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Borderline serous ovarian neoplasm: case report of a diagnostic challenge in intraoperative frozen sections

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ABSTRACT

Surface epithelial tumors of the ovary account for 25% of all ovarian neoplasms. When composed predominantly of fibrous stroma, with glands and cysts forming a minor component, their appearance on imaging is often complex; cystic- to solid-appearing masses often raise suspicion of a malignant tumor. An accurate frozen histopathological diagnosis of a benign cystadenofibroma of this tumor can facilitate appropriate surgical management. However, it is equally important to diagnose areas of borderline changes/malignancy arising in these tumors, particularly when large or complex surface and inner papillary areas with multilayering or stratification are seen microscopically. We present here a case of bilateral complex ovarian mass in a 68-year-old woman, which was equivocal for malignancy on radiology, per operative gross examination as well as on frozen section evaluation. It was finally diagnosed as a borderline serous tumor (BOT) in a cystadenofibroma on histopathological examination.

1. Introduction

Benign serous tumors of the ovary account for approximately 16% of all ovarian epithelial tumors, with 30–50% of them being bilateral [1]. The majority of surface epithelial-stromal tumors occur in women between the fourth and sixth decade [2]. When the fibroblastic stromal component is prominent, appearing grossly as solid, white, nodular foci in an otherwise typical cystic neoplasm, they are classified as adenofibromas/ adenofibrocarcinomas. These, too, like their purely epithelial counterparts, can be separated into benign (adenofibroma and cystadenofibroma), borderline, and malignant (adenofibrocarcinoma and cystadenofibrocarcinoma) types [1–3].

The preoperative discrimination between the benign, borderline serous tumors (BOTs) and invasive cancers is based on the patient's age, menopausal status, serum CA-125 levels, ultrasound and radiological imaging (e.g. magnetic resonance imaging and positron emission tomography). However, the levels of CA-125 may overlap between patients with benign cysts, BOTs and invasive cancers [4]. Similarly, the imaging findings are not specific to BOTs [5]. Therefore, the diagnosis of BOTs cannot be conclusively established before surgery and intraoperative decisions regarding the extent of surgical management are based the findings of on frozen section examination.

An accurate frozen section diagnosis is of considerable importance in BOTs. Over-diagnosis of BOTs results in overtreatment where conservative, fertility-sparing surgery is desired by women of reproductive age. Similarly, it is important to discriminate BOTs from benign cysts. Patients with a BOT misinterpreted as benign tumor may undergo an inadequate surgical staging that results in subsequent additional interventions and possible tumor spread. This report highlights a similar diagnostic challenge [6].

2. Case Report

A 68-year-old postmenopausal woman, para 5 gravida 4, presented with pain in the abdomen and chronic constipation. Her USG showed a uterine size of 5.6 × 2.3 × 2.0 cm with atrophic endometrium and a right adnexal cyst measuring 12x10x10cm, with thick septations and a solid component. The left adnexa were not visualized. Her CA-125 was normal at 16.3 IU. All other tumor markers were negative. Her calculated Risk of Malignancy Index (RMI) for ovarian cancer was 147 points (i.e. low risk of malignancy) [7,8].

She underwent total abdominal hysterectomy. Intra-operatively the right ovary was 18 × 12 × 10cm in size and found to be solid cystic with focal areas of surface papillary projections. The left ovary was 4 × 3 × 3cm with a similar gross appearance. The histopathological gross evaluation showed a large multi-loculated right ovarian cyst measuring 16 × 13 × 10cm, with bosselated surfaces and prominent vascular markings. Small knobby protrusions measuring 0.5–0.8 cm were noted protruding from a cream-colored thickened intact outer surface of the firm cyst wall. Cut section of the larger cyst measured 12 × 10cm, with focally

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thickened and mostly thinned out cyst wall showing multiple knobby and papillaroid projections, the largest one measuring 2.5 × 2.5 × 1.5 cm. The left ovary measured 3.9 × 3.3 × 2cm. Its intact capsular surface showed a rough papillaroid area measuring 3x2x3cm. Cut section of the ovary showed a multiloculated cyst with solid areas. The largest cyst measured 2 × 1.5 × 1.5 cm, and showed a solid component measuring 2.5 × 1.5 × 2.5 cm (Fig. 1). Bilateral fallopian tubes, uterus and cervix were unremarkable except for a 0.8 cm submucosal myoma. The frozen section examination of the right ovarian cyst was suggestive of a borderline serous tumor with a prominent stromal component and focal areas suspicious of invasion.

