Case Report

Borderline ovarian tumour of mixed seromucinous histology and bilateral presentation: a case report and review of literature

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ABSTRACT

This article reports the case of a 40 year old woman who presented to the gynaecologic outpatient clinic with pain lower abdomen and an abdominopelvic lump. Clinical assessment, biochemical and radiological investigations revealed bilateral complex ovarian masses. Surgical exploration and histology of ovarian masses confirmed a rare bilateral borderline seromucinous cystadenoma. The purpose of this paper is to highlight the importance of thorough examination of women with symptoms of ovarian tumour which can be vague and to emphasize the necessity of a good collaboration between various medical specialties (primary physician/gynaecologist, oncosurgeon, radiologist and histopathologist) for correct diagnosis, optimum care and best outcome. This article also provides overview of the pathology and biology of borderline ovarian tumours, diagnosis, principles of surgical management and to appreciate the value of follow up.

Keywords: Borderline ovarian tumor, Bilateral, Seromucinous, Surgical staging

INTRODUCTION

Borderline ovarian tumors comprise about 15-20% of all epithelial ovarian malignancies with an incidence of 1.8-4.8 per 100,000 women per year.[1-3]

Borderline ovarian tumours (BOTs) demonstrate higher proliferative activity than the benign neoplasms, but do not invade the stroma like malignant ones, therefore are a distinct pathological subgroup of neoplasms.[4] Also known as tumours of low malignant potential (LMP), they were first described by Taylor.[5]

Primary epithelial ovarian tumours were classified and subdivided into three groups: (a) benign cystadenoma; (b) cyst adenoma with proliferating activity of the epithelial cells and nuclear abnormalities, but with non-infiltrative destructive growth; and (c) cystadenocarcinoma by International Federation of Gynaecology and Obstetrics (FIGO) Cancer Committee (1961).[6]

World Health Organization (WHO) applied the designation 'tumour of borderline malignancy' and added the synonym 'carcinoma of low malignant potential' (LMP) in their 1973 classification of ovarian tumours.[7]

The presence single focus or multiple foci of micro invasion has also been recognised recently which may be with a specific histologic characteristics and of intermediate atypia, hence borderline ovarian tumours (BOT) are also referred to as atypical proliferative ovarian tumours (APOTs).[8]

CASE REPORT

A 40 year old female P1L1 presented to the gynaecologic outpatient clinic with diffuse, dull pain lower abdomen and feeling of heaviness in lower abdomen for last 6 months. There were no urinary symptoms. Nausea vomiting, early satiety, fever, vaginal discharge was also not present. The pain was not associated with anorexia and weight loss. Her menstrual cycle was regular with average flow and no pain. There was no reported use of oral contraceptive, she was not ligated and was a widow for over a decade. Her past medical and surgical history was not significant. There was no family history of breast, ovarian or endometrial cancers. On physical examination lower abdominal distension was present and a firm to cystic smooth lump 10x10 cm mobile, tender, extending from pelvis to RIF was found. No fluid thrill or shifting dullness could be elicited. Pelvic examination revealed a smooth tender, right adnexal cystic lump, separate from uterus in the right fornix was felt. Similar small 4x4 cm lump was felt in left fornix too. POD was free of nodules.

On ultrasonography, bilateral solid cystic ovarian masses of size 12x8 cm and 4x4 cm, with increased vascularity and thick walls was noted (Figure 1). Uterus and cervix were unremarkable, there was no evidence of any free fluid collection in the abdominal cavity. Liver echotexture was normal. Provisional diagnosis of bilateral ovarian tumors was made and ovarian tumor markers ordered.
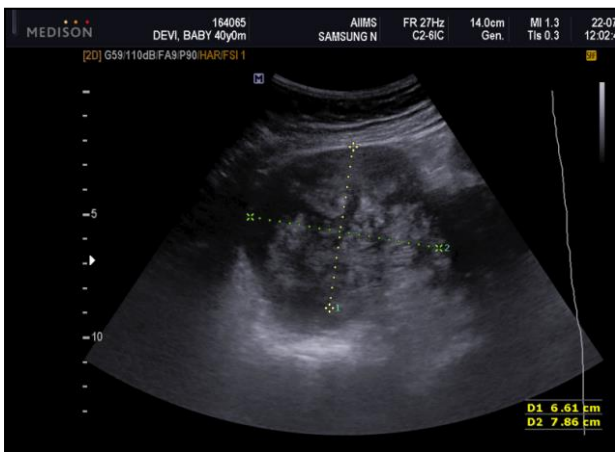

Figure 1: Solid cystic mass arising from right ovary in trans abdominal ultrasound.

