Borderline Clear Cell Adenofibromatous Tumors of the Ovary

- Two Case Reports -

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Borderline clear cell adenofibromatous tumors are rare ovarian epithelial tumors of low malignant potential. Only 26 cases of ovarian clear cell tumors that corresponded to the borderline category have been reported in the English literature. However, they were not classified according to the recently proposed WHO guidelines. We report 2 new cases, review all of the borderline clear cell tumors previously reported and evaluate the biologic behavior and prognosis of this rare neoplasm.

CASE REPORT

CASE 1

A 62-year-old woman (gravida 0, para 0) was admitted to our hospital with a palpable pelvic mass. The patient had been postmenopausal for 10 years but had never used hormone replacement therapy and had been taking only medication for high blood pressure for 30 years. Pelvic examination revealed a left adnexal mass. The patient underwent total hysterectomy and bilateral salpingo-oophorectomy. The intraoperative findings showed a large cystic ovarian mass that measured approximately 11.0 × 7.0 × 4.0 cm with a smooth external capsular surface. On section, the cut surface was cystic with mucoid material, and there was a solid portion with sponge-like minute spaces filled with a similar mucoid material. The uterus had two leiomyomatous masses, up to 1.5 cm in diameter. Examination of the contralateral ovary and fallopian tube revealed patchy dark brown spots on the surface, consistent with endometriosis.

On microscopic examination, the left ovary revealed many tubulocystic glands embedded in a dense fibrous stroma. The glands were lined by one to three layers of clear, eosinophilic or hobnail cells with mild to moderate nuclear atypism, a coarse chromatin pattern, and prominent nucleoli (Fig. 1). The patient was subsequently lost to follow-up.

CASE 2

A 43-year-old woman (parity 2-0-1-2) was admitted with a 1-month history of frequent urination and an abdominal mass. Pelvic examination revealed a two-adult fist-sized mass located in the left ovary. The serum CA-125 level was 62.0 U/mL (nor-
mal <35 U/mL), and the CA 19-9 level was 73.3 U/mL (normal <37 U/mL). Pelvic magnetic resonance imaging (Fig. 2) revealed a huge cystic mass with a large mural protrusion that appeared to have originated from the left ovary. It measured approximately 10.0 × 10.0 cm. An adnexectomy was performed.

Grossly, the ovary measured 10.0 × 10.0 × 6.0 cm with a pale pink smooth external surface. On section, it was a large cyst with a protruding mural mass, measuring approximately 8.5 cm in diameter. The protruding mass had a solid and spongy appearance composed of numerous variably-sized small cysts without hemorrhage or necrosis (Fig. 3).

The histological findings revealed widely spaced and focally crowded, variably-sized glands or tubules embedded in a dense fibrous stroma (Fig. 4). The stromal component was composed of bundles of spindle-shaped cells with plump elongated nuclei that resembled ovarian stromal cells or fibroblasts. The glands or tubules were lined with one to several layers of cells, and some of the glands and tubules showed intraglandular epithelial tufting (Fig. 5A) and stratification (Fig. 5B). The tumor cells were cuboidal or round to polyhedral with clear to eosinophilic cytoplasm and showed, in part, a hobnail growth pattern. A mild to moderate nuclear atypia was noted occasionally with small nucleoli. The small solid nests or single cells found in the stroma around the proliferative glands were considered to represent stromal invasion. However, the invasive foci had a linear mea-

Fig. 1. Many tubulocystic glands are embedded in a dense fibrous stroma. They are lined by one to three layers of clear, eosinophilic or hobnail cells (inlet) (Case 1).

Fig. 2. Pelvic magnetic resonance imaging (Axial T1-weighted) reveals a huge cystic mass with a large mural protrusion that appears to have originated from the left ovary (Case 2).

Fig. 3. The protruding mass exhibits a solid and spongy appearance composed of numerous variably-sized small cysts on cut section without hemorrhage or necrosis (Case 2).

Fig. 4. Widely-spaced and focally crowded, variably-sized glands or tubules are embedded in a dense fibrous stroma. Single cells (arrow) are found in the stroma around the proliferative glands. The longest invasive focus is less than 1 mm in length (inlet) (Case 2).
surement of less than 1 mm (Fig. 4, Inlet). The mitotic figures of the epithelial and stromal components were less than 1/10 high power fields. Endometriosis was not observed. The tumor cells were positive for PAS and focally positive for D-PAS and Alcian blue. Immunohistochemically, the tumor cells were positive for EMA, Cytokeratin 7, 8 and 19, but negative for Cytokeratin 20 and p53. The Ki-67 proliferation rate was 5%.

The patient had been receiving six cycles of postoperative cisplatin and etoposide chemotherapy. One and a half years after surgery, there was no evidence of recurrence or metastasis, and the patient was in good condition.

**DISCUSSION**

Benign and borderline clear cell tumors are rare and almost always adenofibromatous. Roth et al. reported 17 cases of ovarian clear cell tumors with an adenofibromatous pattern and classified the tumors on a histological basis into the three categories of benign, low malignant potential (borderline) and invasive clear cell carcinoma. These cases included 4 typical borderline cases and 2 malignant tumors, with several small foci of invasion of less than 1 HPF.

Bell et al. reported 18 clear cell adenofibromatous tumors that included 3 benign, 12 borderline and 3 malignant tumors, which were predominantly borderline with foci of microinvasion defined as an invasion focus of less than 3 mm in diameter.

Recently, the diagnosis of borderline tumors with microinvasion has been given to tumors where the main portion of the tumor is considered borderline with the presence of minute foci of invasion. However, there is no consensus on either the size criterion or the exact definition of the microscopic pattern of microinvasion, due in part to limited experience with this type of tumor. In fact, Prat suggested a measurement of 10 mm² as the criterion for microinvasion in serous, mucinous and clear cell tumors. Kurman suggested a '10 mm²' criterion for serous tumors, '5 mm in diameter' for mucinous tumors and had no comment on the criterion for clear cell tumors. The WHO classification suggested a '10 mm²' criterion for serous and mucinous tumors and 'minute foci of invasion' was designated as microinvasion for clear cell tumors.

However, considering the commonly accepted '5 mm in diameter' criterion for microinvasion, a total of 5 cases with microinvasion, previously categorized as malignant tumors in the studies of Roth and Bell, should be recategorized as borderline tumors with microinvasion.

The trend to separate borderline tumors with microinvasion from truly invasive tumors with overt stromal invasion is based on studies in the literature indicating that borderline tumors with microinvasion demonstrated an excellent prognosis similar to typical borderline tumors, although most of the applicable cases were serous or mucinous types.

Follow-up information was available for 15 cases of typical borderline clear cell tumors and 5 cases with microinvasion. No recurrence, metastasis or death occurred from the typical borderline tumors. One patient exhibited questionable lung metastasis 4 years after presentation. By contrast, among the five patients with microinvasion, one patient died of her tumor 5.25 years postoperatively and another patient had a pelvic recurrence 3.3 years postoperatively. Thus, previous studies suggest that microinvasion in the clear cell type of borderline tumors might not be an innocuous finding, as it is in serous and mucin-
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nous tumors, because two of five patients suffered recurrences.

In our experience, the first patient (Case 1) was lost to follow-up and the second patient (Case 2) showed no evidence of tumor recurrence or metastasis two years after surgery. Although a microinvasive clear cell type borderline tumor would appear to be potentially aggressive in light of the literature to date, long-term follow-up and a larger sample are warranted to confirm the prognosis.

REFERENCES