Based on the frozen impression, a comprehensive surgical staging was done with peritoneal wash fluid examined for malignant cell cytology. Microscopic examination of formalin-preserved paraffin-embedded sections showed similar histomorphology in the bilateral ovarian tumor sections. A variably thickened, cuboidal epithelium lined densely fibrotic cyst wall with single layered bland cuboidal epithelium lined glands embedded in the fibro collagenous stroma were noted. Foci of branching broad-based papillae lined by single to more than 5- to 8-layered thick epithelium at places with minimal atypia, both on the cyst wall luminal side and on the capsular surface, comprising >10% area were also found. However, increased mitotic activity or well defined invasive areas were not found. The glands embedded in the stroma also showed bland cuboidal epithelium (Fig. 2). A final diagnosis of bilateral borderline serous tumor arising in a cystadenofibroma was made. IHC for p53 showed wild-type staining with ER, PR showing strong intensity staining in >90% of cells. All sampled lymph nodes and peritoneal tissues as well as peritoneal wash fluid were negative for malignancy.

3. Discussion

Ovarian serous cystadenofibromas with borderline changes are uncommon. The usual presentation of these serous ovarian tumors is that of abdominal discomfort or radiologically detected mass in the pelvis. These tumors are predominantly cystic, solid or complex with variable amounts of solid areas [9–11]. Serous borderline tumors (SBT) share molecular and genetic alterations with low-grade serous carcinomas. They can present at advanced stages with peritoneal implants and/or lymph node involvement and hence are categorized as tumors with borderline malignant potential [12]. Because of their solid component, thickened septa, these masses are often raise a suspicion of malignancy on preoperative imaging [9].

On USG, they may be a solitary or a multiloculated cystic mass, with solid areas or papillary projections. 50% of the cases show increased vascularity [9,13]. They therefore cannot be characterized correctly, as their heterogenous appearance mimics a malignant ovarian neoplasm. MRI shows a low signal intensity of the solid fibrous component of the tumor on T2W images, and hence can be the modality of choice to characterize these complex ovarian masses [9,14].

Grossly at the time of surgery, a cyst-adenofibroma may resemble a malignant tumor because of its prominent solid stromal components with embedded small cystic areas [10]. A careful examination of the epithelium for proliferation, cytologic atypia and mitotic activity helps in correctly diagnosing these tumors. The WHO 2014 classification stated >10% borderline histology within a cystadenoma or cystadenofibroma is required to qualify it as borderline ovarian tumor. In contrast, serous cystadenomas with foci qualifying as serous borderline tumors in <10% of the epithelial volume are designated “cystadenoma/fibroma with focal epithelial proliferation” [12,15–17]. They express WT1, PAX8, Bcl-2, estrogen and progesterone receptor on immunohistochemistry [12,18,19].

An accurate frozen section diagnosis may be helpful in these cases. Frozen section analysis of ovarian tumors has a sensitivity between 65% and 97% and a specificity between 97% and 100% in differentiating invasive and non-invasive specimens [20]. Frozen section analysis of BOTs, however, is notoriously difficult, with a significantly lower