On tumour marker analysis, CA 125(2450 U/mL) was highly elevated, but carcinoembryonic antigen (1.89 ng/ml) and α-fetoprotein were within normal ranges. Routine blood analyses showed normal renal and liver function.

Taking into consideration bilateral solid cystic ovarian masses and raised markers, a decision to perform total staging laparotomy with abdominal hysterectomy, bilateral salphingo - opherectomy and omentectomy, peritoneal biopsies, lymph node sampling was taken.

On surgical exploration, bilateral solid cystic ovarian tumor with smooth external surface, no capsule rupture, no excrescence was noted. No surgical spill occurred in abdomen. There was minimal ascites in the abdomen, and exploration of the pelvis, abdominal walls, and peritoneum was not indicative of implants or metastases. Infracolic omentectomy and peritoneal biopsies were also performed. The cut section showed mucinous content, appendectomy was also performed. The surgical specimen (Figure 2) was sent to pathology as facility for frozen biopsy was not available. By surgical staging it was stage 1B ovarian cancer. The postoperative course was uncomplicated.
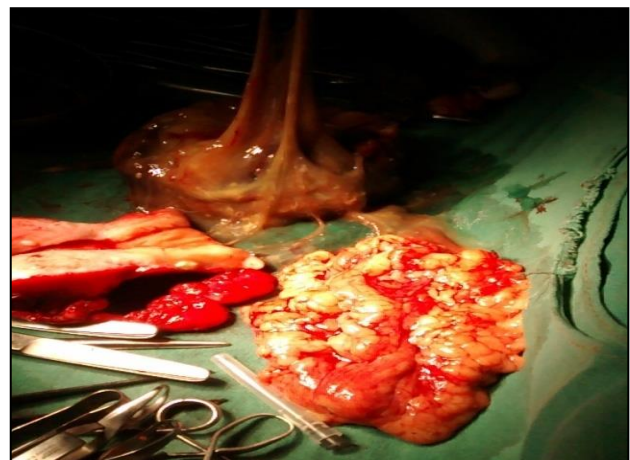

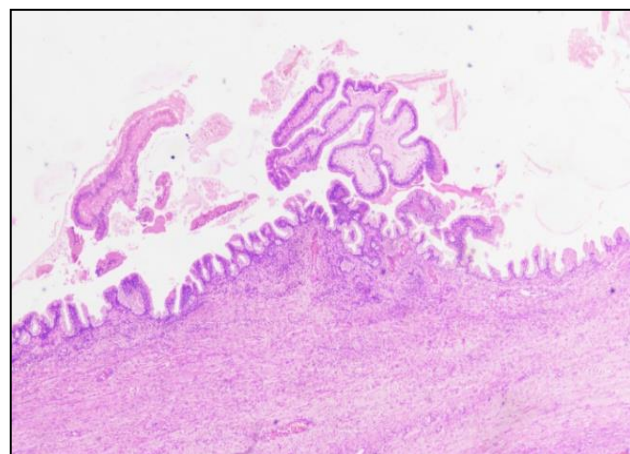**Figure 2: Operative specimen of omentum, uterus and mucinous ovarian mass.**

Figure 3: Mucinous Papillary frond.

On gross examination, specimen comprised of uterus along with cervix and two ovarian masses. (Figure 2) Uterus was unremarkable on external and cut surface and cervix shows inflammatory changes. The bilateral large, solid-cystic ovarian masses measured 11x7 cm and 9x8 cm. and were nodular, greyish white in colour. The

capsule was intact. The cut surface of both the masses showed multi-loculated cyst containing mucinous, gelatinous material. Interspersed between the cysts was solid, greyish white areas. No focus of haemorrhage or necrosis was seen.

