CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Diagnosis problems in a case of ovarian tumor – case presentation

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Abstract

Ovarian epithelial tumors are the most common ovarian neoplasms, standing for more than half of all ovarian tumors. Borderline ovarian tumors represent a distinct group recognized by the *World Health Organization* (WHO), histologically distinct low ovarian carcinomas. They are tumors with low grade of malignancy with good progress and prognosis. The authors present a case of an ovarian tumor with diagnosis problems. It was the case of a 38-year-old patient with no genital pathological history, presenting hypogastric pain, dysmenorrhea, abdominal distension. The imaging performed examinations suggested an ovarian tumor with potential malignancy. The symptoms were nonspecific and the treatment was surgical. The piece was processed by paraffin inclusion and microscopically examined. Although the imaging examinations may be suggestive for potentially malignant lesions, the histopathological relation with the immunohistochemical one is the one that establishes the diagnosis. Following these examinations, there was established an ovarian borderline tumor. This is included in the lesions with low malignancy, the further evolution of the patient being a good one. The purpose of this presentation was the warning of the importance of histopathological examination linked with the immunohistochemical one, although the imaging may present lesions with malignancy criteria. Also, it was performed a literature review of borderline tumors in young women in terms of diagnosis and therapeutic conduct.

Keywords: serous epithelial tumors, borderline epithelial tumors, immunohistochemistry, laparoscopy.

Introduction

The epithelial ovarian tumors are the most common ones, standing for about 60% of all ovarian tumors [1]. The ovarian tumors that raise diagnosis problems are those of the borderline type. The image analysis, raising the suspicion of a tumor with malignant potential, after surgery, is most often the borderline tumors. According to the literature, the borderline epithelial tumors incidence is only 5% of the ovarian epithelial tumors [2]. According to other authors, they stand for about 15% of all ovarian malignant primary tumors [3]. Although the concept of borderline tumor has been accepted for decades, the literature is still confused in terminology and the criteria for differentiation of ovarian carcinomas with a low-grade malignancy. In general, most pathologists accept the recent *World Health Organization* (WHO) classification as synonymous with borderline tumors, with a low malignant potential [4]. These tumors must be differentiated by the serous carcinomas of low grade showing other histo-pathological characters [5]. These tumors with low-grade malignancy, known as borderline tumors, are tumors with atypical epithelial proliferations without a stromal invasion, histologically different, progressing to low-grade malig-nant carcinomas [6]. According to numerous specialized studies, there is supported the stromal microinvasion without destruction and reaction [7, 8]. Such tumors have a long-term good prognosis of five-year survival of 99% [9]. From the histological point of view, borderline ovarian tumors may be of more subtypes: serous, mucinous, and endometrioid with clear cells or with transitional cells (Brenner) [10]. The correct diagnosis of a tumor with diagnosis problems is performed by a histopathological corroboration with the immunohistochemical one. Young patients are treated conservatively by surgery, often-limited laparoscopic one, with the conservation of the contralateral ovary and uterus. In this paper, we present a case of ovarian tumor show problems for positive and differential diagnosis

Patient, Materials and Methods

Patient C.M., aged 38 years, from the urban area, was hospitalized in the No. 4 Clinic of Obstetrics and Gynecology within the "Prof. Dr. Panait Sârbu" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania (Observation sheet No. 17454/06.13.2013) for a hypogastric pain, intensely during the premenstruation period and dysmenorrhea. In 2013, she was diagnosed with coronary heart disease and anxiety-depression disorders, for which she underwent a treatment with Alprazolam 0.5 mg 1 tablet/day.

The clinical examination revealed a patient with normal weight, with no significant pathological changes, the patient

showing the sensation of fullness, dysmenorrhea, except for a diffuse pelvic pain on palpation.

The gynecological examination revealed a closed cervix, a normal volume uterus, improved consistency, regular shape, painless on palpation. The front and lateral sides of the uterus showed a tumoral formation about 7 cm in diameter, sensitive to palpation, with relatively little mobility, of a slightly irregular shape.

The ultrasound examination revealed the presence of a tumoral formation of about 6.5 cm, located on the left adnexal lodge with uneven echostructure (perhaps ovarian tumor). Pelvic native magnetic resonance imaging (MRI) and with contrast substance revealed a left ovary with increased size (83/77/60 mm) with a heterogeneous structure, presenting a previous large mass of 68/63/60 mm, polylobular discrete contour, bounded by its own wall with a heterogeneous internal structure with many fluid areas (hypersignal T2 and hyposignal T1, non-gadolinophilic), with many tissue buds up to 30 mm, with gradual, non-homogeneous gadolinium. The expansive ovarian mass was in direct contact with the superolateral wall of the left side of the uterus with bladder, the sigmoid, executing a mass effect on these organs, without invading them. The rest of the left ovary had a normal structure. The right ovary, uterus presented no pathological changes. There were highlighted no pelvic, groin or pelvic bone lymph nodes. In conclusion, the left ovarian tumor had MRI characters of malignancy, without invasion into the neighboring organs without pelvic lymph nodes.

