CASE REPORT

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Bilateral serous surface papillary borderline ovarian tumor in 19-year-old patient. Ultrasound, immunohistochemical and therapeutic particularities of reproductive age

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Abstract

Borderline tumors have a histological aspect of atypical epithelial proliferation without stromal invasion and typically occur in fertile ages, approximately one-third of women diagnosed are younger than 40. Serous borderline tumors are the most encountered and they can present micropapillary features that are associated with a higher rate of recurrence and the possibility of peritoneal implants. We present the case of a serous borderline ovarian tumor in a young patient and the diagnosis and treatment particularities. The patient presented with no symptoms, for a specialist advice, in the context of failure obtaining spontaneous pregnancy over a period of seven months. Paraclinical, the only modified parameter was CA 125, respectively a slight increase of its value. The atypical appearance on abdominal and transvaginal ultrasound indicated a presumptive diagnosis; both ovaries with multiple irregular vegetation, moderately vascular on Doppler examination, with the starting point in epithelial capsule shell, that appeared thick and hyperechogenic. About 7 cm of pelvic fluid was also present. During exploratory laparoscopic intervention, the surrounding tissue of both ovaries was biopsied and the fragments were sent for histopathological and immunohistochemical exam. Immunohistochemical assays correlated with the histopathological analysis and anatomical clinical data confirmed the diagnosis. After informed consent, the patient underwent radical surgery with a quick and uneventful recovery. The series of investigations had the objective to establish the best management of the case and reviewing the possibility of a conservative surgery. Patient clinical aspect matched with the patterns of ovarian borderline tumors by the asymptomatic presence of the bilateral adnexal masses.

Keywords: serous papillary borderline ovarian tumor, immunohistochemistry, ultrasound ovarian mass.

Introduction

Taylor described borderline tumors of the ovary for the first time in 1929 [1]. They are a heterogeneous group of lesions, with the histological aspect of atypical epithelial proliferation without stromal invasion and had been adopted into the *World Health Organization* (WHO) classification [2]. The percentage of this tumors that are characterized marginally between malignant and benign is 14–15% of all ovarian malignancies, with an estimated incidence of 1.8–5.5% per 100 000 women per year [3]. Another feature that should be mentioned is the occurrence of ovarian borderline tumors in fertile ages, approximately one-third of women diagnosed are younger than 40 [4]. A meta-analysis by Ness *et al.* reported a significant increase in the risk of borderline tumors in women with an unknown cause of infertility [5]. Another study suggests that hormone therapy is a risk factor for developing borderline ovarian tumors; data regarding the link between the hormone therapy and the recurrence of this kind of tumors does not exist [6].

The lack of stromal invasion is in favor of the benignity, instead of cellular proliferation, stratification of epithelial cells, stratification of papillae, nuclear atypia and mitotic activity witch advocates for malignancy.

The most characteristic microscopic feature of a borderline serous tumor is a complex branching papillary pattern of growth [7, 8].

As described by Zaloudek & Ng, unlike a carcinoma, a borderline tumor rarely has solid fleshy appearing areas, hemorrhage and necrosis being uncommon in these situations, unless the tumor has undergone torsion or infarctions [7].

In the larger group of serous tumors, Burks *et al.* distinguished the micropapillary serous tumors, with particularly prominent cellular proliferation, characterized by the presence of micropapillary or cribriform growth, usually admixed with areas of typical borderline serous tumor [7, 9–12].

Histologically, borderline ovarian tumors can be categorized according to origin in: serous (60–75%) and mucinous (11%), most commonly encountered. Other rare encounters are: endometrioid borderline tumors, clear-cell and transitional cell (Brenner) borderline tumors [6,

13–15]. Serous borderline tumors can present micropapillary features that are associated with a higher rate of recurrence and the possibility of peritoneal implants. Usually, at the time of diagnosis, they are limited to the ovary. Bilateral involvement is frequent, in up to 50% of the cases.

