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CASE REPORT

Fertility sparing treatment for bilateral borderline ovarian tumor: a case report and management strategy explication

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ABSTRACT

A bilateral adnexal mass with suspected carcinosis could be a challenging experience for the gynecologist especially in fertile age and in patients with a desire for pregnancy. A 26-year-old patient who came to the outpatient clinical observation for bilateral, multilocular pelvic masses, with more than 4 papillary structures, color score 2, hypomobile compared to the uterus and rectum, respectively of 65 and 68mm in maximum diameter, free liquid in the abdomen and suspected of ovarian neoplasm. Positive tumor markers and a strong desire of a fertility sparing treatment (FST). A 2-step surgical approach managed to perform a diagnosis of bilateral ovarian borderline tumor with implants and a fertility sparing surgery. Harvesting and cryopreserving oocytes prior to the cytoreductive intervention was successfully performed.

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KEY WORDS: Ovarian neoplasms; Fertility; Fertilization *in vitro*.

Borderline ovarian tumors (BOT) account for 10-20% of all ovarian epithelial tumors.[1] Given the high percentage of cases in fertile women, a fertility sparing treatment (FST) is often proposed for young patients with borderline tumors. Unfortunately, 30% will experience infertility, even after FST for the BOT.[2] Surgical treatment with fertility sparing goals is the preservation of the uterus and at least part of one ovary (fertility sparing surgery [FSS]), associated or not with complete surgical staging (peritoneal cytology, omentectomy, multiple peritoneal biopsies, and appendectomy in patients with mucinous BOT).[3] Consequently, the spectrum of FSS varies from cystectomy to salpingo-oophorectomy to treat unilateral BOT. However, salpingo-oophorectomy showed better oncological results with a lower risk of recurrence (10 *vs.* 42%)[4] and a longer disease-free interval (48 *vs.* 16 months).[5] Things become challenging when the disease presents bilaterally. In this variant, FSS involves sparing at least one ovary and is performed with unilateral cystectomy combined with bilateral salpingo-oophorectomy/cystectomy. That makes it difficult for the operator to plan the correct strategy to sacrifice only the

most compromised adnex and reach the disease's complete resection. Furthermore, since the cystectomy site is the most common site of recurrence,[6] this potentially represents an increased risk for the patient. Another strategy, not considered the standard, could be represented by the removal of both affected ovaries, limiting the patient's reproductive potential to the only use of heterologous fertilization as well as exposing her to the risks of early menopause. By the way, it should be emphasized that, even if FST in itself is associated with an increased risk of recurrence (0-25% *vs.* 0-5%),[4] the FSS does not affect the overall survival.[7] However, patients who have a desire for pregnancy should be informed that they have a higher recurrence rate undergoing FSS and that these recurrences occur mainly in the first 2 years of FSS.[8, 9] Moreover, repeated surgery may reduce healthy ovarian parenchyma, increasing the risk of infertility.[10] The occurrence of postoperative adhesions might interfere with fallopian tube function.[11] But, in case the patient does not plan to become pregnant soon, the most appropriate alternative is the use of oocyte harvesting and cryopreservation after FSS.[12] Ovarian stimulation protocols usually include repeated daily FSH injections for 3–14 days that stimulate ovarian estradiol (E2) hypersecretion. Gonadotrophins and steroid hormones are involved in the genesis of ovarian carcinoma,[13, 14] but on the other hand, in vitro studies showed no proliferative effect of FSH or estradiol on primary cultures of BOT.[15] On these bases, Filippi *et al.* report their experience in harvesting and cryopreserving oocytes before surgery as a novel strategy of fertility preservation for patients who had an ovarian relapse after FSS.[16] However, to our knowledge no similar strategy has been described in the case of bilateral BOT presentation. We have decided to apply these principles to a selected case of bilateral BOT with diffused implants.

