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Case report

Fertility-sparing surgery for advanced serous primitive peritoneal borderline tumor. A safe and effective approach ? A case report and review of literature.

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Abstract

Borderline ovarian tumor (BOT) is a non-invasive neoplasm. Primitive peritoneal borderline tumor is histologically similar to non-invasive peritoneal implant of an ovarian serous borderline tumor. BOT carry out a favorable prognosis even at advanced stages. They are often diagnosed in women of childbearing age, so fertility is an important consideration in planning treatment. More welldesigned clinical trials are needed to determine the feasibility of fertility sparing surgery in treating advanced stage BOT according to the International Federation of Gynecology and Obstetrics (FIGO) classification.

We report a case from a 20 years old nulligravid woman treated with fertility conservation for a stage FIGO IIIA2 borderline serous peritoneal tumor. After seven years of follow-up, the patient remains tumor free and three spontaneous pregnancies were achieved. She gave birth to three healthy babies.

Introduction

Borderline ovarian tumors (BOT) represent a unique entity of non-invasive ovarian neoplasms recognized in the 1970s and are also called ovarian tumors of low-malignant potential. They are defined histologically by a complex architecture, multilayered epithelium, mild nuclear atypia, modest increased mitotic activity but no obvious stromal invasion. The majority of BOT have serous or mucinous histology but more rarely endometrioid, clear-cell or transitional cell (Brenner) differentiation are encountered (1). In 2014, the classification of gynecological tumors was revised, renaming 'previous' serous 'borderline tumors' (or 'low malignant potential') as 'atypical proliferative serous tumors' (2).

BOT account for approximately 10 to 20% of all epithelial ovarian tumors (3). When compared to malignant epithelial tumors, BOT have a much better prognosis, are diagnosed at an earlier stage and at a younger age. At the time of diagnosis, disease is limited to the ovary (stage FIGO I) in 80% of the cases but in 20%, the disease is associated with extra-ovarian implants, either as non-invasive or invasive implants, which represent advanced stages (stage FIGO II to IV) (4,5)

Surgery remains the standard treatment for BOT. In case of apparent early stages, surgery has mainly two purposes. The first is to remove the primary tumor by performing an ovariectomy or a cystectomy, while the second aims to stage the disease looking for the presence/absence of microscopic implants in the peritoneum or omentum. In case of advanced stage BOT, a cytoreductive procedure is advised with the objective to completely remove the disease.

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Fertility- sparing surgery preserves the uterus and at least part of one ovary (5). Recent studies have shown that the surgical approach (laparoscopy vs laparotomy) does not affect the recurrence and prognosis of patients with sBOT (6)

Peritoneal implants with serous borderline characteristics have been described without any ovarian BOT. This refers to the rare entity of primitive peritoneal borderline tumor, which are histologically similar to the non-invasive peritoneal implant of an ovarian serous borderline tumor. This diagnosis is only considered when the ovaries are not involved by borderline tumor (7).

Materials and methods

We included only serous borderline ovarian tumor FIGO stage II and III in our review. Others histological subtypes ((mucinous and others) and sBOT FIGO stage I and IV were excluded. Our scientific research has been carried out exclusively on Pubmed.

Case report

A 20-years-old primigravida woman presented in September 2014 to the emergency complaining of abdominal pain. A didelphic uterus was suspected by ultrasonography. An exploratory laparoscopy was performed that confirmed the didelphic uterus and documented multiple peritoneal implants affecting the peritoneal surfaces of the bladder, the sigmoid, both uterine bodies and the Douglas pouch (Figure 1). No tumor was localized on the ovaries. The implants located on the bladder, the right meso-sigmoid, the cul-de-sac of Douglas, the round ligament were biopsied followed by intrauterine exploration of the two uterine cavities. CA125 was elevated at 55 IU/ml. The pathology of the peritoneal biopsies described non-invasive peritoneal implants of a serous borderline tumor (sBT) (Figure 2).

