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Ovarian Mucinous Cystadenoma with Mural Nodule of Anaplastic Carcinoma

The occurrence of malignant mural nodule in benign cystic common epithelial tumor of the ovary have been reported in only three cases; the case one was mucinous cystadenoma with a mural nodule of fibrosarcoma and the others were of carcinomas. Our case was another rare case of ovarian mucinous cystadenoma with mural nodule of anaplastic carcinoma in a 42-year-old woman. The cystadenoma had an unilocular cystic cavity and a mural nodule with thick multinodular solid wall. The internal cystic wall was lined with mucinous cystadenoma without any malignant features. The mural nodule showed anaplastic carcinomatous differentiation and its nature was confirmed by immunohistochemistry and electron microscopy. This tumor had metastasized to the right salpinx, uterus, cul-de-sac, periureter and mesentery.

Key Words: *Ovary; Cystadenoma, mucinous; Mural nodule, anaplastic carcinoma*

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INTRODUCTION

Solid mural nodule within a mucinous cystic ovarian tumor is extremely rare (1). Prat and Scully (2) first reported mucinous tumors of the ovary with "sarcoma-like nodules" describing reactive lesions that histologically mimicked sarcoma. Since then, the mural nodules which were related to mucinous and serous tumors have been reported (3). The term "sarcoma-like nodule" has been used not only to describe the nodules with reactive or pseudosarcomatous changes but also the nodules containing anaplastic carcinoma (4), sarcoma (5) and carcinosarcoma (6). We report a case of ovarian mucinous cystadenoma with an anaplastic carcinomatous mural nodule. The carcinomatous nature of the nodule was confirmed by immunohistochemistry and electron microscopy.

CASE REPORT

A 42-year-old unmarried lady was admitted to the hospital because of a painless pelvic mass. Her gynecologic and obsteric histories were not remarkable. She had regular 30-day cycles. Physical examination revealed a large, fixed, painless lower abdominal mass in the region of the right ovary. The uterus was normal in size but fixed. The left adnexa was unremarkable.

A transabdominal ultrasound study demonstrated a 14-cm round mass with mixed cystic and solid echogenicities in the right lower abdomen. It was adherent to the pelvic wall with multiple echogenic spots in right cul-de-sac and a semisolid nodule in the right cervical wall. Serum CA125 was increased (46.38 U/mL). A posteroanterior chest revealed a small patchy density in the right lower lung, suggestive of pneumonia. The other laboratory data were normal.

Staging exploratory laparotomy was performed. A large cystic mass was confirmed, and multiple metastatic nodules were found in the cul-de-sac, the mesentery of the terminal ileum and the right periureter. A frozen section diagnosis for the right adnexal mass during operation was made to be ovarian malignancy. An extended radical salpigo-oophorectomy with tumor resection, total hysterectomy, lymph node dissection, partial omentectomy and appendectomy were performed. Peritoneal washing fluid was obtained. The postoperative course was uneventful, except for right hydronephrosis due to the periureteral mass. She was treated with adjuvant chemotherapy with cisplastin, adriamycin and cyclophosphamide.

Pathological examinations

All surgical specimens were fixed in 10% buffered formalin and embedded in paraffin for routine histopathologic examination. Five-micrometer tissue sections

were stained with hematoxylin and eosin (H&E), periodic acid Schiff (PAS) and alcian blue (pH 2.5).

Representative formalin-fixed paraffin-embedded sections from the mural nodule were studied with indirect immunoperoxidase techniques (avidin-biotin complex) (7). The reaction was developed with 3-amino-9-ethylcarbazole substrate-chromogen (DAKO). The primary monoclonal and polyclonal antisera used are as follows: (a) anti-cytokeratin (DAKO); (b) anti-carcinoembryonic antigen (DAKO); (c) anti-desmin (Signet Laboratories); (d) anti-vimentin (Signet Laboratories); (e) anti-myoglobin (Signet Laboratories).

Formalin-fixed tissue taken from the mural nodule was also processed for electron microscopic examination. The tissue was fixed in 2.5% glutaraldehyde and postfixed in 1% osmium tetroxide, dehydrated through graded alcohols and propylene oxide, and embedded in epoxy resin. Thick sections were cut for light and ultrastructural correlation and stained with toluidine blue. Thin sections were double-stained with uranyl acetate and lead citrate and examined with a Hitachi H-100 electron microscope.