The laboratory-conducted tests were normal: Hb (hemoglobin) 14.4 g/dL, WBCs (white blood cells) 7200/mm^3, blood glucose 98 mg/dL, urea 16 mg/dL, uric acid 4.6 mg/dL.

There was decided to perform surgery for a therapeutic purpose, but also for the completion of the positive and differential diagnosis. After obtaining the informed consent of the patient, under general anesthesia there was performed laparoscopically left ovariectomy with oophorectomy. The macroscopic examination of tumor formation showed the presence of cystic structures of 8/8/6 cm, with intact capsule, outer smooth surface, renitent consistency. On the longitudinal section, there drained a purulent necrotic content with papilliferous multiple protrusions on the internal surface of yellowish-white color, suggestive for a cystic serous borderline tumor. For the positive and differential diagnosis, there was recommended a histopathological and immunohistochemical study on the pieces fixed in formalin and included in paraffin.

Histopathologically, there were processed tumoral fragments from different areas. On common histochemically stained sections, there were found fragments with microscopic structure, ovary with numerous papillary proliferations of varying sizes with hierarchical distribution, with areas with small buds or epithelial shoots (Figure 1A). On other sections, there are identified epithelial buds of micropapillary aspect, with cells containing eosinophilic cytoplasm, hypertrophic nucleus, slightly irregular shape, evident nucleols (Figure 1B). On the histochemical stains of Goldner–Szekely (GS) trichrome type, there is a highly rich diffuse stromal inflammatory infiltrate of chronic and acute mixed type, dilated vessels with leukocyte exudate (Figure 2A). On other sections, the stroma is variable from fibrous to hialinized sources (Figure 2B), edematous sources (Figure 2C) or myxoid ones (Figure 2D). There are observed papillary sources with epithelial stratifications of cyto-nuclear minimal or moderate atypia, some bicores and an intensely eosinophilic cytoplasm (Figure 2D). The epithelial tumor does not involve external surface, had no cribriform growth, but had sources of micropapillary growth. Instead, no invasive implants were present and no lymph node metastases. The examination on usual histochemically stained sections suggested a serous ovarian borderline tumor with suspicious sources for malignancy.

For the immunohistochemical study, there were used the following antibodies: monoclonal mouse anti-human Ki-67 antigen (clone MIB-1, Dako, 1:50 dilution); monoclonal mouse anti-human p53 protein (clone DO-7, Dako, 1:50 dilution); monoclonal mouse anti-human cytokeratin (CK) 7 (clone OV-TL 12/30, Dako, 1:50 dilution); monoclonal mouse anti-human estrogen receptor (ER) (clone 1D5, Dako, 1:50 dilution); monoclonal mouse anti-human progesterone receptor (PR) (clone PgR 636, Dako, 1:50 dilution).