On histopathology, endometrium and myometrium of uterus were unremarkable. Section from the cervix shows features of chronic cervicitis. Multiple sections of both the ovarian cysts reveal both serous and mucinous component. There was stratification of lining epithelium, papillary fronds and focal atypia of epithelium (<4 cells thickness). The mucinous component shows both intestinal and endocervical type of cells (Figure 3).
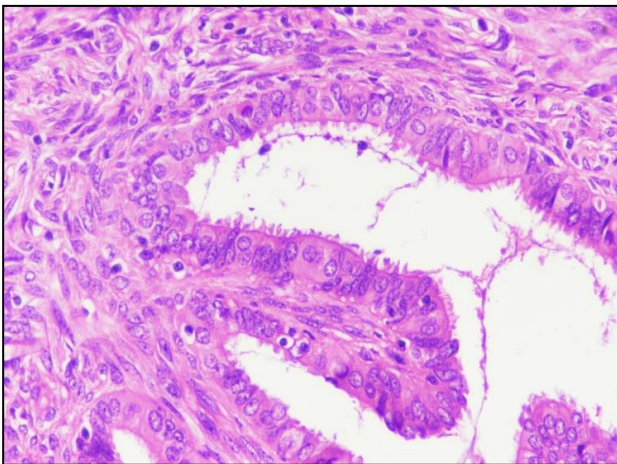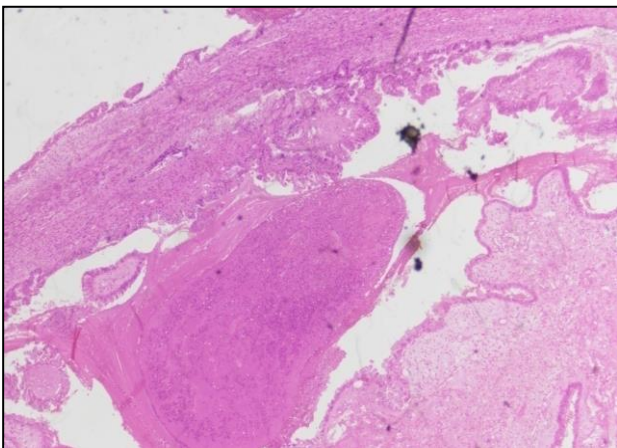

Figure 4: Nuclear atypia.

Figure 5: Inflammation, no stromal invasion.

Infrequent mitosis and nuclear atypia were present (Figure 4). As there was no destructive stromal invasion however areas of necrosis and dense inflammation present (Figure 5) it was characterised as Borderline ovarian tumor. Eosinophilic metaplastic cells were also noted along with some extravasated mucin. Multiple section from omentum show fibrofatty tissue with focal tumor implants without desmoplastic stromal invasion (Figure 6). Peritoneal biopsies were normal. Hence diagnosis of bilateral

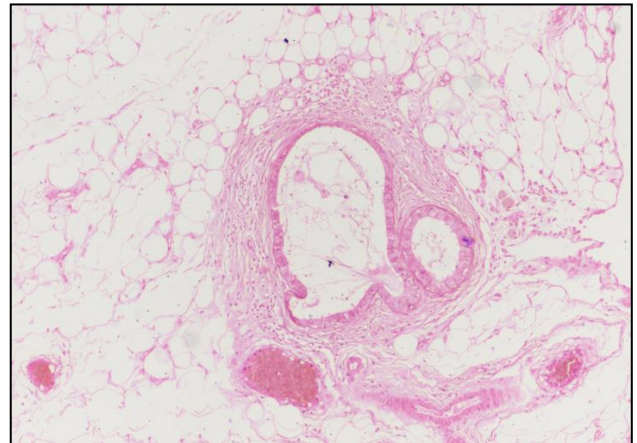borderline ovarian serous and mucinous neoplasm with non-invasive tumor implant was made.

Figure 6: Omentum.

The patient did not undergo adjuvant treatment and continues to undergo close follow-up every three months in first year, then 6 monthly and has shown no evidence of disease recurrence at 3 year from initial diagnosis.