Upon discovery of an ovarian mass, determining the nature of the tumor is essential. Multiple risk factors can be used as a guide in order to establish an accurate diagnosis [15, 16]. *BRCA* gene mutation and high serum CA 125 are predictive for ovarian carcinoma; however, their link with borderline ovarian tumors is uncertain [17].

The presence of ascites leans toward the malignant origin, borderline tumors associate ascites in rare cases.

Concerning the clinical aspect, there are no typical features, borderline ovarian tumors may be presented as asymptomatic in 14%, according to Sood *et al.* [18] and random detection is not uncommon. An ultrasound exam is mandatory but the appearance of borderline tumors is uncharacteristic. Unilocular cyst, papilla or masses with solid and fluid components may point to a borderline tumor [19].

We present the case of a very young patient, diagnosed with bilateral serous borderline ovarian tumors; the diagnosis was established after laparoscopy and the management was radical surgery. The decision of radicality was immunohistochemistry dependent. In the last years, using the principle that each tumor category has a particular immunohistochemical feature, immunohistochemistry became one of the main paraclinical exams for the suggestion or confirmation of a diagnosis [20]. It is important that a panel of markers to be employed, markers which are expected to be positive and negative in the various tumors in the differential diagnosis and also can direct the subsequent treatment [21].

The aim of this report is to emphasize the importance of a personalized medical decision in a case with almost all atypical features, in a world of evidence-based medicine but with no other similar report written by now.

Case presentation

B.E., a 19-year-old asymptomatic female with a non-significant past medical history presented itself in January 2016 for a specialist advice for the failure to obtain pregnancy over a period of seven months. The patient came from rural area. Heredo-collateral antecedents reveal from the paternal side a grandmother deceased of colon cancer and great-grandmother deceased of breast cancer. Personal history includes menarche at 13-year-old and regular periods. She denied weight loss, fever, chills, night sweats, urinary tract symptoms or other gastrointestinal complaints. Clinical examination revealed well appearing, a weight of 52 kg and height of 170 cm. Laboratory tests were normal, except CA 125, which was 128 U/mL. Abdominal and transvaginal ultrasound (US) revealed both ovaries with multiple irregular vegetation moderately vascular on Doppler examination with the starting point in epithelial capsule shell that appears thick and hyperechogenic (Figures 1 and 2).

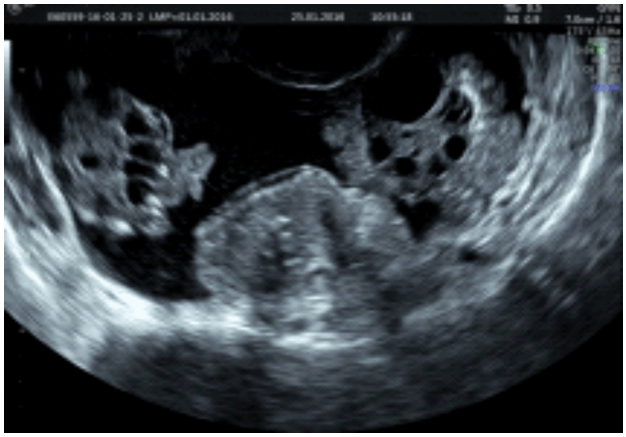

Figure 1 – ***Ultrasonographic 2D appearance of the ovaries: multiple irregular vegetation with the starting point in epithelial capsule shell, that appear thick and hyperechogenic.***

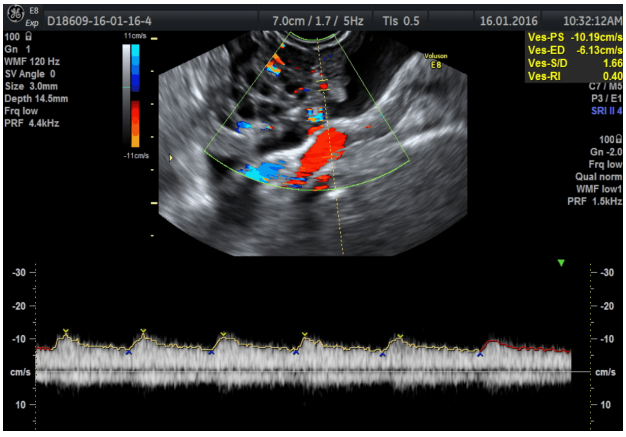

Figure 2 – ***Ultrasonographic color Doppler appearance of the ovaries with moderate and low resistance vascularization of the vegetation.***

