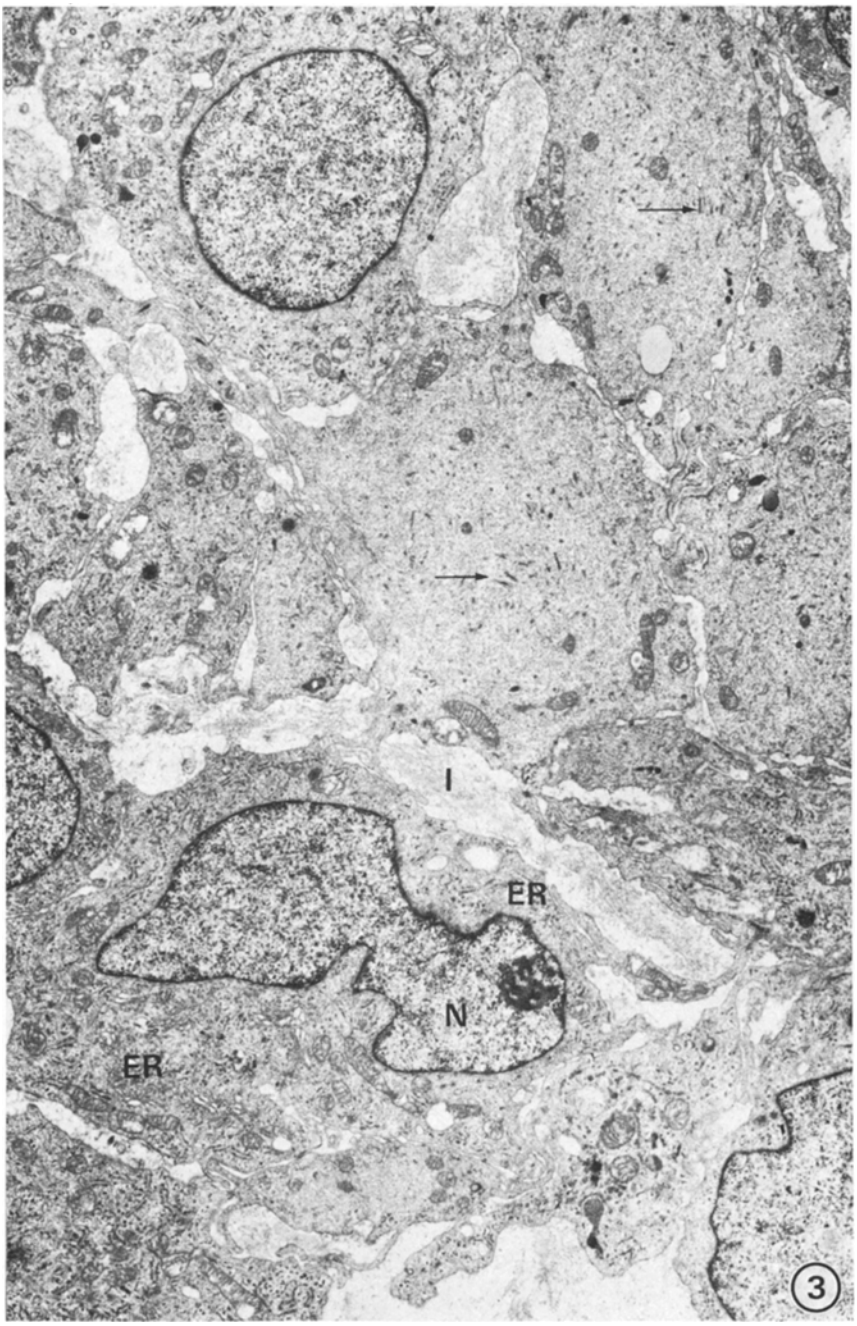

Fig. 3. A low magnification electron micrograph of leiomyosarcoma cells. The cell in the center contains numerous profiles of the granular endoplasmic reticulum *(ER)*. In other tumour cells there are areas of filament accumulations which form occasional denser areas in the cytoplasm (arrows). *N*, nucleus with a prominent nucleolus, *I*, intercellular space containing filamentous material. Case 1. Mag. ×5000