Gross pathology findings

The right ovarian cystic mass was previously opened and measured 13.5 cm in diameter. The outer ovarian surface revealed multiple small hemorrhagic nodules and adhesion. The cut surface of the right ovary showed a predominantly unilocular cyst with focal wall thickening. There was a large protruding solid mural nodule, measuring 12×12×6 cm. The cystic space was filled by dark-brown bloody fluid. The inner cystic surface was smooth. The mural nodule was firm, grey-yellow with focal hemorrhage and necrosis. The right salpinx measured 11 cm in length and 1.0 cm in diameter, and was adhered to the right ovarian mass (Fig. 1). The left adnexa were unremarkable. The uterus showed a solid mass, measuring 5×2.5×2.5 cm in posterior serosal surface of lower segment. The tissues from cul-de-sac, terminal ileal mesentery and right periureter revealed grey-yellow solid mass. The omentum and appendix were unremakable.

Microscopic and immunohistochemical findings

On light microscopic examination of right ovarian mass, the cyst wall was lined by a single layer of mature mucinous epithelium and consisted mostly of nonspecific fibrous tissue (Fig. 2A). Near the mural nodule and partially covering it, the lining was also lined by a single layer of mature mucinous epithelium with focal mild nuclear atypia (Fig. 2B). The surface of the mural nodule was denuded or ulcerated, and covered by thick fibrin tissue with evidence of hemorrhage, chronic inflammatory reaction and calcification (Fig. 2C). There was no findings of proliferation of the lining epithelium.

The mural nodule was made up of a bizarre, pleomorphic, densely cellular population with a sarcomatous appearance. Although generally well demarcated, numerous clusters of neoplastic cells invaded the surrounding stroma and blood vessels. The individual tumor cells are made up of round to oval or spindle-shaped hyperchromatic nuclei with prominent nucleoli and abundant eosinophilic moderately granular cytoplasm with well-defined borders (Fig. 3A). Many of atypical tumor cells were multinucleated and showed several large nucleoli. Mitotic figures were frequently seen. There were, in addition, foci of clearly recognizable glandular and acinar formation in intimate admixture with the anaplastic component (Fig. 3B). Small areas of necrosis, hemorrhage, foam cell accumulation, and diffuse mixed inflammatory infiltrate were also seen. Occasional tumor cells in the nodule were alcian blue-positive. PAS stain was negative.

The right ovarian capsule was invaded by pleomorphic tumor cells. The right salpingeal wall showed many tumor emboli, but the salpingeal mucosa was intact. The uterus, and the tissues from the cul-de-sac, terminal ileal mesentery and right periureter showed an evidence of tumor extension. The contralateral adnexa, omentum, appendix and pelvic lymph nodes were unremakable. The cytology of peritoneal washing showed the tumor cells.

The pleomorphic tumor cells in the mural nodule showed a diffuse cytoplasmic positivity for cytokeratin

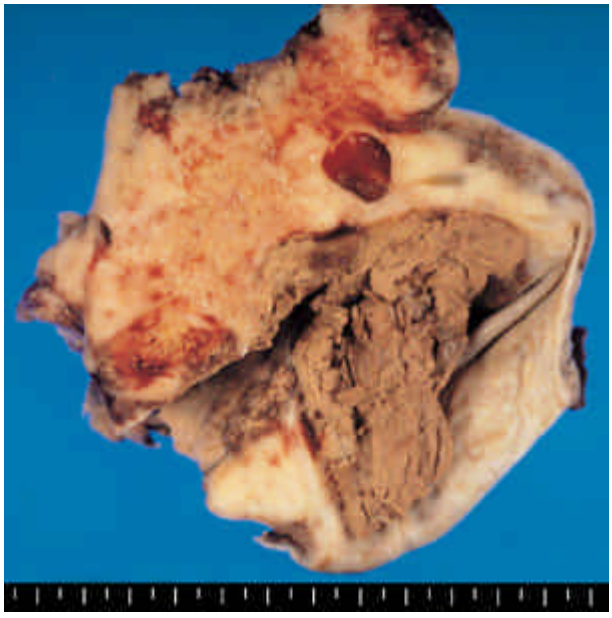

Fig. 1. A unilocular mucinous tumor of the ovary with a mural nodule that protrudes into the lumen and shows marked necrosis, and adhesion to the salpinx.