Both ovaries presented the ultrasound criteria for polycystic ovary syndrome (PCOS), which were completely surrounded by fibrocystic tissue. We also detected 7 cm of pelvic fluid in Douglas's cul-de-sac (Table 1). Computed tomography (CT) scan examination confirmed the presence of ascites fluid surrounding the uterus and adnexal areas, without aspects that can raise suspicion of malignancy. The patient was admitted in University Emergency Hospital, Bucharest (Romania) and an informed consent regarding therapeutic approach and publication of the medical record with respect of confidentiality was obtained.

An exploratory laparoscopic intervention was indicated and applied in order to decide if the fertility-sparing surgery, conservative or the radical surgery will be the best decision, regarding the age of the patient, macroscopic and microscopic appearance and the presence or absence of extra-ovarian implants. During the intervention, the surrounding tissue of both ovaries was biopsied and the fragments were sent for histopathological and immunohistochemical analysis (Table 1; Figure 3). Following the investigations described above implicitly the presence of peritoneal implants (Figure 4), the tumor was included in stage III C. The obtained histopathological result was bilateral borderline ovarian-micropapillary variant/non-invasive low-grade serous carcinoma with non-hierarchical branching architecture, in which fine micropapillae

emanate directly from large, fibrotic papillae. The cells lining the micropapillae are rounded, cuboidal to polygonal with a high nuclear to cytoplasmic ratio and more atypical nuclei (Table 1; Figures 5–8).

Table 1 – ***Diagnosis, surgical management, pathology and outcome***

US findings	▪ multiple irregular vegetation moderately vascular on Doppler (both ovaries); ▪ starting point in epithelial capsule shell (thick and hyperechogenic); ▪ ultrasound criteria for PCOS; ▪ 7 cm of pelvic fluid in Douglas's cul-de-sac.	
CT findings	▪ ascites fluid surrounding the uterus and adnexal areas.	
Exploratory laparoscopy	***Samples***	▪ surrounding tissue of both ovaries; ▪ pelvic fluid; ▪ peritoneal implants.
	Histological examination	▪ bilateral borderline ovarian-micropapillary variant/non-invasive low-grade serous carcinoma; ▪ non-hierarchical branching architecture; ▪ fine micropapillae emanate directly from large, fibrotic papillae; ▪ cells lining the micropapillae – rounded, cuboidal to polygonal; ▪ ↑↑↑ nuclear to cytoplasmic ratio; ▪ more atypical nuclei.
	Immunohistochemical analysis	▪ CK 7, WT1, and PAX8 – diffuse strong expression; ▪ P53 (+) – 25% in the tumor cells; ▪ ER (+) – 85% in the tumor cells; ▪ PR (+) – 85% in the tumor cells; ▪ Ki67 (+) – 15% in the tumor cells.
	Surgical specimens/ Samples	***Outcome***
Radical surgery	▪ uterus; ▪ uterine cervix; ▪ bilateral annexes; ▪ peritoneal fluid; ▪ external iliac lymphadenectomy; ▪ obturator lymphadenectomy.	▪ six months/one year after the intervention; ▪ CT scan – no sign of peritoneal changes, normal pelvic postoperative aspect, homogenous minimal fluid collection in Douglas pouch.

US: Ultrasound; PCOS: Polycystic ovary syndrome; CT: Computed tomography; CK 7: Cytokeratin 7; WT1: Wilms tumor protein 1; PAX8: Paired box 8; ER: Estrogen receptor; PR: Progesterone receptor.

