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Case report

Carcinoid tumor of the uterine cervix

A light and electron microscopic study

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Summary. A case of carcinoid tumor of the uterine cervix is reported. The patient was a 76-year-old Japanese woman with a complaint of vaginal bleeding. She was clinically diagnosed as stage IVb carcinoma of the uterine cervix. Light microscopically, the tumor was characterized by formation of solid cell nests and, in limited areas, glandular structures. The tumor cells in solid cells nests showed positive argyrophil reaction but were negative for argentaffin reaction. At the ultrastructural level, the cytoplasm of the tumor cells contain numerous neurosecretory granules, microfilaments and well-developed Golgi complexes. On the bases of histochemical and electron microscopic features of tumor cells, the tumor was diagnosed as carcinoid tumor of the uterine cervix.

Key words: Carcinoid – Uterine cervix – Histopathology – Ultrastructure

The carcinoid tumor of the uterine cervix is a newly established entity of the cervical neoplasm. A well documented case of the tumor was first reported by Albores-Saavedra et al. (1972), as a tumor composed of small cells having a characteristic endocrine arrangement, and fine argyrophil granules were histochemically demonstrated in the cytoplasm. Since this time, the number of reported cases has been increasing (Tateishi et al. 1975; Albores-Saavedra et al. 1976; Kodousek et al. 1976; Daw 1977; Habib et al. 1979; MacKay et al. 1979; Matsuyama et al. 1979; Warner 1979; Mullins and Hillard 1981; Stahl et al. 1981). At the ultrastructural level, the tumor cells contain distinctive neurosecretory type of granules in the cytoplasm, and are regarded as a member of APUD system. Other terms, such as argyrophil cell carcinoma or apudoma, have also proposed to designate this type of cervical neoplasm (Tateishi et al. 1975; Kodowsek et al. 1976). We report here a case of carcinoid tumor of the uterine cervix with a partially adenocarcinomatous appearance.

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Report of a case

A 76-year-old gravida 7, para 7, Japanese woman was admitted to the Department of Gynecology at Ehime University Hospital for work-up of a cervical neoplasm. She complained of vaginal bleeding of 6 months duration. Class V cytology was found by Papanicolau smear. Pelvic examination disclosed a endocervical neoplasm which seemed to extend directry into the parametrium and pelvic wall. Chest X-ray revealed multiple coin lesions in both lungs. The patient was clinically diagnosed as stage IVb, T3b, NX, MI carcinoma of the uterine cervix. Because of the advanced clinical stage, only irradiation and chemotherapy were applicable. The patient died 8 months later. No autopsy was performed.

Materials and methods

Biopsy material was fixed in 10% formalin. In addition to the routine haematoxylin and eosin (H-E), periodic acid-Schiff (PAS), Grimelius' argyrophil and Masson-Fontana's argentaffin stains were prepared for the light microscopic examination.

For electron microscope, small pieces of tissue specimen were immersed in fixative containing 3% glutaraldehyde and 1% paraformaldehyde buffered with 0.1 M sodium cacodylate-HCl solution, pH 7.2, for 2 h at room temperature, followed by the postfixation with 2% osmium tetroxide for 1 h. Blocks of the fixed tissue specimen were immersed in satulated aqueous solution of uranylacetate for 1 h, dehydrated by graded changes of ethanol, then embeded in Epon 812. Thin sections, 0.5 μm in thickness, were cut and stained with toluidine blue for pre-examination by light microscope. Ultrathin sections were cut and stained with uranylacetate and lead citrate, and were examined by JEM-100B electron microscope.

Light microscopic findings

Numerous solid tumor cell nests with various size and shape are observed in most part of the biopsied material. The cell nests are composed of round or polyhedral medium-sized cells with oval vesicular nuclei and moderate amount of eosinophilic cytoplasm (Fig. 1). Cell boundaries are indistinct. Nuclear pleomorphism is minimal and mitotic figures are rarely observed. Darkly stained tumor cells are occasionally noted. Neither keratinizing foci nor intercellular bridges are found. Characteristic histological patterns of carcinoid tumors, such as trabecular arrangement or formation of rosettes, are not detected in the present case. Cell nests are separated each other with thick collagenous stroma. In limited parts, glandular structures are also observed (Fig. 1). In such areas, tumor cells are relatively small and nuclei appear more basophilic. Glandular spaces are filled with PAS-positive materials. Some capillaries are invaded by tumor cells.