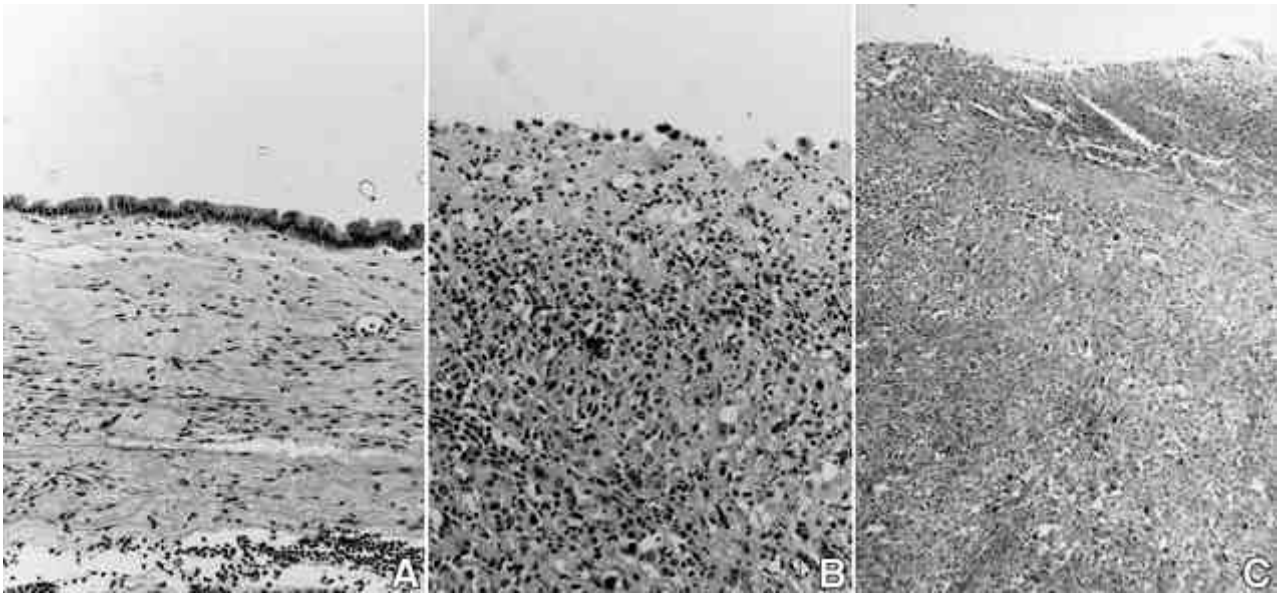

Fig. 2. Unilocular cystic wall. A: Epithelial lining of mucinous cystadenoma. B: A single layer of mature mucinous surface epithelium with mild atypia over the nodule. C: A thick fibrin cap covering the ulcerate surface of the mural nodule (H&E, A&B: ×100, C: ×40).

and carcinoembryonic antigen, and a focal positivity for vimentin. Desmin and myoglobin were negative.

Electron microscopic findings

Electron microscopic examination showed that the pleomorphic tumor cells of the mural nodule were composed of groups of gland-forming cells surrounded by an incomplete basal lamina. Intracellular and intercellular lumina lined by stubby microvilli were found (Fig. 4). The cytoplasm contained mitochondria, rough endoplasmic reticulum, lipid droplets and Golgi complex. Junctional complexes were found.