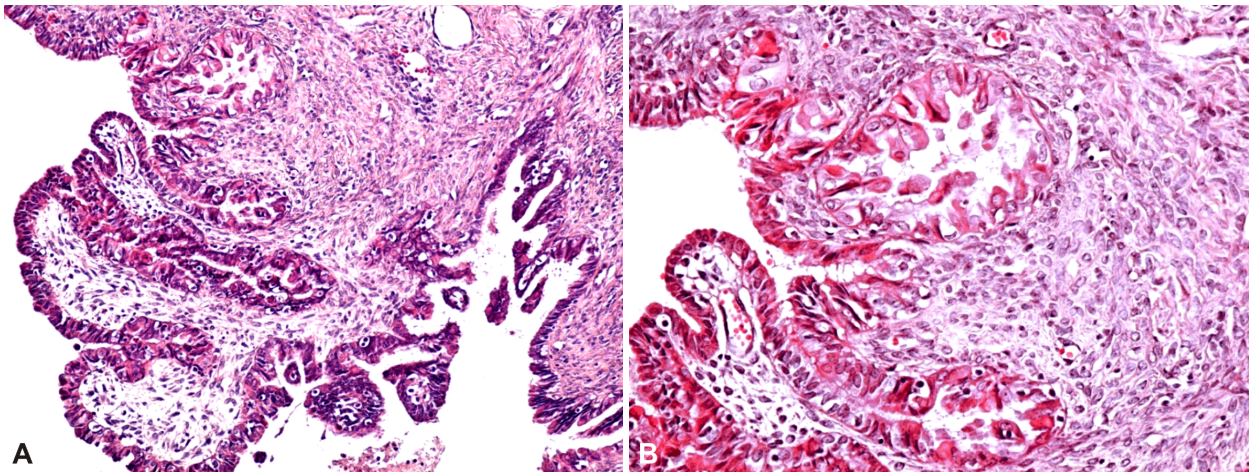

Figure 1 – ***(A) Ovary fragment with branched papillae and epithelial buds, stromal pseudoinvasion; (B) Another piece of ovary with epithelial stratification and atypical cytocores, micropapillar outbreaks. HE staining: (A) ×100; (B) ×200.***

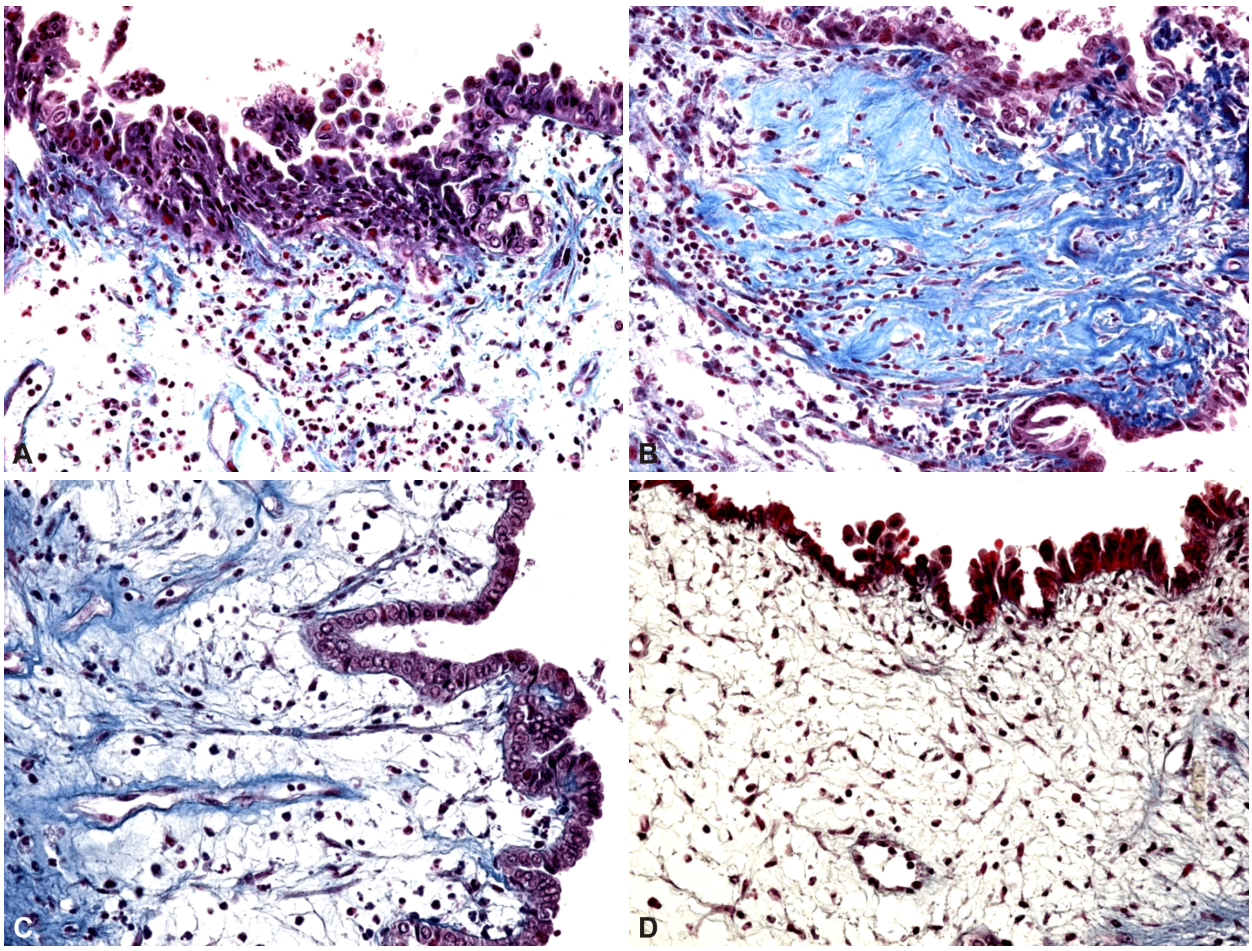

Figure 2 – ***(A) Fragment of ovary with inflammatory infiltrate rich stroma mixed type with stratified epithelium with cyto-nuclear atypia; (B) Another fragment with stroma and acute inflammatory infiltrate; (C) Another fragment with edematous stroma; (D) Another fragment with edematous stroma, papillary outbreaks with epithelial stratification of cytoplasmic nuclear atypia. GS trichrome staining, ×200.***

