Treatment of recurrent serous borderline tumors with noninvasive peritoneal implants

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Case description

A patient in her 70s initially presented in 2005 with an adnexal mass and elevated serum CA125 and subsequently underwent a hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies and appendectomy. Final pathology showed a serous borderline ovarian tumor (Figure 1A) with foci of microinvasion and one non-invasive implant (Figure 1B) in the omentun measuring 5 mm (2021 International Federation of Gynecology and Obstetrics (FIGO) stage: IIIB). The patient was presented at a tumor board, where it was decided to recommend routine surveillance with physical examination and tumor markers.

In May 2014, the patient presented with abdominal pain and a computed tomography (CT) scan was performed showing intra-abdominal implants. At that point, the patient underwent a resection of the implants localized in the vagina, right diaphragm, and left paracolic gutter. A complete cytoreductive surgery was achieved. Pathology at that time showed serous borderline tumors with non-invasive implants. The tumor board recommended routine surveillance for the patient. In October 2015, a CT scan showed a pelvic lesion suggestive of tumor recurrence. A rectosigmoid resection with colorectal anastomosis was performed. The final pathology showed serous borderline tumors with non-invasive implants. At that point continued surveillance was recommended.

In December 2017, a CT scan reported pelvic and intra-abdominal recurrence. A laparotomy was performed with small bowel resection (80 cm), vaginal resection and low rectal resection with left colostomy. Final pathology revealed non-invasive implants of serous borderline tumors in all the

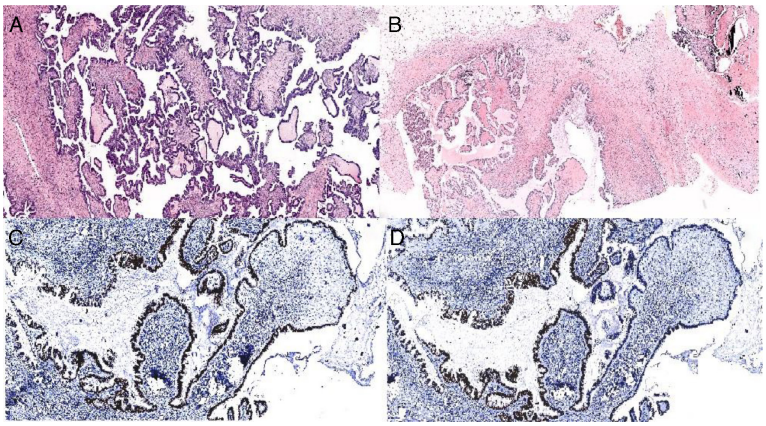

Figure 1 Pathology Review. (A) Serous borderline tumor diagnosed in 2005 (H&E stain). (B) Non-invasive implants of serous borderline tumor (H&E stain). (C) Estrogen receptor was positive. (D) Progesterone receptor was positive. H&E: hematoxylin and eosin.

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resected structures. Once again, routine surveillance was decided in the tumor board. The patient was without disease until December 2022, when CT scans showed intra-abdominal implants and abdominal wall implants. A percutaneous biopsy of the abdominal implants revealed noninvasive implants in the right iliac fossa and subcapsular hepatic lesions, in segment IV and in segment III. At that time no further treatment was recommended for the patient. In December 2023, a routine CT scan showed evidence of new implants in the anterior epicardial recess/right anterior mediastinum and growth of the implants already seen in 2022. A percutaneous biopsy was performed and showed once again non-invasive implants of serous borderline tumors with positive hormone receptors (estrogen receptor positive 60% and progesterone receptor positive 70%, Figure 1C,D). At this point the recommendation from the tumor board was for treatment with an aromatase inhibitor (anastrozole 1 mg daily) and this was started in February 2024. CT scans in June 2024 showed a stable disease.

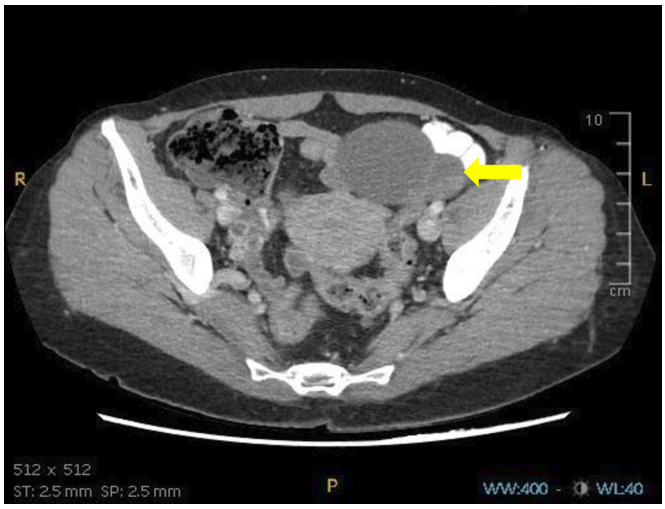

Figure 2 CT scan image. Left adnexal mass with borderline suspicious component, in 2005.