DISCUSSION

Prat and Scully (2) reported the first seven cases and

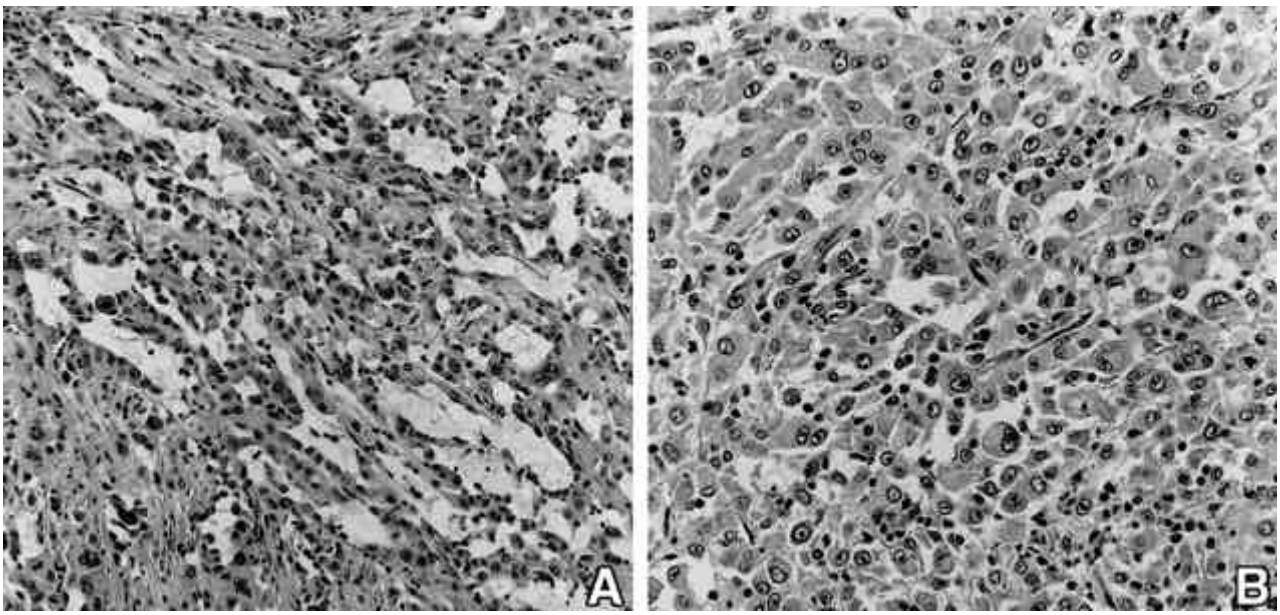

Fig. 3. Mural nodule. A: Glandular formation of the pleomorphic cells. B: Sheets of anaplastic carcinoma cells with pleomorphic nuclei and abundant cytoplasm with well-defined cytoplasmic borders (H&E, ×250)

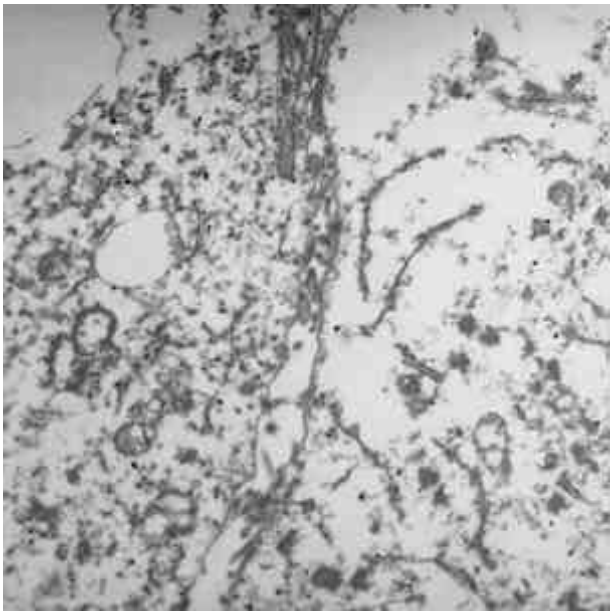

Fig. 4. Tumor cell showing intercellular lumina lined by stubby microvilli. The cytoplasm contains mitochondria and rough endoplasmic reticulum.

reclassified them. Three patterns were encountered in the mural nodules: pleomorphic and epulis-like, pleomorphic and spindle-cells, and giant cell-histiocytic. They concluded that these nodules were reactive sarcoma-like lesions resulting from hemorrhage in the cyst walls. The epithelial components of the tumors were borderline malignancy and well-differentiated carcinoma. The same authors also reported two cases of true sarcomatous nodules within mucinous ovarian tumors (5). One of the tumors was a fibrosarcoma associated with a mucinous cystadenoma; the other was an undifferentiated sarcoma in a mucinous cystadenocarcinoma.

In 1982 Prat et al. (4) again described another histologic variant of the mural nodules within mucinous ovarian tumors. The nodules were composed of anaplastic carcinomatous cells. The lining epithelial components of the tumors were mucinous adenocarcinoma and mucinous tumor of borderline malignancy. Subsequently, the epithelial nature of the malignant cells in the nodules was confirmed by electron microscopy (9) and immunohistochemistry (10). The other report (11) was interesting in that a microfocus of anaplastic carcinoma was present within a sarcoma-like mural nodule.