DISCUSSION

Epidemiological studies of ovarian cancer have combinedly studied risk factors for borderline ovarian tumours and invasive carcinomas. Younger women are more likely to have borderline tumours compared with older women. Childbirth and lactation have been found to be protective. Factors linked with BOTs include menarche, age at first pregnancy and delivery, history of smoking and history of ovarian cancer in family. However, unlike invasive ovarian cancer, oral contraceptive use is not protective against the development of borderline ovarian tumours, suggesting it is a disease that is distinct from invasive ovarian cancer.[9]

Genetic studies have proved that, women with mutations of the BRCA genes who are predisposed to malignant ovarian cancers, are not at increased risk of developing BOTs.[10] Two distinct forms of ovarian cancer, high-grade and low grade serous cancers are reported by molecular studies. High grade ovarian cancers (commoner type), are associated with high rates of p53 mutation. Low-grade tumours, including borderline ovarian tumours, are characterised by mutations of the BRAF/KRAS pathway.[11,12] Two different mutation pathways prove that one type does not progress to the other. Even if BOT's progress to invasive disease, it tends to be the low-grade invasive phenotype rather than the high grade.[13]

Histological features are defined by epithelial cellular proliferation greater than that seen in benign tumours (Table 1).[14] Borderline ovarian tumours have epithelial stratified proliferation, cellular pleomorphism, nuclear atypia and increased mitotic activity. The main diagnostic criteria of

Borderline ovarian tumors is absence of stromal invasion which distinguishes them from invasive carcinomas.[15]

Table 1: Classification of BOT.

Type	Origin	Subtype	Characteristics
Serous 53-63% (bilateral 30%)	Germinal epithelium	Subtype- • Micropapillary • Microinvasive	• Multi-layered epithelium >4 cell layers • Not >4 mitoses per 10 HPF • Mild nuclear atypia • Increased nuclear/cytoplasmic ratio • No destructive stromal invasion • Peritoneal implants (20-46% of serous BOT).[14], can be invasive 15-25% and non-invasive 75-85%.
Mucinous 32-46%	Uncertain: ? appendix	• Intestinal (gastrointestinal)-85% • Endocervical/ Mullerian-15% (seromucinous)	• peritoneal pseudomyxoma (10%) • intestinal : unilateral common • mullerian : bilateral 40%, mixed seromucinous histology and associated with endometriomas or pelvic endometriosis
Others-4% • Endometrioid • Clear cell • Brenner and mixed			

Borderline ovarian tumours can be asymptomatic (23% cases) or incidentally diagnosed at routine examination. BOT can have a longer duration of symptoms as compared invasive tumours.[18] There may be complaints of pelvic pain, bloating, dyspareunia, menstrual irregularities and pressure symptoms of bladder and bowel like frequency of micturition and constipation as is found in any adnexal mass.

Imaging modality of choice to assess adnexal pathology is a transvaginal ultrasound which provides information regarding cyst diameter, thickness and regularity of cyst wall, complexity (solid areas, septa, intra-cystic papillary projections) and presence of ascites. Colour Doppler demonstrates intra-cystic blood flow and is sensitive in differentiating malignancies from benign tumour.[19,20] A wide variety of appearances, ranging from unilocular cysts, minimally septate cysts with papillary projections and markedly septate lesions with plaque-like excrescences to solid lesions with exophytic papillary projections, can be demonstrated on magnetic resonance imaging (MRI). MRI can characterize adnexal masses into benign and malignant in up to 93%.[21] MRI and positron emission tomography-computed tomography (PET-CT) are usually reserved for selected cases where presence of peritoneal and extraovarian lesions aids surgical planning in women being considered for conservative surgery. Computed tomography (CT) is useful in the case of an adnexal mass with suspected BOT or malignancy, to detect intra-abdominal presence of disease.[22]

The serum tumor marker CA 125 is often negative in patients with borderline tumors.[23] Serum CA 125 levels may be raised in 75% of serous and 30% of mucinous borderline ovarian tumours.[24] Other tumour markers, CA15-3 and CA72-4 are not specific and may be raised or be only minimally elevated. Engelen et al, found CA-125 levels to be high in only 24% patient (n=33), 9% had raised CEA and 46% increased levels of CA 19-9.[25] Serum CA19-9 levels are frequently raised in mucinous borderline ovarian tumours.