Dr. Andújar: Please review the findings noted on this patient's pathology

In 2020, The WHO defined borderline ovarian tumors as low grade, proliferative serous epithelial neoplasms without invasion.[1] They are classified into two morphologic subtypes: the conventional subtype which shows hierarchically branching papillae and the micropapillary/cribriform subtype which encompasses nonbranching filiform structures.

Our patient had a conventional serous borderline tumor in 2005, with foci of microinvasion. Microinvasion is defined as 'Individual cells to rounded clusters invading papillary or intracystic stroma with retraction clefting' and 'minimally atypical cells with cytoplasmic hypereosinophilia, scant nonatypical mitoses (<3 - 4/10 high power fields) and lower Ki67 index than surrounding tumor'.[2] Frequently, there are multiple foci of microinvasion into the same tumor, if so any individual focus must be <5 mm.

The WHO 2020 differentiates between non-invasive and invasive implants. Invasive implants are defined as 'in most cases the epithelial component predominates, especially with a micropapillary/cribriform pattern associated with retraction artifact, and there is destructive invasion of underlying structures or obliteration of normal omental architecture by invasive tumor'.[1] Invasive implants are defined as extra-ovarian low grade serous carcinoma.

Non-invasive implants are subclassified into two histologic subtypes which do not have clinical significance: desmoplastic and epithelial. Our patient presented with desmoplastic implants which are defined as 'true papillae with clusters of or single hypereosinophilic cells blending into (compressed by) inflamed fibroblastic, granulation tissue-like stroma'.[2]

Dr. Rubio: Please describe the radiologic findings throughout the course of the patient's history

*In 2005, in the CT scan, the patient presented a left adnexal cystic mass measuring 52×72×59 mm with a solid component and partitions inside, which raised suspicion of a neoplastic process (*Figure 2*). Regarding comparison of CT scans between 2022 and 2023 a disease progression was shown: The implant in the right iliac fossa grew, with the appearance of cystic formations, 33×25 mm axial plane (previous 11×14 mm), in intimate contact with a segment of ileum (*Figure 3A, B*). There was growth of the solid cystic implant in the anterior abdominal wall, 93×41 (previous 59×20 mm axial plane) which was in intimate contact with the transverse colon (*Figure 3C,D*). Appearance of two implants in the anterior epicardial recess/right anterior mediastinum, the largest measuring 18×12 mm, in close contact with the sternal body. Growth of focal subcapsular hepatic lesions, in segment IV (30×18 vs. previous 26×14 mm) and in segment III (19×15 vs. previous 16×9 mm).*

Dr Arencibia: What is the role of chemotherapy in a patient with serous borderline tumors?

The European Society of Gynaecological Oncology (ESGO) Guidelines[3] do not recommend adjuvant chemotherapy for primary treatment of serous borderline tumors with extraovarian invasive and non-invasive implants. However, National Comprehensive Cancer Network (NCCN) guidelines[4] consider chemotherapy for invasive implants but not for non-invasive implants. Adjuvant chemotherapy use for invasive implants remains controversial. If applied, the chemotherapy regimen is similar to that used in ovarian cancer (carboplatin plus paclitaxel).

One retrospective study which included 36 patients with invasive implants showed that 11% recurred as low-grade serous carcinoma showing a possible benefit of adjuvant chemotherapy for invasive implants.[5] Shih[6] et al., studied 65 patients with stage III–IV with invasive and non-invasive implants. Seventeen patients received adjuvant chemotherapy. The authors did not find differences in progression- free survival between patients who received chemotherapy and those who did not.[6]

Dr. Martin: What is the role of hormonal therapy in patients with serous borderline tumors?

NCCN guidelines[4] recommend surgery for patients with recurrent serous borderline tumors. The guidelines also recommend observation in patients with noninvasive implants. This is why there was a continued recommendation for cytoreductive surgery for three occasions. However, in the fourth recurrence in 2022 the risks of a fourth surgery outweighed the benefits, and therefore, we decided to recommend surveillance. However, progression of disease was