Case report

A 26-year-old patient came to our clinic for persistent dull abdominal pain. She had no comorbidities or previous surgery. The clinical evaluation and Trans-vaginal ultrasound (TV) showed bilateral, multilocular pelvic masses, with more than 4 papillary structures, color score 2, hypomobile compared to the uterus and rectum, respectively of 65 and 68 mm in maximum diameter, free liquid in the abdomen and suspected of ovarian neoplasm. The patient was then directed to perform a dosage of the tumor markers, which detected CA 125 779.6 IU/L (nr 0.0-37), CA 15.3 24.8 IU/L (nr 0.0-37), CA 19.9 18.6 IU/L (nr 0.0-37) alphafetoprotein <1 ng/mL (nr 0.0-10); and to MRI with the description of "increase in the volume of the adjoining region bilaterally, supported by masses partly confluent with uneven solid structure, of the maximum dimensions of about 9 cm on the right and 8 cm on the left. Cystic formations with a maximum diameter of about 2.4 cm are observed bilaterally in the adnexa. Diffuse regular thickening of the peritoneum is also observed with involvement of the mesentery and serosa of the tenuous loops. The free liquid in perihepatic and perisplenic regions, and along with the bilateral parieto-colic excavation and in the pelvic excavation." In consideration of the impossibility of discriminating between ovarian cancer and BOT, of the young age of the patient and her desire for a future pregnancy, it was decided for a 2-step surgical approach: first diagnostic than therapeutic. First, a diagnostic laparoscopy was performed to acquire a histological sample. Ascitic fluid was present and was aspirated and sent for cytological examination (negative for the presence of neoplastic cells). Adnexa were prolapsed in Douglas and were the site of exophytic papillary neoformations of about 6cm. No evidence of healthy ovarian tissue was described. The uterus was fused ventrally to the abdominal wall and was the site of multiple pericentimetric implants on the serous. Diffuse nodules laid into Douglas' peritoneum. As well there were diffuse thickening of the pelvic and parietal peritoneum, "omental cake," diffuse nodules affecting the tenuous mesentery without retraction. Sigma was attached to the left abdominal wall and was the site of nodulations. A diagnostic sampling of a peritoneal nodule and right ovary was then performed. The samples obtained were diagnosed as borderline ovarian serous tumor with non-invasive desmoplastic implants. A second referral cancer center

performed a validation of the diagnosis. Considering this anatomopathological finding, and in consideration of the failure to find healthy ovarian tissue at surgical exploration, the patient was counselled on the possibility of resorting to techniques of harvesting and cryopreserving oocytes before the cytoreductive intervention. Therefore, she was first evaluated with dosage on the third day of the menstrual cycle of FSH 2.1 mIU/mL (n.r. 2-13); LH 1.8 mIU/mL (n.r. 2-12); Progesterone 7.03 ng/mL; 17 beta-estradiol 272.4 pg/mL (n.r. 0-300). Then the patient underwent an oocyte stimulation cycle. On the second and third day of the menstrual cycle, she was given 150 mcg daily of corifollitropin-alfa, followed by 450 IU/*die* of follitropin-alfa from the 4th day to the 9th, then the dosage was again reduced to 150 IU/*die*. On the 6th day, when at least one follicle reached the diameter of 14 mm, 0,25 mg/*die* of ganirelix acetate were administered as GnRH antagonist. 10,000 IU of Chorionic Gonadotropin were administered as ovulation trigger when two follicles reached 22 mm of diameter, one 20 mm, one 16 mm, one 13 mm and five 12 mm. Matured follicles were found in both ovaries. Pick up was made on the 13th day, which was the day of the planned operation, which immediately followed. 5 oocytes were retrieved and cryopreserved. After that, a laparotomic xifo-pubic incision was made, with the intent to apply FSS if possible. In 3 and a half hours, we performed salpingo-oophorectomy, left cystectomy, omentectomy, and complete peritonectomy, including removal of the uterine serous. Left cystectomy could not have been planned before surgery. The tuba has been surgically removed because it was involved with extensive nodulations. Therefore, the residual ovarian tissue was left for endocrinological and non-reproductive purposes. It was also necessary to cut the left uterine artery to complete the posterior pelvic peritonectomy. Complete cytoreduction was reached (CC-0). The patient was discharged with no complications on the 4th day. The final histopathological diagnosis was Serous BOT with non-invasive epithelial implants. A month after the operation, the patient has resumed her menstrual flow and after 60 months of follow-up, she has no disease recurrence. Follow-up is routinely performed every 6 months with tumor markers dosage and TV ultrasound. Currently, she has no immediate desire for pregnancy.