Risk of Malignancy Index (RMI) which is a reliable scoring for malignancy on the basis of ultrasound features, CA-125 and menopausal status having sensitivity of 80%, specificity of 92% and positive predictive value of 83%, using an RMI cut-off level of 200 to indicate malignancy.[26] However, as BOTs occur in younger, premenopausal women, the risk of malignancy index (RMI), which uses menopausal status, is often low.[26] In a study by van Holsbeke et al, the RMI missed 73% of BOTs (31/42 cases).[27] Individualised approach is the key and consideration should be given on the age of the woman, fertility desire, staging, and the nature of the peritoneal implants (Figure 7).

Surgery is the initial treatment for BOTs with the aim to remove all macroscopically visible disease as in invasive tumors. Standard management is accurate surgical staging and cytoreductive surgery where appropriate. The recommended surgical staging includes an exploration of the

entire abdominal cavity with peritoneal washings for cytology followed by hysterectomy, bilateral salpingo-oophorectomy, inframesocolic - omentectomy, multiple peritoneal biopsies and appendicectomy in mucinous tumors.
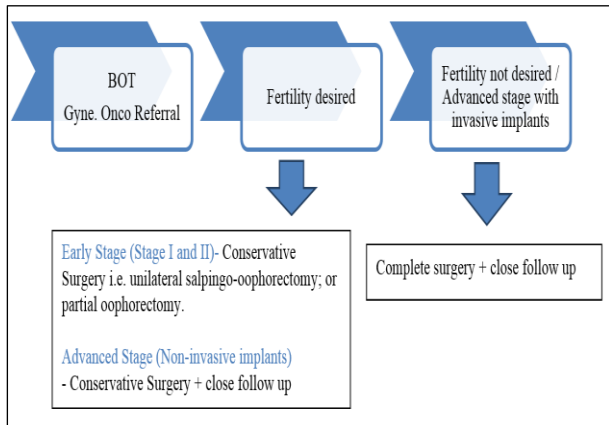

Figure 7: Treatment flowchart for suspected BOT.

A 25-30% BOTs are reported as benign and similar number as malignant in frozen section samples. Also, one-third of cases reported as borderline at frozen section are later reclassified as invasive.[28] Therefore frozen section biopsies are not much helpful.

Pelvic and aortic lymphadenectomy does not improve the disease-free interval or overall survival rate for women with BOT and is not considered necessary.[29]

Post-surgery, further management should be planned according to the histology, grade, stage, DNA ploidy status, fertility preferences and completeness of primary surgery by a multi-disciplinary team.

Most of literature recommend routine repeat surgery for completing the staging and to detect peritoneal implants, in cases where primary surgery was done for a seemingly benign ovarian cyst.[30]

As opposed to malignant epithelial tumors, borderline ovarian tumors are often found at an early stage. (stage I 70-80% BOTs vs 25% carcinomas).[17,31] A diagnosis of BOT in stages II and III is rare, and exceptional in stage IV.

Comprehensive surgical staging of borderline ovarian tumours is of significant prognostic value. The FIGO stage classification is considered to be the greatest prognostic factor for recurrence and survival of BOT.[6,17] About 95% of borderline ovarian tumours are diploid which are associated with an excellent prognosis. Aneuploid tumours and BOTs with invasive implants (31% versus 21% non-invasive implants over 5 years) has high recurrence (Table 2).[16]

Table 2: Survival and mortality of bot according to staging.

Type of BOT		Survival & mortality[32, 33]
Serous	Stage I with non-invasive implants	95% to 100% survival rate
	Stage II & III with invasive implants	34% mortality rate
Mucinous	Stage I	~ 100% survival
	Stage II and stage III	Paucity of data due to association with pseudomyxoma peritonei i.e. represent secondary ovarian involvement from a gastrointestinal neoplasm and should not be classified as ovarian

Patients with stage I disease confirmed by comprehensive staging have a recurrence rate of approximately 15%. Overall survival for women with BOT is excellent: 90-100% in most reports depending on age at diagnosis, FIGO stage and histologic type.[31,34,35] It has been seen that younger women and serous BOTs have better survival than older age and mucinous BOTs.