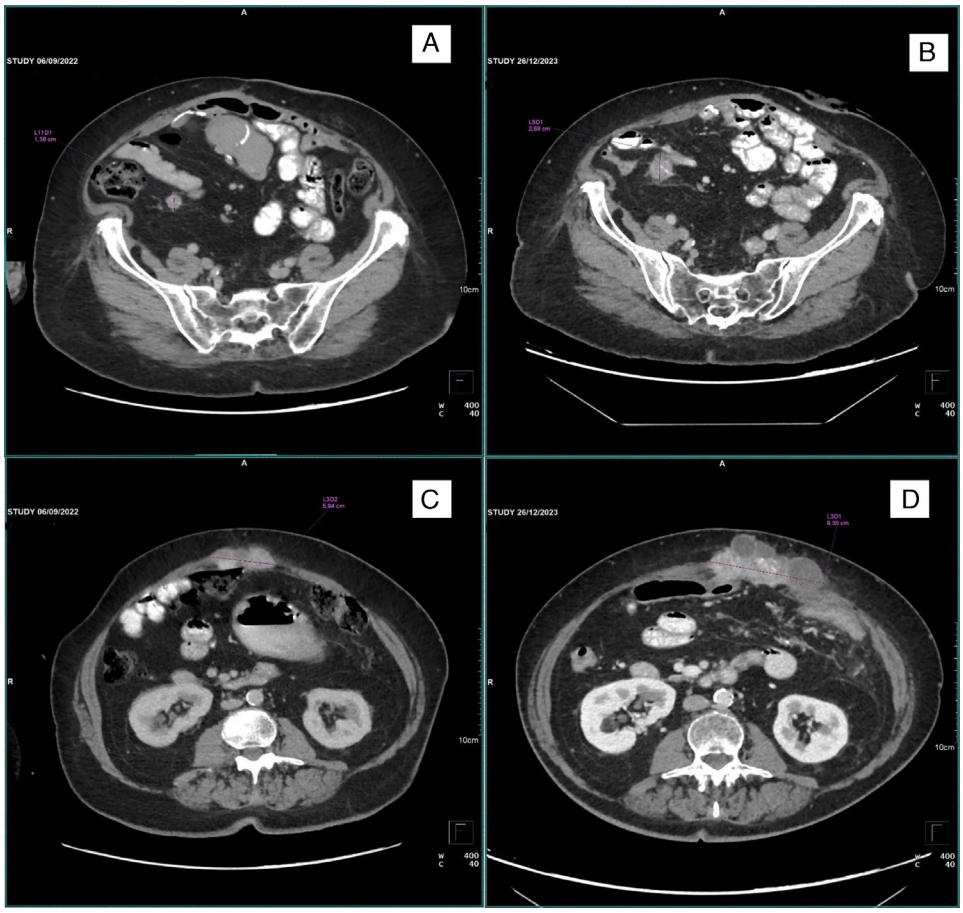

Figure 3 CT scan images. (A) Implant in right iliac fossa in 2022; (B) Implant in right iliac fossa which increased in 2023; (C) Implant in anterior abdominal wall in 2022; (D) Implant in anterior abdominal wall which increased in size in 2023.

documented on CT scans in 2023, thus we decided to give anti-hormonal treatment.

It is known that borderline serous tumors harbor estrogen receptors and progesterone receptors. Thus, anti-hormonal treatments may be useful in recurrent and advanced cases. The PARAGON trial[7] was a phase II prospective study which enrolled 36 patients with recurrent and metastatic low grade ovarian cancer. In the trial serous borderline tumors were treated with anastrozole and 64% of patients had a clinical benefit rate at 3 months, whereas 61% had a clinical benefit rate at 6 months. Also, anastrozole was well tolerated among patients.[7]

CLOSING SUMMARY

Serous borderline tumors represent 15% of ovarian serous tumors.[2] Their prognosis is excellent andoverall survival at 5 years is *around 95%.[8] Most cases present in young patients (<40 years old) and in the early stages of disease. However, extraperitoneal implants are present in 15%–40% of patients. Residual disease after cytoreductive surgery and the type of peritoneal implants are important factors for prognosis in the advanced stages.[8] Survival is worse in patients with invasive implants compared with non-invasive.[8] A meta-analysis of 97 studies including 4129 women showed that survival of non-invasive implants was 95.3% while it was 66% for those with invasive implants (p<0.0001).[8] Moreover, because of the worse prognosis associated with invasive implants and despite the lack of evidence, many practitioners still empirically propose adjuvant chemotherapy for serous borderline tumors with invasive implants. In addition, a retrospective cohort study of 36 serous borderline tumors and invasive implants treated with surgery and chemotherapy showed a 5 year disease free survival of 67% and overall survival of 96%.[5]*

Genetically, borderline serous tumors have the same alterations as low-grade serous carcinomas, with KRAS mutations detected in approximately 17–39.5% and BRAF mutations in 23–48% of serous borderline tumors.[9] Moreover, ovarian low-grade serous carcinomas present KRAS mutations in 19–54.5% of cases. Apparently, there is an association between KRAS G12v mutation and a more aggressive phenotype of serous borderline tumors that recur as low-grade serous carcinomas. However, cancer cell lines with KRAS G12v mutation are more sensitive to selumetinib than cell lines with wild-type KRAS. Also, bractoppin, a BRCA1 carboxy-terminal domain inhibitor promotes the apoptosis of ovarian cancer cell lines and inhibit the homologous recombination and non-homologous end joining pathway repair ability of tumor cells, therefore it may be useful in borderline serous tumors.[10]

Treatment consists of surgery with total hysterectomy, bilateral adnexectomy, omentectomy, appendectomy, peritoneal biopsies and resection of implants if present. Fertility sparing surgery may be considered in stages I-II with safe oncologic results.

In conclusion, expert pathology evaluation is very important in the diagnosis of borderline tumors and in the assessment of risk factors for recurrence. Early stages have favorable prognosis and fertility sparing

surgery should be considered in all cases. However, advanced stages have worse prognosis and adjuvant treatment is still to be defined. In these cases, complete cytoreductive surgery appears to be an important factor for survival, but the role of adjuvant chemotherapy and hormonotherapy is still unclear.

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