The performed immunohistochemistry shows different immunophenotypes for CK, estrogen, progesterone, Ki-67 and p53 proliferation markers. The immunohistochemical results for CK7 have a strong intracytoplasmic positivity, presenting an anarchic papillary proliferation with epithelial positivity (Figure 3A). The same intensity is highlighted in the epithelial buds with focal stratification and nuclear atypia (Figure 3B). The hormone markers for estrogen or progesterone have a strongly nuclear positivity of the tumor cells (Figure 4, A and B). The expressions of Ki-67 and p53 proliferation markers are features of borderline tumor. Thus, Ki-67 is focally positive in tumor cells, less than 2% (Figure 5A). As noted in Figure 5B, the lack of p53 overexpression in the tumor cells is characteristic for the serous borderline tumor. The corroboration of the histopathological outcome with the immunohistochemical one allowed the diagnosis of serous epithelial borderline tumor.

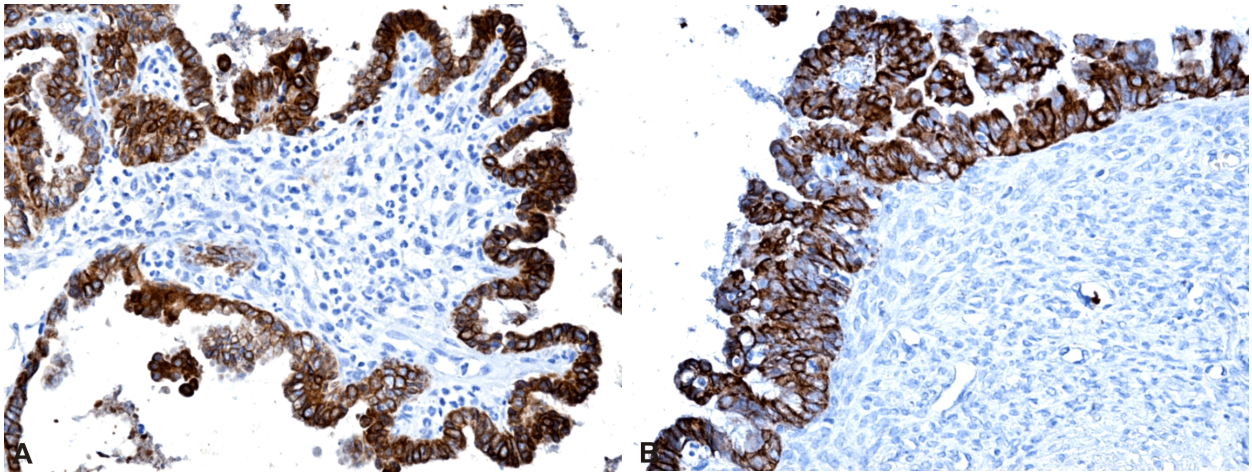

Figure 3 – ***Fragments of tumor with intense epithelial cells reaction at CK7 in branched papillae (A) and epithelial buds (B). Anti-CK7 antibody immunostaining: (A) ×100; (B) ×200.***