The patient strongly wanted to maintain her fertility. After multidisciplinary oncologic concertation, and after obtaining a second opinion from an international expert team, we proposed to proceed with cytoreductive surgery and preservation of fertility. Informed consent was obtained from the patient and her family concerning the increased risk of recurrence, and the lack of information concerning the fertility outcomes in such circumstances.

The surgery was performed by midline laparotomy. Given the multifocal locations of the peritoneal implants, large pelvic peritonectomy was performed with the conservation of the uterus, the ovaries and the Fallopian tubes. The surgery was completed by abdominal staging, including omentectomy, abdominal peritoneum resections (colic gutters, right diaphragm) and lymph node biopsies (resection limited to enlarged nodes in the pelvis and para-

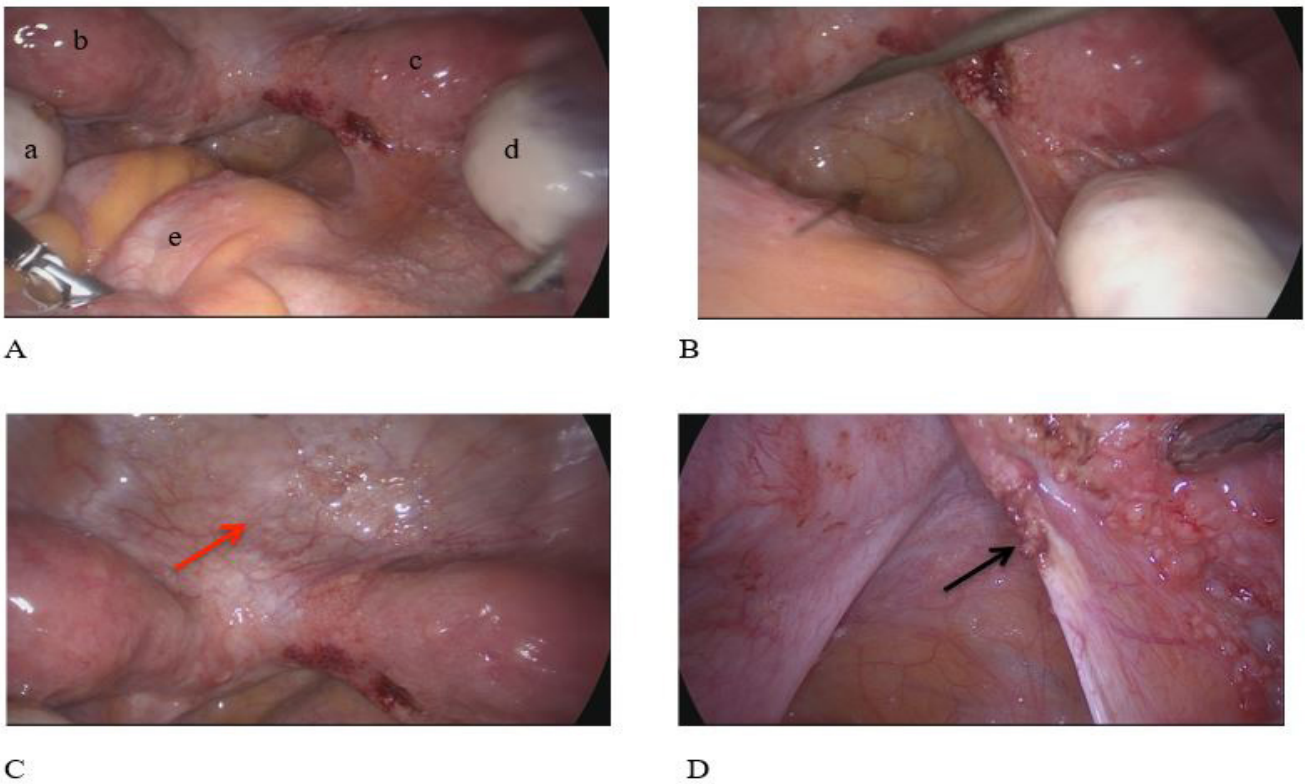

Figure 1: *Photographs of diagnostic laparoscopy. (A) Peritoneal implants on left ovary (a), left hemi-uterus (b), right hemi-uterus (c), right ovary (d), sigmoid (e). (B) Peritoneal implants in the Douglas pouch (white arrow). (C) Peritoneal implants on the bladder (red arrow). (D) Implants on the right uterosacral ligament (black arrow).*