The main prognostic factors in same stage disease are the presence of invasive implants and residual disease following surgery.

Fertility sparing (Conservative) surgery should include complete surgical staging, preservation of the uterus and at least a part of one ovary. As 30% of women with BOT are diagnosed before 40 years old, and many of them may not have completed their family and childbearing.[16] Unilateral oophorectomy should be the optimal treatment, while cystectomy should usually be performed in cases of bilateral tumor and/or in patients with only one ovary. Oophorectomy has been shown to have a lower recurrence rate than cystectomy. Infracolic omentectomy, peritoneal washings and peritoneal biopsies must accompany the procedure. Systematic biopsies of a macroscopically normal contralateral ovary are not recommended.

Conservative surgery has a higher rate of recurrence than complete surgery (10-20% vs. 5% for radical surgery), but the recurrences are almost always borderline tumors (not invasive disease) on the spared ovary.[32] Extra-ovarian recurrence is seen more in advanced stage BOTs rather than early stage (20% vs 22%). Hence the importance of careful, regular and long-term follow-up has to be counselled to the patient.

After a conservative surgery for BOT, 50% of patients conceive spontaneously without any deterioration in the survival rate.[36] However, infertility is frequently observed in patients with BOTs (35%). Postoperative infertility in BOTs can be due to adhesions and reduced ovarian tissue after resection. Ovulation induction with ovulation inducing drugs can be tried in these women but should be limited to stage I disease and few stimulation cycles.

With laparoscopy in oncology, there are major concerns regarding the possibilities of cyst rupture, development of port-site metastases and under staging of disease; higher risk of recurrence and worsened survival.[17,37,38] In the absence of clear evidence to the contrary, staging and treatment of borderline ovarian tumours should ideally be performed by midline laparotomy.

Evidence does not support chemotherapy as it has not been found to decrease relapse rates or improve survival in patients with BOTs.[32,38,39] The general consensus is that borderline tumors with non-invasive implants do not require any further therapy. No role for adjuvant chemotherapy has been demonstrated. Chemotherapy may be considered in BOT with invasive implants and recurrent BOT that is not amenable to surgical resection.

The overall recurrence rate for patients previously treated for BOTs is estimated to be up to 11%.[35] Relapses can occur even 10-15 years after the primary surgery and hence the need for long and intensive follow up.

In stage I BOT treated by conservative surgery, clinical examination, vaginal ultrasound and CA-125 levels are useful for early detection of recurrence.[40]

Currently, follow up every 3 months for the first 2 years, every 6 months for the next 2 years and annually thereafter is followed and vaginal ultrasound is the most effective technique for these patients.[38]

With respect to contraception, C.D.C. classifies BOTs as category I (there is no restriction on the use of contraceptives).[41] Treatment for relapse of BOT is dependent on patients wish for fertility, accepting the high risk of recurrence and repeated surgery and ability for close and long term follow up. Conservative treatment can be tried again in case of all criterias are met.[31,34] If not, maximum cytoreduction should be the goal of treatment for relapsed BOTs.[42]

Borderline ovarian tumors are uncommon ovarian tumors but have excellent long term survival. Commonly arise from epithelial and intestinal/endocervical cells, implants mostly non-invasive, can be present. They present early and at younger ages and hence fertility sparing surgery remains an option for some. Imaging by ultrasonography is method of choice, ovarian tumor markers may give inconclusive results. Frozen section and lymph node dissection has little role on survival. Proper staging and complete removal of macroscopic disease is an important prognostic factor. FIGO staging, age and presence of invasive implants decide further prognosis. Surgery should be by laparotomy, but laparoscopy can be safe in hands of expert oncology laparoscopist. Post-operative adjuvant therapy has no role, but regular intensive and long term follow up of patients by transvaginal USG is recommended to detect recurrences.

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Cite this article as: Borderline ovarian tumour of mixed seromucinous histology and bilateral presentation: a case report and review of literature Anant M, Samanta S, Sinha R. Int J Res Med Sci 2020;8:1172-9.