Grimelius' staining reveals the presence of argyrophil granules in the cytoplasm of the tumor cells in the solid cell nests. Tumor cells arranged in glandular structures do not show positive reaction with this staining. None of the tumor cells show positive argentaffin reaction with Masson-Fontana's staining. Based on these results, a diagnosis of carcinoid tumor of the uterine cervix associated with partial adenocarcinomatous differentiation was made.

Ultrastructural findings

The areas which are exclusively composed of solid cell nests without glandular elements were taken for electron microscopic examination. Adenocarcinomatous regions were not included in the specimen for the electron microscopy.

Ultrastructurally, the tumor cell nests are composed of polyhedral cells with abundant cytoplasm, in which well-developed cell organelles are seen (Fig. 2). Ocasionally, degenerating cells characterized by the dark cytoplasm and dilated cistern of both Golgi complexes and rough endoplasmic reticulum are observed (Fig. 2).

The most striking feature of the cytoplasm is the presence of granules of neurosecretory type (Fig. 3). These granules are oval to round in shape, are from 120 to 300 nm in diameter, and are enclosed by a single limiting membrane. Each granule has a electron-dense core at

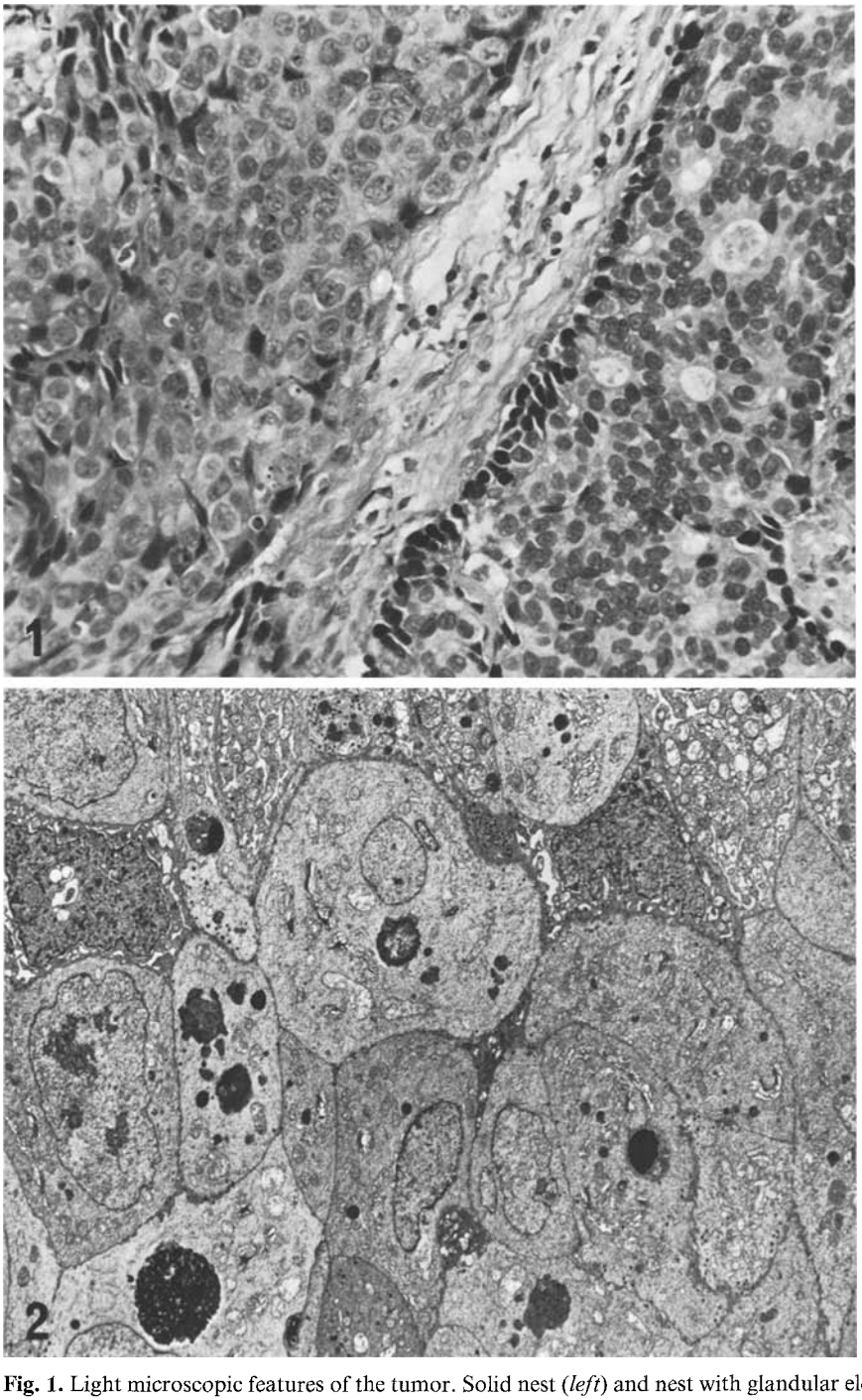

Fig. 1. Light microscopic features of the tumor. Solid nest (*left*) and nest with glandular element (*right*) are noted. H-E, × 400

Fig. 2. Closely packed tumor cells with adundant cytoplasm. In this field, although neurosecretory granules are relatively small in number, most tumor cells contain granules. Golgi complexes and lysosomes are prominent. × 3,500

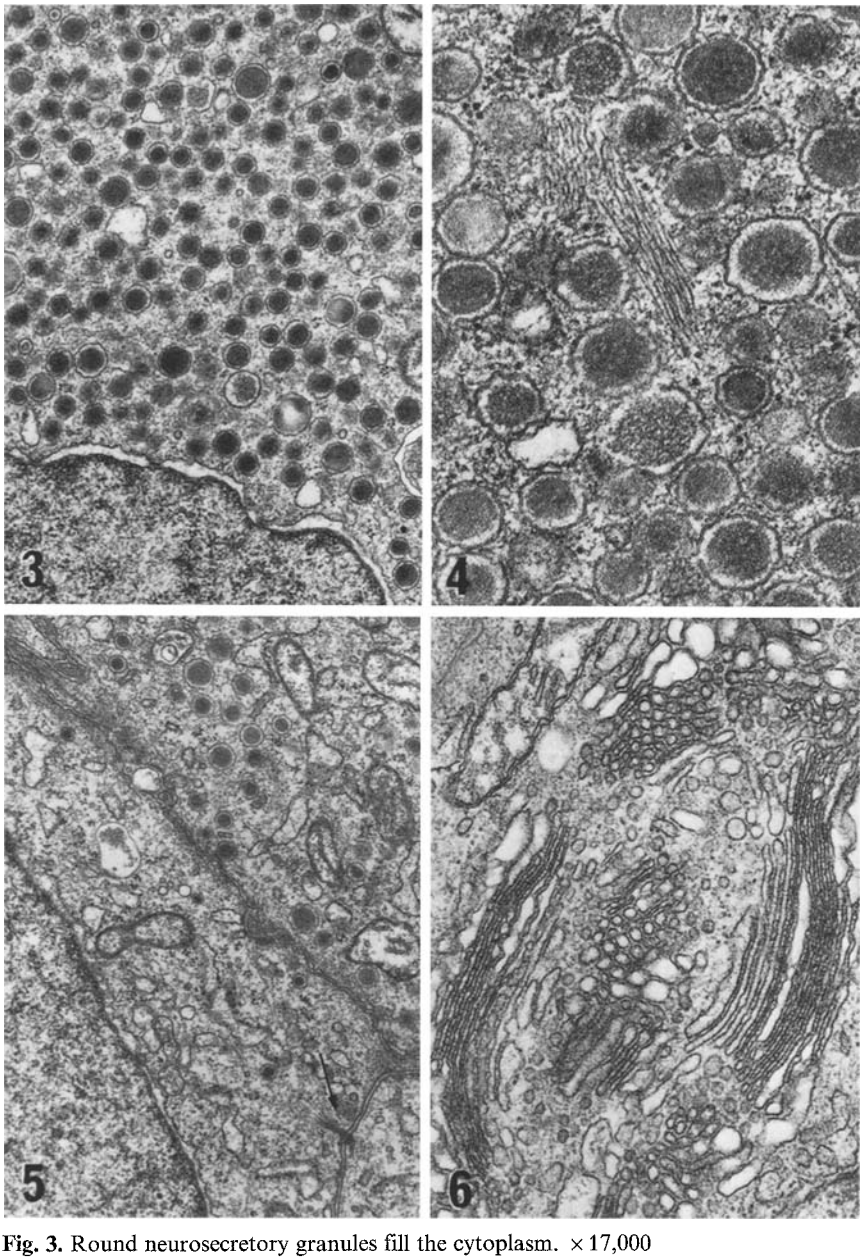

Fig. 3. Round neurosecretory granules fill the cytoplasm. × 17,000

Fig. 4. High magnification of neurosecretory granules. Microfilaments are also evident. × 50,000