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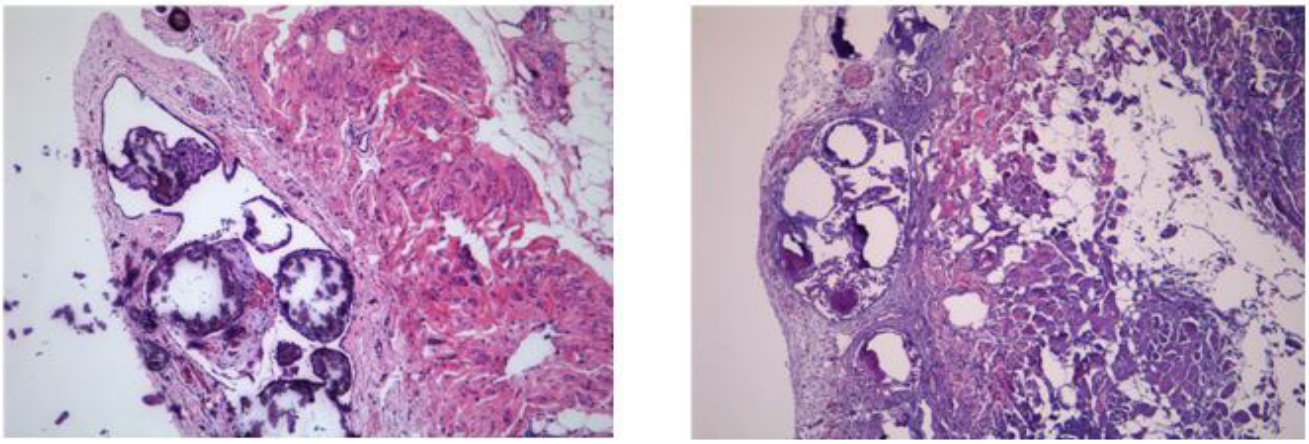

A B

Figure 2: *Histopathological features of serous borderline ovarian tumours. A and B. Peritoneal non-invasive epithelial implant of serous borderline tumor. Mild cytologic atypia with clefting and micropapillary architecture (hematoxylin-eosin, original magnification, x200)*

aortic areas). The cytoreduction was complete, without any macroscopic residual disease (R0). The surgery and the post-operative period proceed without complications. The definitive pathologic examination described the presence of non- invasive serous borderline implants on the pelvic peritoneum, the parieto-colic gutter peritoneum and the omentum. Nodes were negative. According to the FIGO classification, a stage IIIA2 was allocated. After multidisciplinary discussion, no adjuvant treatment was proposed but a closed gynecological follow-up was highly recommended. She was advised to proceed with her fertility wishes. She gets pregnant three times, spontaneously. She gave birth to healthy babies. The remission was documented after per-cesarean exploratory laparotomy for her first baby, two years after cytoreduction. Diagnostic biopsies showed a deciduose and no signs of recurrence. After almost 7 years of close follow up, the patient remains tumor-free according to radiological work-up and CA-125 monitoring.

Discussion

We report the case of a young woman with an advanced stage primary peritoneal serous borderline tumor (PPsBT) who strongly desired to maintain her fertility and refused a radical surgery. After obtaining a full informed consent, we proceeded to a complete cytoreduction with preservation of the uterus and the adnexa. The borderline implants were diffusely observed in the peritoneal surfaces of the pelvis (Figure 1), but without any evidence of borderline cyst on the ovaries. All peritoneal implants were removed to obtain a complete cytoreduction (R0). All implants had histological characteristics of borderline tumor (Figure 2) and no invasive implants were documented. We therefore considered the diagnosis of a PPsBT and allocated a stage pTIIIAN0 or FIGO IIIA2. PPsBT are considered to have similar natural history, prognosis and oncologic outcomes than sBOT and are therefore managed accordingly (7).