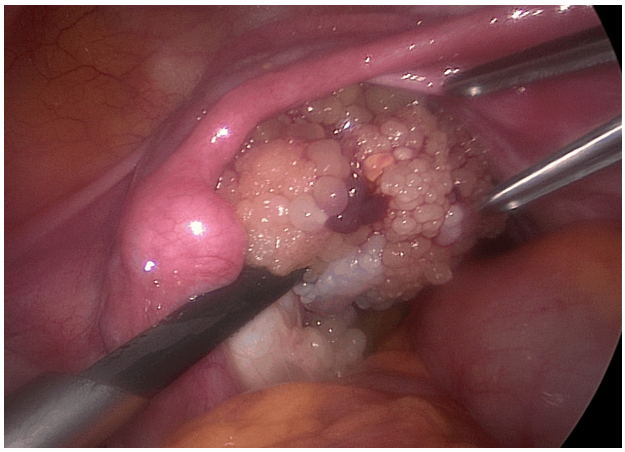

Figure 3 – ***Laparoscopic appearance of one of the ovary.***

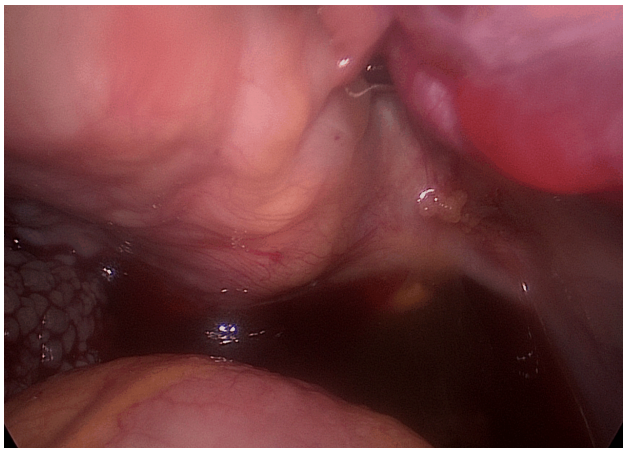

Figure 4 – ***Laparoscopic aspect, pelvic fluid and peritoneal implant.***

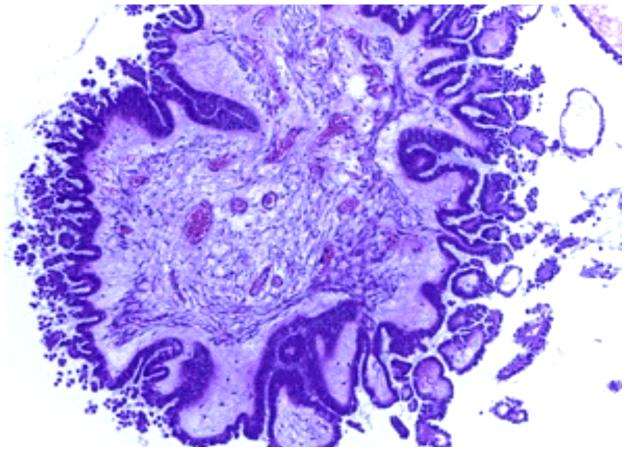

Figure 5 – ***Borderline ovarian serous tumor (HE staining, ×100).***

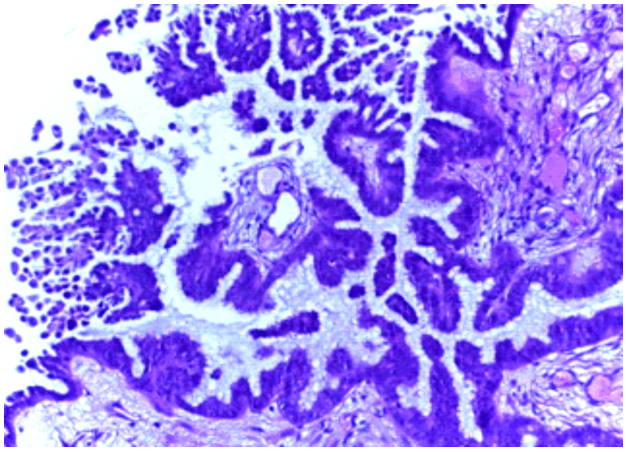

Figure 6 – ***Borderline ovarian serous tumor (HE staining, ×100).***

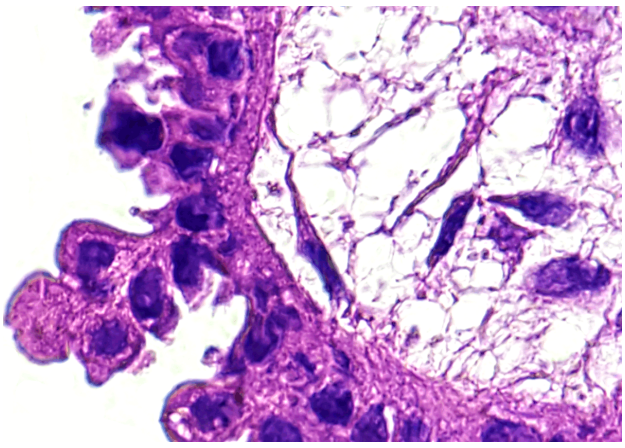

Figure 7 – ***Borderline ovarian serous tumor aspect with micropapillae and cellular atypia (HE staining, ×400).***

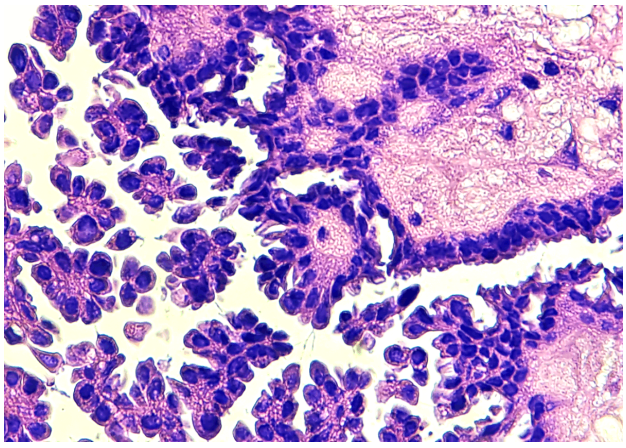

Figure 8 – ***Borderline ovarian serous tumor aspect with micropapillae and cellular atypia (HE staining, ×200).***

Immunohistochemistry study

The immunohistochemistry (IHC) was performed on 3 µm sections from 10% formalin-fixed paraffin-embedded tissues according to the IHC method an indirect bistadial technique performed with a polymer-based detection system (Max Polymer Detection System – Leica Ref. RE 7280-k). Tissue sections were spread on poly-L-lysine-coated slides immersed in three changes of xylene and rehydrated using a graded series of alcohol.

