Clinical Case Report

Ovarian mucinous cystic tumor associated with sarcomatous mural nodule and benign Brenner tumor
A case report and literature review
Shaolong Yang, MD\textsuperscript{a}, Li Wang, MD\textsuperscript{b}, Kai Sun, MD\textsuperscript{c,∗}

Abstract
Rationale: Ovarian mucinous tumor with malignant mural nodule is exceedingly rare. We report a case of ovarian mucinous cystic tumor associated with sarcomatous mural nodule and benign Brenner tumor and accompanied by nodular histiocytic aggregates in the greater omentum.

Patient concerns: A 60-year-old postmenopausal woman was presented with a history of one month of lower abdominal discomfort, abdominal distension, nausea, and vomiting. A physical examination revealed a hard, palpable mass with mild tenderness in her right lower abdomen.

Diagnoses: The mucinous tumor was solid and cystic and contained benign, borderline, and malignant elements. Within the solid areas, two nodules representing pleomorphic undifferentiated sarcoma and benign Brenner tumor were identified. The diagnosis of malignant mural nodule was based on vascular invasion and marked nuclear atypia, including atypical mitoses and mitotic activity.

Interventions: Bilateral salpingo-oophorectomy and partial omentectomy were performed. Malignant cells were not found on cytologic examination of the peritoneal washing fluid. The patient underwent three cycles of chemotherapy with 210 mg paclitaxel liposome via an intravenous drip, 20 mg nedaplatin via an intravenous drip, and 80 mg nedaplatin via intraperitoneal perfusion.

Outcomes: The patient has been followed up for 3 years without evidence of tumor recurrence and metastasis.

Lessons: Careful classification of a mural nodule is important to triage patients in need of aggressive adjuvant treatment.

Abbreviations: CD = cluster of differentiation, CK = cytokeratin, FIGO = International Federation of Gynecology and Obstetrics.

Keywords: Brenner tumor, mucinous cystic tumor, mural nodule, ovarian tumor, pleomorphic undifferentiated sarcoma

1. Introduction
Ovarian mucinous cystic tumors are commonly associated with other types of ovarian neoplasms, for example, Brenner tumor.\textsuperscript{[1]} However, ovarian mucinous tumors with mural nodules are rare.

Most such nodules are reactive or benign, although there have been sporadic reports of malignant mural nodules, such as anaplastic carcinoma, clear cell carcinoma, and neuroendocrine carcinoma, giant-cell carcinoma, carcinosarcoma, and sarcoma. The most common type of mural nodular malignancy is anaplastic carcinoma; however, a few cases of sarcoma have also been reported.\textsuperscript{[2–4]} Cases of pleomorphic undifferentiated sarcoma as a primary ovarian tumor\textsuperscript{[5]} or as a component of a teratoma\textsuperscript{[6]} are rare, and to our knowledge, pleomorphic undifferentiated sarcoma as a malignant mural nodule in an ovarian mucinous neoplasm has never been reported. Herein, we describe the case of a postmenopausal woman with an ovarian intermixed mass composed of a mucinous cystic tumor and mural nodules of pleomorphic undifferentiated sarcoma and benign Brenner tumor and associated with multifocal nodular histiocytic aggregates on the surface of the greater omentum. The clinicopathological characteristics in this patient are discussed.

2. Case presentation
A 60-year-old postmenopausal woman (gravida 4, para 1) was presented with a history of one month of lower abdominal discomfort, abdominal distension, nausea, and vomiting. A physical examination revealed a hard, palpable mass with mild tenderness in her right lower abdomen. An ultrasound scan and a computed tomography scan of the abdomen revealed a large oval cystic and solid mass measuring 9.4 cm × 8.4 cm × 8.3 cm with irregular separation. The preoperative serum levels of cancer
antigen (CA)-125, CA19-9, CA72-4, human epididymis protein 4, carcinoembryonic antigen, and alpha-fetoprotein were all within the normal range. A laparotomy revealed a large right ovarian cystic mass with an old surface rupture (1.0 cm × 1.0 cm) and proliferation of granulation tissue. Bilateral salpingo-oophorectomy and partial omentectomy were performed. Malignant cells were not found on cytologic examination of the peritoneal washing fluid. The tumor was staged as International Federation of Gynecology and Obstetrics (FIGO) grade IC. The postoperative course was uneventful. The patient underwent three cycles of chemotherapy with 210mg paclitaxel liposome via an intravenous drip, 20mg nedaplatin via an intravenous drip, and 80mg nedaplatin via intraperitoneal perfusion. She has been followed up for 3 years without evidence of tumor recurrence and metastasis.