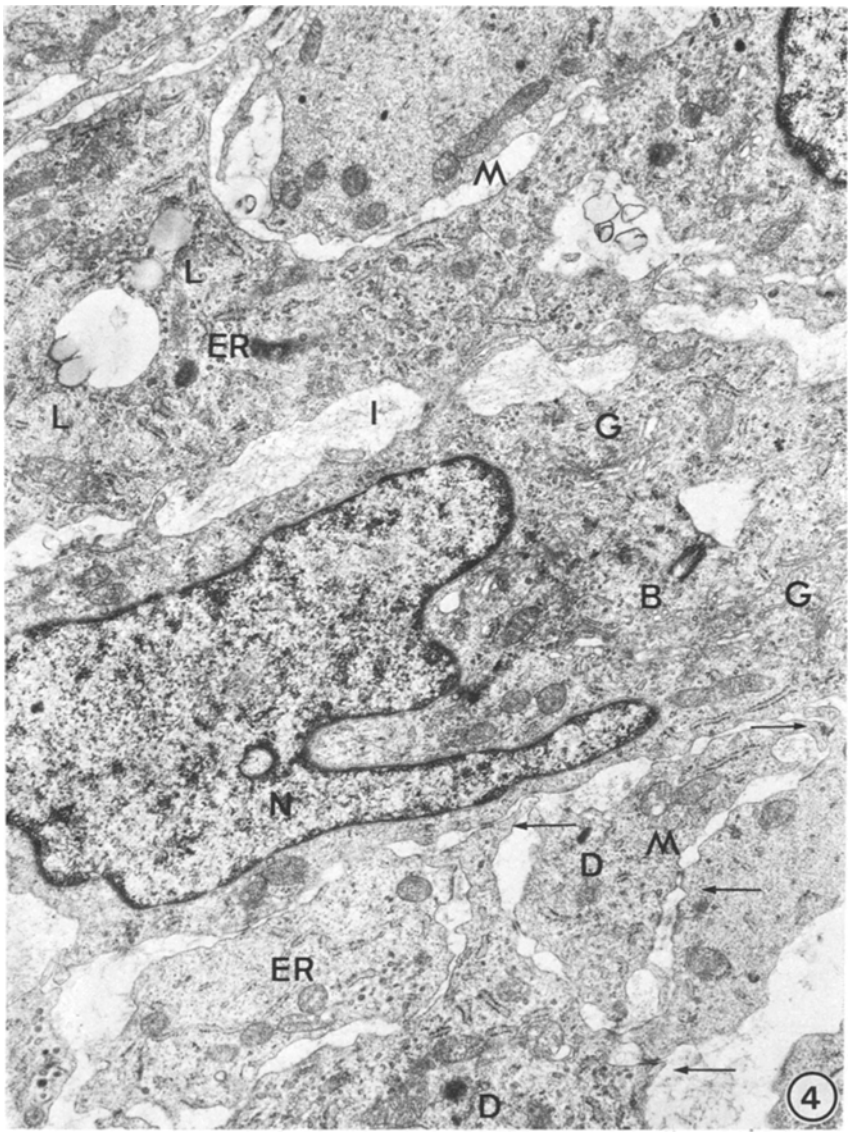

Fig. 4. The nuclear membrane shows a deep invagination and a nuclear pocket *(N)*. In addition to mitochondria *(M)* there are profiles of granular endoplasmic reticulum *(ER)*, lipid droplets *(L)*, and lysosome-like dense bodies *(D)* in the cytoplasm. The Golgi apparatus *(G)* is well developed and there is a basal body *(B)* in the Golgi area. The arrows point to junctions between adjacent tumour cells. *I*, intercellular space with filamentous material. Case 1. Mag. ×10000

Patient 2 was a businessman aged 57 with a diagnosis of colonic diverticulosis and diverticulutis which had been made six months before presentation. He complained of ill-defined pains in the stomach. For 2–3 months the patient had suffered from pains within upper abdomen, which had been different from those previously experienced; stools had been periodically black. An X-ray examination was performed on the stomach; it showed a tumour, ca. 5 cm in diameter, in the

Fig. 5. Microfilaments are oriented in a roughly parallel fashion in the cytoplasm of a leiomyosarcoma cell and form occasional denser areas (arrows). *M*, a mitochondrion. Case 1. Mag. ×45000

fundus, with ulceration in the middle. Gastroscopy verified the finding, after which the patient was taken into the surgical ward. His general health was excellent; there was no sign of anemia. At the operation a solid tumour, 10 cm in diameter, was found adhering to the upper portion of major curvature. There were numerous metastatic tumour nodules in the omentum and in the gastrohepatic and gastrolienal ligament. Subtotal gastrectomy was performed and the metastases were removed by omental resection. When the tumour was inspected it was observed to bulge into the lumen of the stomach and there was a necrotic ulcer in the middle of the lesion. The patient recovered well and at the time of this report, approximately six months after the operation, there are no signs of recurrence or metastasis of the tumour.