Antigen retrieval was performed in microwave oven. In each section, endogenous peroxidase was blocked by 20 minutes incubation in 3% hydrogen peroxide. The sections were incubated with primary antibody: cytokeratin (CK) 7 (Leica, 1:50, OV-TL 12/30), PAX8 (Cell Marque, 1:50, MRQ-50), estrogen receptor (ER) (Leica, 1:40, 6F11), progesterone receptor (PR) (Leica, 1:50, 16), WT1 (Leica, 1:30, WT49), p53 (DAKO, 1:50, DO-7) and Ki67 (DAKO, 1:100, Mib-1) at room temperature for one hour. The Max Polymer Detection System – Leica Ref. RE 7280-k was then applied for 30 minutes. Finally, the sections were incubated in 3,3'-diaminobenzidine (DAB) for 5 minutes, counterstained with Meyer's Hematoxylin and mounted. The slides were examined and photographed on Leica DM750 microscope. Negative controls were obtained by replacing the primary antibody with non-immune serum. As a positive control, an ovarian tissue section was used.

Immunohistochemically, the tumor cells presented a diffuse strong expression for: CK 7 (Figure 9), WT1 (Figure 10), and PAX8 (Figure 11). P53 was positive in about 25% in the tumor cells (Figure 12), ER was positive in about 85% in the tumor cells (Figure 13), PR was positive in about 85% in the tumor cells (Figure 14) and Ki67 was positive in about 15% in the tumor cells (Figure 15). Immunohistochemically assays correlated with the histopathological picture and anatomical clinical data confirm the diagnosis cited above (Table 1).