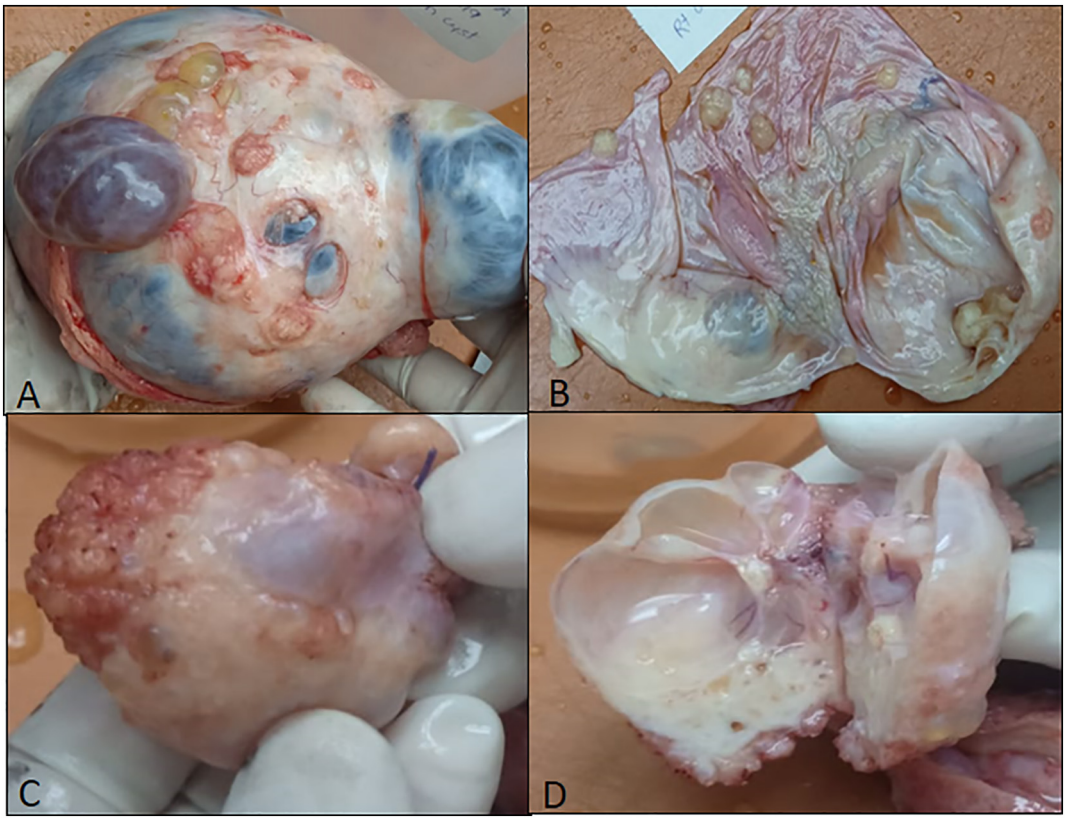

Fig. 1. A, B: Right ovarian cyst with bosselated surfaces with inner papillaroid projections C, D: Left ovarian cyst with surface papillaroid projection and solid firm cystic areas on cut section.