Results

Histological examination revealed similar tumour structures in both cases (Figs. 1 and 2). The tumours consisted of solid sheets of relatively small, often slightly elongated cells with relatively abundant cytoplasm. There were moderate numbers of mitoses. In the electron microscope the tumour cells were elongated in shape with centrally located nuclei. The nuclear shape was variable, some nuclei were round or oval (Fig. 3) whereas others showed deep invaginations and "nuclear pocket"–formations in the nuclear membrane (Fig. 4). The nu-

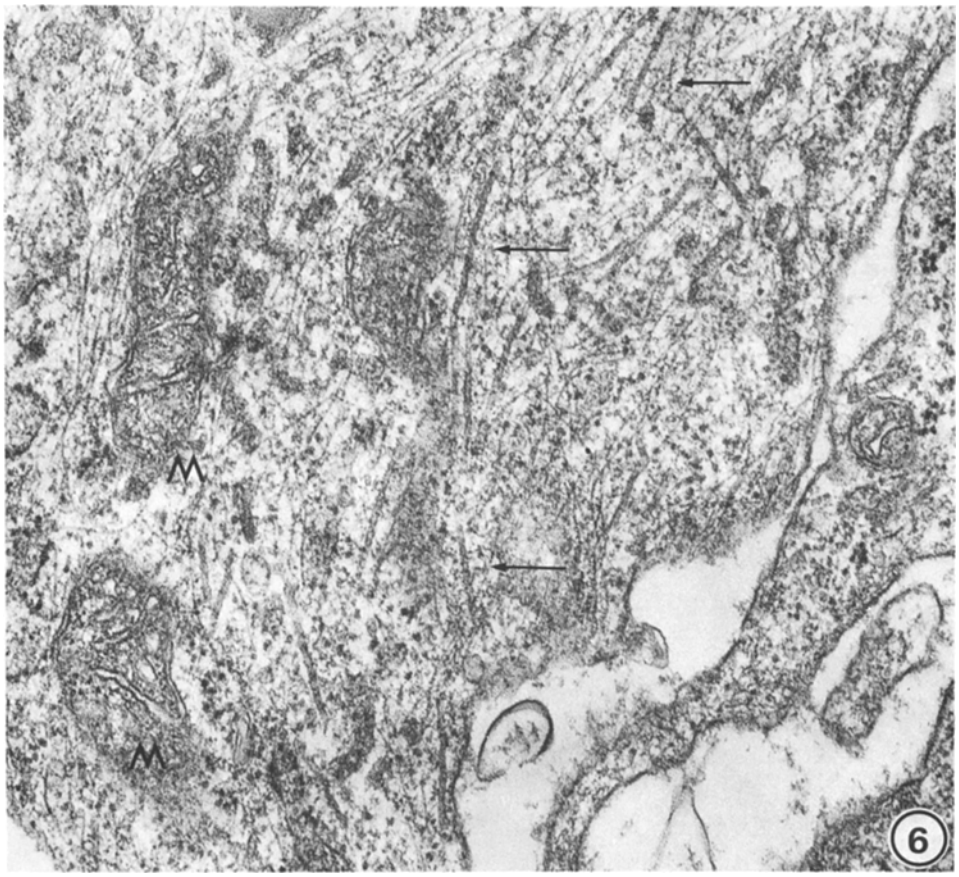

Fig. 6. In addition to microfilaments there are microtubules (arrows) oriented parallel to the former in the cytoplasm of a leiomyosarcoma cell. *M*, mitochondria. Case 1. Mag. ×45000

cleoli were round and compact (Fig. 3). In some cells there were abundant profiles of the granular endoplasmic reticulum and free ribosomes (Figs. 3 and 4). The cytoplasm in the majority of the tumour cells was occupied mainly by filamentous structures which gave a relatively transparent appearance to the cytoplasm at low magnification (Fig. 3). The Golgi apparatus was well developed in some cells (Fig. 4), there were occasional cilia and basal bodies (Fig. 4) and in addition to mitochondria frequent lipid droplets and lysosome-like bodies were seen in the cytoplasm (Fig. 4). Zonula adherens-type cell junctions were seen between adjacent tumour cells (Fig. 4), the intercellular space contained abundant thin filamentous material (Figs. 3 and 4) but only a few collagen fibres.

A characteristic feature of the leiomyosarcoma cells was their abundant cytoplasmic filaments. The filaments were arranged roughly parallel to the long cell axis with occasional areas of increased density which appeared as dark bodies at low magnification (Figs. 3 and 4) and were relatively uniform. They

measured approximately 50–90 Å in thickness (Figs. 5 and 6). In addition to microfilaments there were numerous microtubules, approximately 250 Å in thickness, in the cytoplasm of some tumour cells (Fig. 6). The microtubules were oriented parallel to the microfilaments and topographically closely associated with them.