Macroscopic examination of the right ovary showed a brownish mass with a smooth outer surface. The mass was composed of multilocular cysts filled with turbid tan fluid or clear mucinous material. Yellowish papillary structures were found projecting into the cystic cavities. The septa of these cysts had uneven thickness, from 0.2 cm to 0.5 cm. The mass contained two distinct solid nodules. The larger one measured 3.0 cm × 2.8 cm × 2.5 cm, protruded into the cystic lumen, and was well-circumscribed. It was gray-brown, with a medium consistency and visible hemorrhage and necrosis. The smaller nodule measured 1.6 cm in diameter and was gray and hard. The right fallopian tube was found adherent to the capsule of the tumor. The left ovary and fallopian tubes were unremarkable. The surface of the greater omentum showed numerous small sallow nodules of various sizes, from 0.2 to 0.4 cm in diameter.

Microscopic examination showed that the right ovarian tumor was composed of three distinct components. The cystic component was preponderant, and the cysts were lined largely by low columnar or cuboidal well-differentiated mucinous epithelium, indicating a benign tumor with focal borderline changes and intraepithelial carcinoma (Fig. 1A). The second component was mesenchymal. The larger mural nodule underneath the mucinous epithelium consisted of ovoid mononucleated cells and numerous multinucleated osteoclast-like giant cells (Fig. 1B). The mononucleated cells contained abundant eosinophilic cytoplasm with ill-defined borders and showed marked nuclear pleomorphism and atypia with vesicular hyperchromatic nuclei and prominent nucleoli. Multinucleated giant cells were distributed evenly between the mononuclear cells. Foci of extensive or focal necrosis and hemorrhage presented throughout the tumor, but only a sparse inflammatory infiltrate was observed. Local hypocellular areas formed spongy-appearing foci, which were filled with diffusate or erythrocytes. Mitotic figures were frequent and sometimes atypical (Fig. 1C), and approximately 25 mitoses per 10 high-power fields were recorded. Vascular invasion was also observed in this mural nodule (Fig. 1D). The larger nodule was sharply demarcated from the epithelial elements. As the third component, the smaller nodule consisted of nests of transitional epithelium, which embedded in a dense fibromatous stroma (Fig. 1E). Occasional transitional nests with central dilation were present in the transition areas of mucinous tumor and Brenner tumor. The greater omental lesions consisted of little nests or sheets of cohesive polygonal-to-oval epithelioid cells with distinct cell borders, abundant cytoplasm, and inconspicuous nucleoli (Fig. 1F).

Immunohistochemical staining for two mural nodules was performed using the Ventana BenchMark XT system (Roche Ltd., Basel, Switzerland). The mononucleated and multinucleated cells in the sarcomatous mural nodule were positive for vimentin (Fig. 2A), cluster of differentiation (CD)56, CD68 (Fig. 2B), and α-smooth muscle actin (Fig. 2C). The multinucleated osteoclast-like giant cells were positive for vimentin (Fig. 2D), CD117 (Fig. 2E), and CD68 (Fig. 2F). The multinucleated osteoclast-like giant cells were negative for α-smooth muscle actin (Fig. 2G) and CD56 (Fig. 2H). The mononucleated cells in the sarcomatous mural nodule were negative for α-smooth muscle actin (Fig. 2I), CD117 (Fig. 2J), and CD68 (Fig. 2K). The multinucleated osteoclast-like giant cells were negative for α-smooth muscle actin (Fig. 2L), CD117 (Fig. 2M), and CD68 (Fig. 2N). The mononucleated cells in the sarcomatous mural nodule were positive for vimentin (Fig. 2O), CD117 (Fig. 2P), and CD68 (Fig. 2Q). The multinucleated osteoclast-like giant cells were positive for vimentin (Fig. 2R), CD117 (Fig. 2S), and CD68 (Fig. 2T). The mononucleated cells in the sarcomatous mural nodule were negative for α-smooth muscle actin (Fig. 2U), CD117 (Fig. 2V), and CD68 (Fig. 2W). The multinucleated osteoclast-like giant cells were negative for α-smooth muscle actin (Fig. 2X), CD117 (Fig. 2Y), and CD68 (Fig. 2Z).
human alpha1 antichymotrypsin, but negative for pan-cytokeratin (CK), CK7, CK20, desmin, α-smooth muscle actin, calretinin, CD10, and P63. Some mononucleated cells showed positive staining for S-100 protein. Staining with CD34 revealed intravascular tumor emboli and vascular invasion (Fig. 2C). MIB-1 staining indicated that the mononucleated cells had very high proliferative activity (approximately 35%). The mononuclear cells on the surface of the greater omentum showed diffuse and strong reactivity against vimentin (Fig. 3A) and CD68 (Fig. 3B). There were a few scattered mesothelial cells among the mononuclear cells that stained positive for calretinin (Fig. 3C) and CK5/6. MIB-1 staining indicated that these cells had very low proliferative activity (approximately 3%).