Pathologically, mural nodules of anaplastic carcinoma may be confused on gross and microscopic examinations with true sarcomas and sarcoma-like nodules. Although distinguishing of anaplastic carcinoma from sarcoma may not have any prognostic significance, both of them should be distinguished from sarcoma-like nodules because of the favorable prognosis of the latter. Mural nodules with anaplastic carcinoma have a more homogeneous cell population than reactive nodules, a poor microscopic circumscription, a stromal or vascular invasion, and an absence of a prominent inflammatory reaction (4, 8). In contrast to the mural nodules with anaplastic carcinoma, the sarcoma-like nodules show a heterogeneous population epulis type, a sharp circumscription, and no vascular or stromal invasion (8). The presence of glands and intracellular mucin within the nodule of our case made the distinction from sarcomatous and sarcoma-like nodule easy. The carcinomatous nature of our case was also

Table 1. Ovarian tumors with mural nodules of anaplastic carcinoma

Author	Histologic type	
	Epithelial tumor	Mural nodule
Chan et al. (1)	Mucinous, borderline	Carcinoma
Clarke (3)	Serous, borderline	Carcinoma
Prat et al. (4)	Mucinous, carcinoma	Carcinoma
	Mucinous, borderline	Carcinoma
	Mucinous, carcinoma	Carcinoma
	Mucinous, carcinoma	Carcinoma
Baergen et al. (8)	Mucinous, carcinoma	Carcinoma
Czernobilsky et al. (9)	Mucinous, carcinoma	Carcinoma
Hayman et al. (10)	Mucinous, carcinoam	Carcinoma
Rosa et al. (12)	Serous, low malignant potential	Carcinoma
Nichols et al. (13)	Mucinous, low malignant potential	Carcinoma
	Mucinous, low malignant potential	Carcinoma
	Mucinous, carcinoma	Carcinoma
	Mucinous, benign	Carcinoma & reactive
Kessler et al. (14)	Mucinous, carcinoma(?)	Carcinoma
Yamana et al. (15)	Mucinous, carcinoma	Giant cell carcinoma
Buzzi et al. (16)	Mucinous, carcinoma	Carcinoma
Jones et al. (17)	Mucinous, benign	Neuroendocrine carcinoma
Present case	Mucinous, benign	Carcinoma

attested to by the presence of homogeneous pleomorphic cell population, an invasive margin of the nodule, many vasular invasions, absence of prominent inflammatory reaction and metastasis to extraovarian tissue, and confirmed by immunohistochemistry and electron microscopy. Our pleomorphic cells were positive in both cytokeratin and vimentin. Immunohistochemistry has showed that carcinoma cells in the nodules were positive for cytokeratin (1, 3, 10, 12, 13), and vimentin was negative (1, 3, 12) or weakly positive (13). Electron microscopy showed epithelial differentiation of the tumor cells within the mural nodule, including formation of intercellular and intracellular lumina, microvilli, and intercellular junctional complexes, which are similar findings to those of previous reports (1, 3, 8, 9).

Eighteen cases of ovarian mural nodules composed of anaplastic carcinomas have been reported (1, 3, 4, 8-10, 12-17), and one present case is added: seventeen in mucinous tumors (10 cystadenocarcinomas, 4 borderline and 3 benign) and two in serous ovarian tumors of borderline malignancy (Table 1). Only three cases of mucinous cystadenomas with malignant mural nodules have been reported: the one mural nodule was a fibrosarcoma (5), and two nodules were a combined moderately differentiated carcinoma-reactive spindle cell nodule (13) and a neuroendocrine carcinoma (17).

The pathogenesis of nodules of anaplastic carcinoma within mucinous ovarian tumors is still a mystery. Czernobilsky et al. (9) believe that they develop by progressive dedifferentiation of the mucinous carcinoma cells with concomitant loss of ability to produce mucin. This is based on the observation of their single case in which foci of mucinous carcinoma merged with anaplastic elements. In our case there was no discrete continuity between the associated epithelial component of mucinous cystadenoma and the carcinomatous mural nodule. More case studies are needed before the pathogenesis of this interesting lesion can be fully substantiated.

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