Discussion

The case we have shown appears to be particular for the numerous issues that it raised during the planning of the correct approach strategy. First of all, the clinical presentation, with the impossibility of preoperatively distinguishing the nature of the ovarian neoplasm, as well as the presence or absence of healthy ovarian tissue, made it difficult to determine the most appropriate radicality in surgery. Neither TV ultrasound nor MRI can certainly distinguish between BOT and low-grade ovarian carcinoma,[17] but this information is crucial in planning FST for a patient with bilateral ovarian masses for two major reasons: If we consider the disease as a low-grade ovarian cancer, given the presence of suspected carcinomatosis, we interface with a clinical stage incompatible with FST.[18] In addition, because of the unclear possibility of saving normal ovarian tissue, we would have been forced to resort to an ovarian stimulation cycle, which is highly discouraged both in the case of ovarian cancer or invasive BOT implants.[12] Because of this, we were forced to anticipate this evaluation in a preoperative phase. To overcome this hurdle, we decided to split the surgery into two steps. Therefore, we started with a diagnostic laparoscopy and obtained a histological diagnosis of the ovarian masses and peritoneal implants. Even if this decision seems obvious, it foresees the acceptance of a "compromise:" that the peritoneal nodule removed and examined was representative of all the other nodules disseminated in the abdomen. This assumption, therefore, required careful and tailored counselling with the patient, who indirectly, together with the health care providers, accepted this diagnosis as the closest to reality, although it was not a diagnosis of certainty.[19] Furthermore, in this case, it also carries another fundamental data to guide the management. The surgeon who performed the diagnostic laparoscopy and FSS, in agreement with the ultrasound and MRI data, did not believe that there was healthy residual ovarian

tissue. Thus, the patient 's only hopes for fertility rested on preoperative oocyte harvesting and cryo-preservation techniques. This opened up a new scenario. In addition to the hypothetical risk associated with the diagnostic doubt not resolved by diagnostic surgery, induced follicular growth (IFG) finds difficulties in its application. The follicular growth monitoring may be hampered by the presence of multilocular lesions, which may mimic a stimulated follicle. Fortunately, our experienced operator (GMT) has encountered no difficulty in distinguishing compromised ovarian tissue from grown follicles. Similarly, the fixity of the adnexal masses, the multilocular nature and the presence of nodulations in Douglas may make oocyte retrieval challenging. Only the clinical experience of the operator could solve these problems, going beyond the boundaries defined by the scientific literature. Ovarian stimulation also created problems that were reflected in the operating theatre, as the hormonally stimulated ovaries had significantly increased in volume (15cm *vs.* 6cm, confirmed at histopathological diagnosis). This condition made the intent to practice a cystectomy on at least one of the two ovaries more difficult. In addition, the uterus had to be desierosed, which can be particularly challenging and is associated with a substantial risk of bleeding. As mentioned, the left uterine artery was sacrificed to reach complete cytoreduction. This manoeuver, from a point of view of its impact on fertility, cannot be evinced from similar cases in the literature. We can modulate them from experience with radical trachelectomy for FST of cervical cancer, in which sacrifice of one or both uterine arteries have been shown not to affect uterine vascularization (risk of uterine necrosis <1/3000) or reproductive capacity.[20] Since the removal of both tubes has become necessary, the treatment done can be considered as FST only because the patient has undergone IFG and pick up before surgery. Even if the patient is not currently looking for a pregnancy, having cryopreserved 5 oocytes offers her the opportunity to plan her fertility in peace. Finally, in case of disease recurrence, the sacrifice of the remaining ovary will not definitively compromise the patient's fertility, provided that the uterus is preserved. We wanted to share our experience to highlight the difficulties we faced in designing it. This is a rare case that forces the clinician to move beyond the boundaries of guidelines. Our two-step strategy allowed us to preserve the patient's fertility, but the absence of further similar data in the literature does not make it possible to define a "gold standard." In addition, the absence of case images limits its informational power. Unfortunately, the evolution of management has not allowed the optimal planning of its publication.

Conclusions

A bilateral adnexal mass with suspected carcinosis could be a challenging experience for the gynecologist especially in fertile age and in patients with a desire for pregnancy. When faced with a presentation with diffuse peritoneal nodules, the patient should be informed that the diagnostic power of a single nodule specimen is inversely proportional to the spread of the disease. in addition, the risks associated with the procedure and stimulation cycles should be thoroughly discussed together. Although there is no standard of care applicable to the case under examination.

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