An oncological examination was performed that indicated a radical surgery accompanied by external iliac and obturator lymphadenectomy. After informed consent, the patient underwent radical surgery with a quick and uneventful recovery. The removed pieces, uterus, bilateral annexes, specified lymph nodes and a sample of peritoneal fluid, were transmitted for the histopathological and cytological examination (Table 1).

Subsequent monitoring of the patient rests for the oncologist that had to decide the necessity of applying the chemotherapy treatment, which after aggressive surgical debunking and identified invasive implants, such as in our case, was recommended. The patient presented a severe allergic reaction to all oncological treatment; in this condition, the only applicable management remained clinical and radiological surveillance.

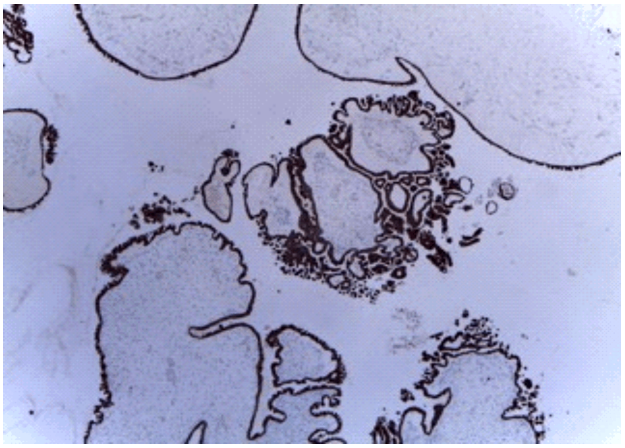

Figure 9 – ***Borderline ovarian serous tumor CK 7 diffuse positive in tumor cells (IHC staining, ×40).***

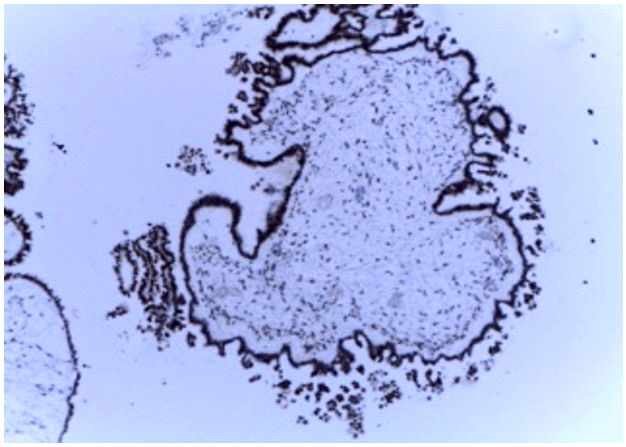

Figure 10 – ***Borderline ovarian serous tumor WT1 diffuse positive in tumor cells (IHC staining, ×40).***

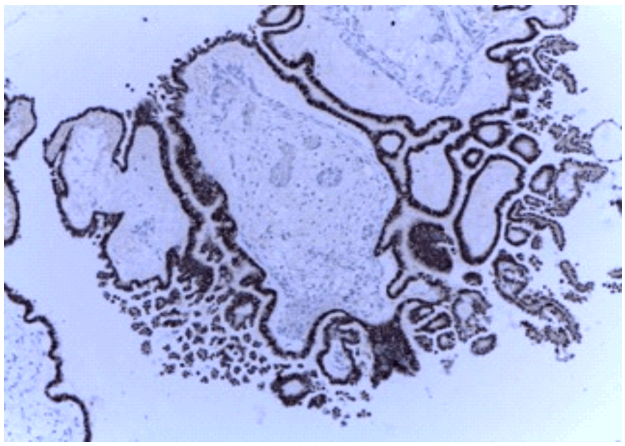

Figure 11 – ***Borderline ovarian serous tumor PAX8 diffuse positive in tumor cells (IHC staining, ×40).***