The final diagnosis was ovarian mucinous cystic tumor (including mucinous cystadenoma, mucinous cystadenoma of borderline malignancy, and intraepithelial carcinoma) associated with mural nodules of pleomorphic undifferentiated sarcoma and benign Brenner tumor, and accompanied by nodular histiocytic aggregates in the greater omentum.

3. Discussion

Mural nodules of different origins have been described in ovarian mucinous tumors in a number of reports.[2,3,7] Sarcoma-like mural nodules are the most common ones and have a favorable prognosis. Malignant mural nodules are infrequent, including foci of anaplastic carcinoma and sarcomatous or carcinomasarcomatous mural nodules. Although the relationship between ovarian mucinous tumor and Brenner tumor is well known, the coexistence of three types of ovarian tumors has not yet been reported. This report describes an ovarian intermixed tumor composed of mucinous cystic tumor, mural nodules of pleomorphic undifferentiated sarcoma and benign Brenner tumor, and accompanied by nodular histiocytic aggregates in the greater omentum.

This tumor was composed of malignant epithelial and mesenchymal elements, which distinguished it from a malignant mixed mesodermal tumor. Although the sarcomatous nodule was observed within the ovarian mucinous cystic tumor, the nodule was sharply demarcated from the epithelial component without an intimate admixture of neoplastic epithelium and sarcoma. In addition, the epithelial component showed mucinous cystadenoma of borderline malignancy with focal intraepithelial carcinoma, which is different from the high-grade adenocarcinoma of malignant mixed mesodermal tumor. The immunoprofile of the sarcomatous component in this case failed to assign the nodule to any of the other sarcomas due to its lack of immunoreactivity for markers of smooth muscle, skeletal muscle, and endothelial differentiation, in addition to its negativity for epithelial and mesothelial markers. Therefore, it was interpreted as a pleomorphic undifferentiated sarcoma, not otherwise specified.

Mural nodules of pleomorphic undifferentiated sarcoma have similar histomorphological features with sarcoma-like mural nodules, including a composition of mononucleated cells and multinucleated giant cells, cellular pleomorphism and atypia, numerous mitotic figures, and extensive necrosis; therefore, their differential diagnosis is very difficult. Prat and Scully reported

![Figure 2. Immunohistochemical features of mural nodule of pleomorphic undifferentiated sarcoma. Mononucleated and multinucleated cells are positive for vimentin (A, ×200) and CD68 (B, ×200). CD34 staining shows tumor cells infiltrating capillary vessels (C, ×400).](image)

![Figure 3. Immunohistochemical features of nodular histiocytic aggregates in the greater omentum (×200). The mononuclear cells on the surface of the greater omentum show diffuse and strong reactivity against vimentin (A), CD68 (B), and scattered positivity for calretinin (C).](image)
Numerous atypical mitotic figures are present in these tumors, which are likely to behave aggressively. The mural nodule is an exceedingly rare neoplasm, and an extensive review of the English literature showed only nine well-documented cases. Roma et al. reported that up to 27% of Brenner tumors were associated with sarcomatous mural nodules, and malignant Brenner tumors were associated in 47% of mucinous tumors. Many morphological, immunohistochemical, and molecular studies suggest a common origin of sarcomatous nodules and mural nodules, which are in the early clinical stage and undergo appropriate treatments. Although ovarian mucinous tumors are rarely associated with sarcomatous mural nodules, reports of such cases have been described in the literature.

### Table 1

| References (year) | Cases | Epithelial ovarian mucinous tumor | Tumor size (cm) | Mural nodule | Nodule size (cm) | Age (years) | FIGO stage | Therapy |
|-------------------|-------|----------------------------------|----------------|-------------|----------------|-------------|------------|---------|
| McFarland (2015)  | 2     | Cystadenocarcinoma               | 29 cm in maximum diameter | Osteosarcoma | 2 cm          | 34          | IA         | TAH + BSO + Omen | NED, 18 months |
| Desouki (2014)    | 1     | Borderline cystadenocarcinoma    | 11 × 5 × 2 cm | Osteosarcoma | -             | 18          | IC         | UO      | NED, 12 months |
| Rahilly (1994)    | 1     | Cystadenocarcinoma               | 4.0 × 3.6 × 2.1 cm | High grade sarcoma | 3.0 to 11.0 cm | 25          | IA         | UO      | - |
| Tsujimura (1992)  | 1     | Cystadenocarcinoma               | 12 × 9 × 6 cm | Fibrosarcoma | -             | 69          | IB         | TAH + BSO + append | NED, 3 months |
| Buijn (1987)      | 1     | Cystadenocarcinoma               | 15 cm in diameter | Rhabdomyosarcoma | 15 × 12 × 11 cm | 57          | IA         | USO + Omen | - |
| Ongkasuran (1983) | 1     | Cystadenoma                      | 17 cm in diameter | Fibrosarcoma | 4.0 × 2.5 cm | 27          | IA         | USO + append | - |
| Pat (1979)        | 2     | Cystadenoma                      | 16.0 × 10.5 × 9.0 cm | Fibrosarcoma | 10.0 × 4.5 cm | 61          | IA         | TAH + BSO + append + RT | Died of hepatic metastases, 1.5 years |
| Present case      | 1     | Borderline cystadenoma with intraepithelial carcinoma | 9.4 × 8.4 × 8.3 cm | Pleomorphic undifferentiated sarcoma and benign Brenner tumor | 3.0 × 2.8 × 2.5 cm and 1.6 cm in diameter | 60          | IC         | BSO + Omen + CHt | NED, 3 years |