Discussion

Gastric leiomyosarcoma is an uncommon tumour; representing only 1.4–4.4 per cent of malignant tumours of the stomach (McNeer and Pack, 1967; Stout, 1953). The histologic diagnosis of malignancy of smooth muscle cell tumours is based on the size of the cells, the degree of pleomorphism, irregularities of cell and nuclear shape, the number of mitotic figures, and hyperchromatism of nuclei. It must be noted, however, that bizarre degenerating cells can occasionally be observed in biopsies from apparantly benign leiomyomas (Morson and Dawson, 1972; Skandalakis and Gray, 1962). It is well known that smooth muscle tumours may appear perfectly benign histologically but behave clinically as malignant neoplasms or vice versa. Therefore the bizarre leiomyomas (leiomyoblastomas) should be regarded as at least potentially malignant (Cornog, 1974).

There are no specific symptoms of gastric leiomyosarcoma. Common signs and symptoms include ulcer-type pain in the upper abdomen, gastrointestinal bleeding, and a palpable tumour (Giberson et al., 1954). The most useful diagnostic procedure is the X-ray examination of the ventricle. This will reveal some abnormality in at least 90 per cent of patients (ReMine, 1970). Gastroscopy may be helpful in diagnosis.

Grossly leiomyosarcomas vary greatly in shape but generally they have a characteristic lobulated or nodular appearance. Necrotic changes are often noted as well as cystic degeneration and the tumour may contain fluid from necrotic tissue, or old blood (Giberson et al., 1954). Because of the necrosis within the tumour, communications between the inside of the tumour and the lumen of the stomach tend to form by perforation. Invasion of blood vessels or lymphatics and metastasis to lymph nodes is rarely observed on exploration (Maingot, 1974).

Over 90 per cent of gastric sarcomas are resectable. With subserous leiomyosarcomas extensive resections are as a rule unnecessary; the tumour and the pedicle to the stomach can be removed by wedge resection. The intragastric leiomyosarcomas are best treated by partial, subtotal or total gastrectomy (Maingot, 1974). When the tumour has been removed completely at operation the prognosis is relatively good, the five year survival has been reported to be 54 per cent (ReMine, 1970).

The morphological resemblance of leiomyosarcoma cells to normal muscle cells depends on the grade of differentiation (Böcker and Strecker, 1975). Smooth muscle cells contain abundant contractile microfilaments in their cytoplasm, both actin and myosin have been demonstrated in these cells and it is reasonable to believe that these are the major proteins involved in the contractile mechanism.

Thin (30–80 Å) and thick (100–350 Å) myofilaments have been described by electron microscopy (Campbell et al., 1971; Cooke and Fay, 1972; Gwynn et al., 1974; Kelly and Rice, 1969; Rosenbluth, 1971; Yamauchi and Burnstock, 1969). The ultrastructure of leiomyosarcoma cells of tumours at various sites have been described: uterus (Fereczy et al., 1971; Böcker and Strecker, 1975), vagina (Tobon et al., 1973), stomach (Kay and Still, 1969), maxillary sinus (Kanabe et al., 1969), and lung (Wang et al., 1974; Pritchett et al., 1975). No sharp line can be drawn ultrastructurally between leiomyosarcomas and leiomyoblastomas (Hajdu et al., 1972; Kay and Still, 1969; Salazar and Totten, 1970). The characteristic features of smooth muscle cells such as myofilament bundles, dense bodies, invaginations of the plasma membrane, polysaccharide cell coat, and cell junctions are usually incompletely developed in tumour cells. The tumour cells in the present study displayed abundant cytoplasmic microfilaments and occasional microtubules. These are structures typical of well differentiated smooth muscle tumours and characterize the myoblastic cell type of leiomyosarcoma (Böcker and Strecker, 1975). The well developed Golgi apparatus, granular endoplasmic reticulum, and free ribosomes found in the cytoplasm of some tumour cells in the present study are typical features of the immature cell type of leiomyosarcoma (Böcker and Strecker, 1975).

Microtubules, which consist of a specific protein, tubulin, perform various functions in different cells. They are widely distributed in eukaryotic cells and are believed to be involved in axonal flow of neurones, ciliary motility, intracellular movements and secretory phenomena in various cells and chromosome movements during mitosis (Dustin, 1972; Inoué and Ritter, 1975). Their presence in a number of the leiomyosarcoma cells in the present study most probably reflects the mitotic activity of the tumours.

The ultrastructure of the gastric leiomyosarcoma cells is quite distinctive. It can be concluded that electron microscopic identification of the ultrastructural features typical of smooth muscle cells, provides a valuable aid in the differential diagnosis of gastric neoplasms.

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