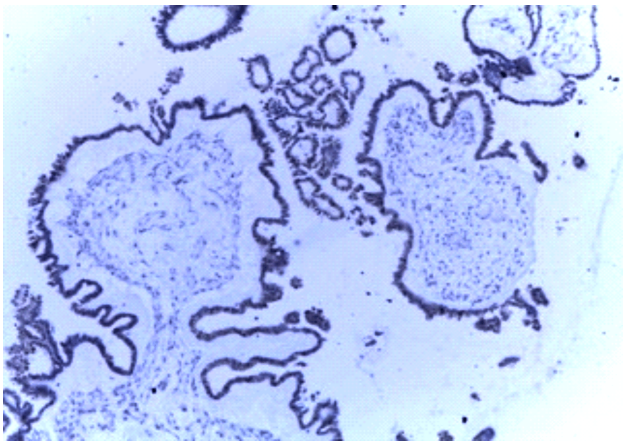

Figure 12 – ***Borderline ovarian serous tumor p53 positive in approximately 25% of tumor cells (IHC staining, ×40).***

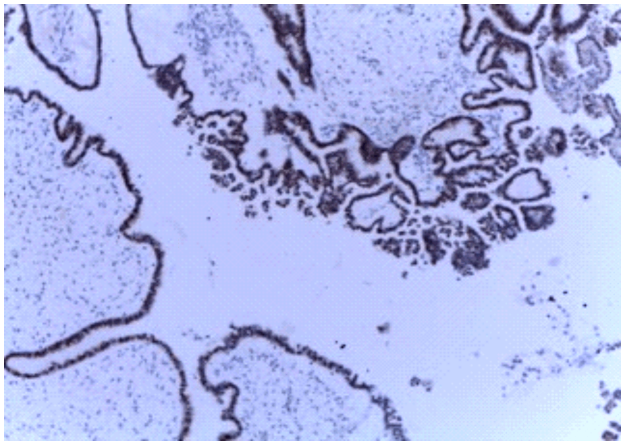

Figure 13 – ***Borderline ovarian serous tumor ER positive in about 85% of tumor cells (IHC staining, ×40).***

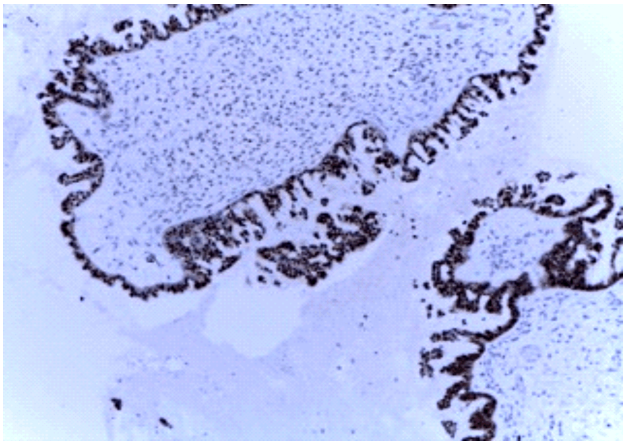

Figure 14 – ***Borderline ovarian serous tumor PR positive in about 85% of tumor cells (IHC staining, ×40).***

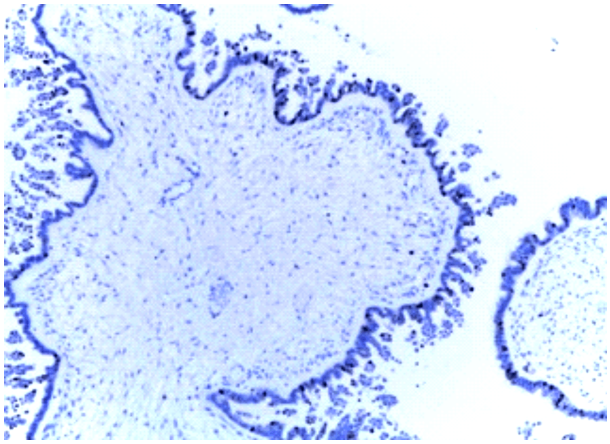

Figure 15 – ***Borderline ovarian serous tumor Ki67 positive in approximately 15% tumor cells (IHC staining, ×40).***

The control CT performed six months after the intervention and one year after the intervention revealed no sign of peritoneal changes in neoplastic context, with normal pelvic postoperative aspect with the persistence of a homogenous minimal fluid collection in Douglas pouch (Table 1).