- = unknown, appen = appendectomy, BSO = bilateral salpingo-oophorectomy, CHt = chemotherapy, FIGO = International Federation of Gynecology and Obstetrics, NED = no evidence of disease, Omen = omentectomy, RT = radiation therapy, TAH = total abdominal hysterectomy, UO = unilateral oophorectomy, USO = unilateral salpingo-oophorectomy.
report of such a complex tumor arising in an ovarian mucinous cystic tumor.

Author contributions
Methodology: Shaolong Yang, Li Wang.
Resources: Shaolong Yang, Li Wang.
Writing – original draft: Shaolong Yang, Kai Sun.

References
[1] Tafe LJ, Muller KE, Ananda G, et al. Molecular genetic analysis of ovarian Brenner tumors and associated mucinous epithelial neoplasms: high variant concordance and identification of mutually exclusive RAS driver mutations and MYC amplification. Am J Pathol 2016;186:671–7.
[2] McFarland M, Dina R, Fisher C, et al. Osteosarcoma as malignant mural nodule in ovarian mucinous neoplasms of intestinal type: report of 2 cases. Int J Gynecol Pathol 2015;34:369–73.
[3] Desouki MM, Fadare O, Kanbour A, et al. Immunophenotype and K-RAS mutation in mucinous ovarian adenocarcinoma with mural nodule of high-grade sarcoma: case report. Int J Gynecol Pathol 2014;33:186–90.
[4] Zhang Y, Yuan Z, Sun K, et al. Ultrasonic and pathological characteristics of ovarian mucinous cystic tumors with malignant mural nodules: two cases report. Medicine (Baltimore) 2017;96:e8636.
[5] Kurtoglu E, Celik H, Kokcu A, et al. Undifferentiated pleomorphic sarcoma with focally rhabdomyosarcomatous differentiation of the ovary. Eur J Gynaecol Oncol 2016;37:401–3.
[6] Savitchi E, Rao S. Squamous cell carcinoma and pleomorphic sarcoma (MFH) arising in a mature cystic teratoma of the ovary. Int J Gynecol Pathol 2012;31:443–6.
[7] Prat J, Scully RE. Ovarian mucinous tumors with sarcoma-like mural nodules: a report of seven cases. Cancer 1979;44:1332–44.
[8] Rahilly MA, Caudill W, Al-Nafussi A. Fibrosarcoma arising in an ovarian mucinous tumor: a case report. Int J Gynecol Cancer 1994;4:211–4.
[9] Tsujimura T, Kawano K. Rhabdomyosarcoma coexistent with ovarian mucinous cystadenocarcinoma: a case report. Int J Gynecol Pathol 1992;11:58–62.
[10] Brujin JA, Smit VT, Que DG, et al. Immunohistology of a sarcomatous mural nodule in an ovarian mucinous cystadenocarcinoma. Int J Gynecol Pathol 1987;6:287–93.
[11] Ongkasuwan C, Taylor JE, Tang CK, et al. Angiosarcomas of the uterus and ovary; clinicopathologic report. Cancer 1982;49:1469–75.
[12] Prat J, Scully RE. Sarcomas in ovarian mucinous tumors: a report of two cases. Cancer 1979;44:1327–31.
[13] Roma AA, Maxand RP. Different staining patterns of ovarian Brenner tumor and the associated mucinous tumor. Ann Diagn Pathol 2015;19:29–32.
[14] Wang Y, Wu RC, Shwartz LE, et al. Clonality analysis of combined Brenner and mucinous tumours of the ovary reveals their monoclonal origin. J Pathol 2015;237:146–51.
[15] Abbas AM, Amin MT. Brenner’s tumor associated with ovarian mucinous cystadenoma reaching a huge size in postmenopausal woman. J Cancer Res Ther 2013;11:1030.
[16] Ly Y, Li P, Zheng J, et al. Nodular histiocytic aggregates in the greater omentum of patients with ovarian cancer. Int J Surg Pathol 2012;20:178–84.