Approximately one-third of sBOT affect young women during their reproductive age and the majority of sBOT are limited to the adnexa (FIGO stage I) (3,8). In this specific context, an uni/bilateral cystectomy or unilateral ovariectomy are adapted procedures to obtain a complete resection of the disease, allowing fertility preservation. If the overall prognosis of early stage sBOT is excellent, data showed that fertility preserving approach is associated with an increased risk of recurrence without affecting survival, since the recurrences mostly occur on the remaining ovaries and/or the peritoneum (3,9,10). Relapses can often be safely resected by conservative surgery (11).

In contrast to early stage BOT, the safety of fertility sparing surgery of advanced-stage sBOT is much less documented (11). When peritoneal implants are documented either in the pelvis (stage II) and/or in the abdomen (stage III), data concerning the efficacy and safety of fertility sparing management are limited to small retrospective series (all series reported in Table 1, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20).

The main publications on the topic are listed in the Table 1. The majority of the series reported on 20 patients or less, with only 2 series reporting on more than 50 patients. All studies have a retrospective design. The recurrence rates as borderline tumor range from 20 to 60% but the relapse rate as invasive disease range from 0 to 33.3% (Table 1).

The recent multi-institutional retrospective italian study is the largest series that reported on 91 patients with advanced-stage sBOT treated by fertility sparing surgery (19). The authors documented a recurrence rate of 53,8% but the disease-specific survival (DSS) does not seem impacted (19). The authors consider that the risk of recurrence is not related to the ovarian preservation per se, but to the natural history of the initial peritoneal spread

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Table 1: *Published studies about oncological outcomes and fertility rates after fertility sparing surgery of stage II-III sBOT.*

	Type of study	N sBOT stage II-III	Follow-up Up Median/Mean (months)	N recurrence / N patients (%)	N recurrence as invasive relapse *	Time to relapse Median (months)	N deaths (DOD/ DID)	N pregnancy / N patients attempting conception	N live births
Zanetta et al. 2001 (12)	UIRS	24	70 (median)	10/24 (-41.6%)	1 (1 IOC)*	NR	0	NR	NR
Camatte et al 2002 (10)	UIRS	17	60 (median)	9/17 (52.9%)	2 (2 inv impl)*	17	0	8/7	NR
Prat et al. 2002 (13)	UIRS	10	85 (median)	3/10 (30%)	1 (1 IOC)*	NR	NR	NR	NR
Longacre et al 2005 (14)	UIRS	21	105 (mean)	5/21 (23.8%)	0	24.6	0	NR	NR
Kane et al 2009 (15)	UIRS	41	57 (mean)	22/41 (-53.6%)	3 (3 IOC)*	35	NR	NR	NR
Vigan et al. 2010 (16)	UIRS	10	91 (median)	6/10 (60%)	1 (1 inv impl)*	NR	0	0/0	0
Uzan et al. 2010 (9)	UIRS	41	57 (median)	22/41 (-53.6%)	3 (3 IOC)*	48	1 (1 DOD)	18/14	NR
Song et al. 2011 (17)	UIRS	5	71 (median)	1/5 (20%)	0	47	0	5/4	NR
Lu et al. 2019 (18)	UIRS	21	74 (median)	5/21 (23.8%)	0	26	0	4/10	NR
Falcone et al. 2021 (19)	MIRS	91	127 (median)	49/91 (-53.8%)	3 (1 inv impl, 2 IOC)*	22	1 DOD	24/29	22
Gouy et al. 2021 (20)	UIRS	65	73 (median)	38/65 (-58.4%)	(5 IOC, 38others)*	NR	3 (2 DOD, 1 DID)	24/29	17
Total	/	346	/	170/346 (-49.1%)	22	31.4	5 (4 DOD, 1 DID)	83/93	39

(19).

The large uni-institutional series published by French group reported on 212 patients with advanced stage sBOT treated between 1971 and 2017 (20). Among these patients, 65 underwent conservative treatment, including 8 patients with invasive implants (20). Among patients treated conservatively,

58% experienced a recurrence (20). Again the authors documented that fertility sparing management is associated with a decreased disease free survival (DFS), but without affecting the overall survival (OS). It seems therefore essential to inform patients that the recurrence rate is high and that some recurrences could not be salvaged leading to three deaths (20).