Discussion

The particularity of the presented case lies in the young age of the patient, 19 years, and the atypical appearance of the tumor sonographically and macroscopically, also, the absence of any symptoms until stage III C. The WHO *Classification of Tumors of Female Reproductive Organs* shows two forms of serous borderline ovarian tumors: serous borderline tumor/atypical proliferative serous tumor (8442/1) and serous borderline tumor – micropapillary variant/non-invasive low-grade serous carcinoma (8460/2). The importance of this classification is that for the first form radical surgery is not indicated, instead the second one demands it [22].

The series of investigations had the objective to establish the best management of the case and reviewing the possibility of a conservative surgery. Patient clinical aspect matched with the patterns of ovarian borderline tumors by the asymptomatic presence of the bilateral adnexal masses. A series of five similar cases was reported by Ludovisi *et al.* [23], which had analyzed the ultrasound aspects of serous surface papillary borderline ovarian tumor. In order to nuance the differences in clinical appearance, diagnosis and management of synchronous ovarian tumors we mention a recently presented case of synchronous bilateral primary ovarian carcinoma with a similar approach and a good postoperative outcome [24]. The choice between conservative and surgical management, relies on the ultrasound exam that can reveal a suspicious appearance (papillary vascularized excrescences) and guide the clinician to other investtigations that can confirm the suspected diagnosis. As

mentioned above, borderline tumors tend to occur at fertile ages; therefore, in less suspicious cases the goal is to preserve fertility and ovarian function. If both ovaries are involved, or the mass has the potential to be malignant, it is essential a preoperative discussion of patient preferences and options regarding conservative or radical surgery. Before surgery, a preoperatory staging is essential. The staging of borderline ovarian tumors complies with the staging of malignant tumors of the ovary. The complete staging of ovarian tumors includes total abdominal hysterectomy and bilateral salpingo-oophorectomy with peritoneal washing, diaphragm samples, omentectomy, and resection of grossly visible metastases, applied for women with stage II or higher. Lymphadenectomy is not regarded as compulsory in the staging and in the treatment of borderline ovarian tumors, but a positive lymph node sampling indicates an unfavorable outcome.

Lymph node dissection is supported by Leake *et al.* in a comprehensive study including 171 cases with epithelial ovarian tumors of low malignant potential, because they found that a small number of women with tumors apparently confined to the ovary had lymph node involvement, and that, while these women had an excellent prognosis, they were more likely to have a recurrence than those who did not have lymph node involvement [25].

Due to the surgery described above, we can detect an occult invasion and the prognosis of recurrence is more easily to follow and evaluate. Higher-stage disease is the major risk factor associated with recurrence [26]. Post-treatment surveillance is important and follows the guidelines of *Society of Gynecologic Oncology* (SGO) and *National Comprehensive Cancer Network* (NCCN). Adjuvant chemotherapy is mandatory for the ovarian malignant tumors treatment, but for the borderline tumors its effectiveness is controversial, and it is recommended only if invasive implants are identified on surgery [27, 28], as it was in our case.

Conclusions

Borderline tumors have an excellent prognosis, but the risk of malignant transformation remains unclear. In case of recurrence, the optimal approach appears to be surgical cytoreduction. Borderline ovarian tumors are more difficult to diagnose correctly than are benign and invasive malignant ovarian tumors; regarding the age of the patient, a series of complex investigations aimed to confirm the diagnosis and the necessity of the radical surgery have to be done.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Roxana Elena Bohîlţea and Nicolae Bacalbaşa equally contributed to this article.

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