Fig. 5. Microfilaments tend to accumulate beneath the cell boundary. *Arrow* indicates desmosome. × 12,000

Fig. 6. Prominent Golgi complexes. × 22,000

the center and a enclosing electron-lucent halo is seen inside the limiting membrane (Fig. 4). Slight variation is noted in the electron density of the core of the granules, smaller ones seem to be more electron-dense than larger ones. Although the number of the granules extensively varies from cell to cell, most tumor cells contain the granules in the cytoplasm (Fig. 2). In the tumor cells in which only a small number of granules are present, the granules tend to accumulate at the peripheral part of the cytoplasm, close to the cell boundary. No granules of pleomorphic type, which are reported in argentaffin carcinoid tumors, are observed.

Intracytoplasmic microfilaments are also observed in the most of the tumor cells (Fig. 4). They are scattered throughout the cytoplasm, or are arranged in parallel array along the cell border (Fig. 5). They are sometimes terminated in the desmosomes, frequently encountered intercellular connecting device (Fig. 5). Cytoplasmic membrane of the adjacent cells is closely apposed. Most tumor cells exhibit well-developed Golgi complexes (Fig. 6). Lysosomes are also prominent.

Discussion

The carcinoid tumor of the uterine cervix is a rare entity. Albores-Saavedra et al. (1979) found 14 cases in a review of more than 4000 malignant tumors of the uterine cervix. Tateishi et al. (1975) also reparted 5 cases in a survey of 97 cases of invasive cervical carcinomas. The tumors have been classified into two groups based on the histopathological features, well differentiated and poorly differentiated types (Albores-Saavedra 1976). The well differentiated type is characterized by the medium-sized cells which are arranged in solid-sheets, ribbons, trabeculae or pseudoglandular configulations, while the poorly differentiated type is composed of small tumor cells with scanty cytoplasm showing a comparable histological appearance to oat cell carcinoma of the lung. Similar histological variation was also described by others (Tateishi et al. 1975). Although the present case seems to be a well differentiated type because of the size and shape of the tumor cells, the tumor does not show any distinctive light microscopic architectures which have been described in well differentiated type except the presence of some glandular structures. This initially caused a difficulty for us in making a histopathological diagnosis of carcinoid tumor until histochemical and electron microscopic examination was carried out. This experience prompts us to speculate that there may be more cases of carcinoid tumors of the uterine cervix among the cervical neoplasms which were previously diagnosed as small cell nonkeratinizing squamous cell carcinoma or adenosquamous carcinoma.

Our ultrastructural observation reinforces the previously reported findings in carcinoid tumors of the uterine cervix (Tateishi et al. 1975; Albores-Saavedra et al. 1976; Habib et al. 1978; Matsuyama et al. 1979). The presence of neurosecretory type of granules and abundant intracytoplasmic microfilaments have been reported to be the most characteristic feature in this type of tumors, as well as in apudomas of other sites. In addition, well developed Golgi complexes and frequent occurrence of desmosomal attachment were also prominent features in our case.

The histogenesis of the carcinoid tumor of the uterine cervix seems to be somewhat obscure. Feyrter (1951) demonstrated the presence of diffuse endocrine cell system, "argyrophilen Helle-Zellen-System", in the urogenital

organs including the uterine cervix. These cells are normally present in a small number in the cervical mucosa, and Tateishi et al. (1975) postulated that the carcinoid tumors arose from these argyrophil cells. A similar opinion on histogenesis was also propsed by others (Albores-Saavedra et al. 1979). Mullins and Hillard (1981) proposed another possible theory based on their experience of a cervical carcinoid tumor associated with endocervical adenocarcinoma. They proposed common mesodermal totipotential precursor cells which are capable of differentiation into columnar cells, squamous cells or argyrophil cells in the uterine cervix. A similar theory on the histogenesis is also proposed in cases of carcinoid tumors of the gastrointestinal tract (Miller and Sumner 1982). APUD cells in the gastrointestinal tract were shown experimentally to develop from undifferentiated precursor cells instead of cells originating from the neural crest (Cheng and Leblond 1974). The frequent occurrence of the composite type of mixed adenocarcinoma and carcinoid tumor may also substantiate this theory. At present, the common precursor cell theory seems to be the more convincing in order to explain the histogenesis of the carcinoid tumor of the uterine cervix.

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