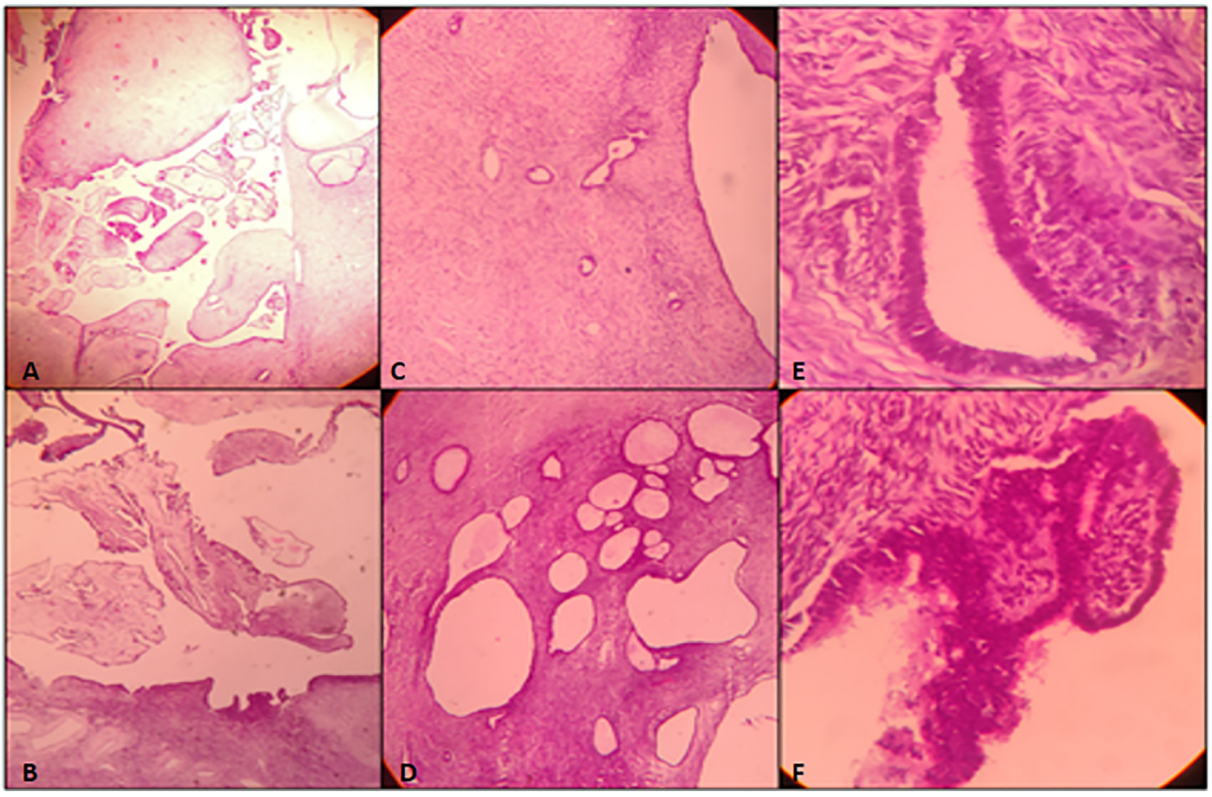

Fig. 2. A(Right ovary)B (Left Ovary)-50× -surface epithelial proliferation with branching papillary architecture in bilateral ovaries, C(right ovary)& D (Left Ovary)-100×- small glandular lumina lined by mostly bland signal layered epithelium embedded in a densely fibrotic stroma, E (Right ovary)-400×- Gland lined by cuboidal epithelium with minimal nuclear atypia & no mitotic activity and F(Left Ovary) -400×- papillary structure lined by stratified epithelium with minimal atypia.

sensitivity and specificity compared with benign tumors of the ovary and ovarian cancers [21].

Although advanced-stage ovarian cancer is usually evident at the time of surgery, the distinction of benign, borderline, and malignant tumors macroscopically confined to the ovaries is more difficult [22]. Frozen section diagnosis offers an important and helpful adjunct to the intra-operative diagnosis and greatly helps in difficult gynecologic oncology cases.

When the pathologist examining the frozen section f is uncertain whether a lesion represents a simple cystadenofibroma vs a cystadenofibroma with focal epithelial proliferation or atypia suggestive of borderline changes, is better to err on the side of reporting focal epithelial proliferation or atypia. A communication that it may turn out to be a borderline serous neoplasm gives the clinician the option of complete surgical staging rather than returning for surgery later [23].

An intraoperative assessment when combined with a direct interaction between surgeon and pathologist makes them aware of the limitations. It is important for the surgeons to be informed that frozen section diagnosis is based on microscopy of only a few sections from the grossly identified most suspicious area of the tumor, while the final diagnosis is made after the evaluation of an internationally agreed standard of a minimum of one section per cm of maximal tumor diameter [24]. The surgical management of BOTs based only on intraoperative frozen section diagnosis should be used with caution because this strategy may result in undertreatment of a substantial number of patients or overtreatment in a few cases. However, when frozen section examinations reveal a BOT in patients who do not wish to preserve fertility, the surgeon should perform a standard staging [25]. In these cases, large peritoneal biopsies and deperitonealisation of all suspicious regions are required [26]. Obviously, close follow-up is required of women who undergo conservative treatment [27].

Contributors

All authors were involved in reporting of the case and contributed to the preparation of this case report.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient Consent

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Provenance and Peer Review

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