One meta-analysis was conduced by Huang et al. to assess the feasibility of fertility-sparing surgery in treating advanced-stage sBOT, pooling the results of four small retrospective series (21). The meta-analysis concluded that conservative surgery could be proposed to young patients who want to preserve their fertility. However, the validity of data is limited by the following characteristics: the small sizes of the cohorts, the retrospective design of the studies, the observational and nonrandomized natures of the trials (21).

The initial FIGO stage, the presence of invasive implants and the completeness of the surgery are considered as the most important prognostic factors for recurrence (22). The multivariate analysis from Wang et al. revealed that FIGO stage III is an independent risk factor for recurrence (6). Multivariate analysis focusing on patients under 40 years old identified advancedstage and fertility-sparing surgery as independent prognostic factors negatively affecting DFS (5, 8).

The up-dated series by Gouy et al. led to a change in their initial conclusions (20). The authors confirm that the risk of recurrence is increased after conservative treatment compared to radical surgery and that OS rates are similar in both surgical approaches. However, if they initially suggested that patients with invasive implants should not be managed conservatively, their conclusion has been amended since their recent data on oncological outcomes of patients with invasive implants suggest that the prognosis is probably related to the natural history of the peritoneal disease and not to the use of a fertility-sparing strategy itself. Therefore, the type of implants does not seem to be a selection factor to consider a conservative surgical approach in stage II or III disease, but this proposal should be treated with caution (20). The recent study by Falcone et al. confirmed that fertility-sparing treatment should be considered even in context of invasive implants (23). According to Wang et al., patients treated with ovarian cystectomy may be follow closely if post-operative imaging are negative (24).

After fertility-sparing surgery, the patients are advised to proceed with their fertility program as soon as possible (25). The pregnancy rate after fertility sparing treatment in advancedstage sBOT is much less known than its oncologic safety (19). Only a few studies have reported the fertility outcome of fertility-sparing management in women with advanced sBOT (21). Spontaneous fertility is favored since the impact of in vitro fecondation (IVF) in the natural history of borderline tumor remain unclear (10). Uzan et al. reported on fertility results about their series of 80 patients treated conservatively for Stage II or III BOT restricted to patients with non-invasive peritoneal implants. Their results confirm that spontaneous pregnancy occur after a conservative treatment of advanced disease (9). Song et al. reported their experience about 25 women treated for advancedstage BOT. Five underwent fertility-sparing surgery, four attempted to conceive and five pregnancies occurred (17). In a series of 59 patients treated for advanced-stage BOT, Helpman L et

al. reported fertility sparing procedure on 33 patients, 34 pregnancies occurred on 21 patients who attempt conception, but the FIGO stage is not specified (26). A total 26 live births were documented among 21 patients who attempt to conceive (26). Encouraging fertility data were also reported by the two most recently published series by Falcone et Gouy (19, 20). In the series of 91 patients, reported by Zanetta et al., among the 29 patients (31.8%) who attempted to conceive, 20 patients achieved at least one pregnancy and 18 gave birth to a healthy child (12). In the French series, 24 pregnancies were observed in 20 women among the 29 patients who wanted to become pregnant. 13 pregnancies were spontaneous (20).

Conclusion

While fertility sparing surgery is considered as a safe approach for early stage BOT, it is less documented for advanced BOT. Here, we report the case of a young women presenting with a PPsBT who wish to maintain her fertility. A complete up-front cytoreduction has been achieved with uterine and adnexal preservation. Invasive implants have been ruled out. After a close follow up of 7 years, this patient remains disease free. She gave birth to 3 healthy children, born at term. We consider that multidisciplinary management is mandatory including expert pathology to rule out invasive peritoneal implants. Patients should be advised that fertility sparing surgery for advanced borderline tumor is associated with a high rate of recurrence but does not seem to adversely affect OS. However, larger series and longer follow-up are required to confirm the safety and effectiveness of such management.

Conflict of interest: We have no conflict of interest to declare in relation to this work

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