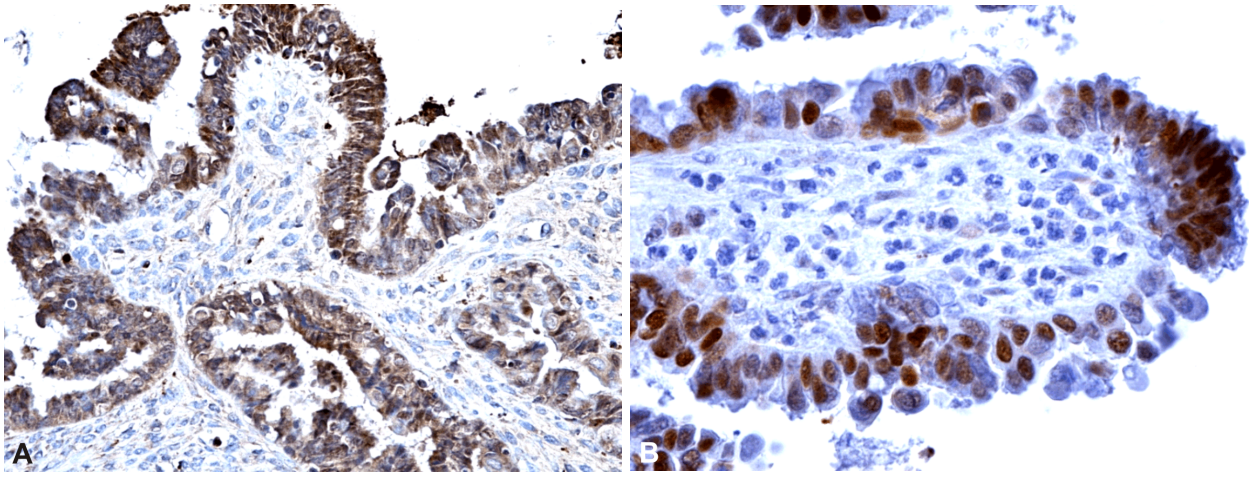

Figure 4 – ***Fragments of borderline epithelial tumor with intense positive reaction to anti-ER antibody (A, ×200) and anti-PR antibody (B, ×400).***

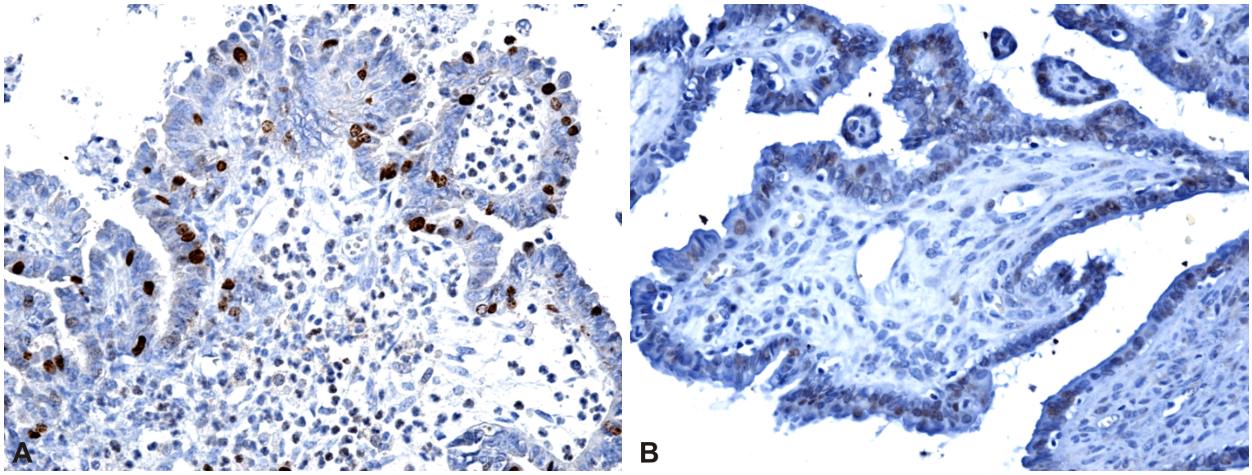

Figure 5 – ***Fragments of borderline epithelial tumor with Ki-67 positive focal reaction (A, ×200) and negative reaction to anti-53 antibody (B, ×200).***

Discussion

Epithelial ovarian tumors are the most common tumors of the ovary, the serous ones representing more than 50%. Among them, the most numerous are benign over 30%, 5.5% borderline and malignant 16.5% [11]. According to the latest WHO classification, the serous ovarian tumors include several subtypes, so the benign ones are cystadenoma, adenofibroma and cystadenofibroma, respectively, with a papilloma surface. The serous borderline tumors have two subtypes – serous borderline tumor or serous proliferative and atypical tumor and serous borderline tumor, with a micropapillary version. Malignant serous tumors are of two types: low-grade serous carcinomas and high-grade serous carcinomas [12]. Our case was diagnosed as borderline serous tumor. These tumors were first described by Taylor, in 1929, as "semimalignant tumors" [13]. The serous borderline tumors present both benign and malignant characters, the last ones being with low malignancy without destructive invasion characteristics and tumoral necrosis. Thus, WHO defines borderline serous tumors (TSBI) as low malignant potential, non-invasive ovarian tumors, presenting atypical epithelial proliferation with serous cells, but the atypia is lower than in serous carcinomas of low grade. Currently, in the same category there were included the microinvasive borderline stromal tumors, some showing more outbreaks [8, 14]. It is defined the concept of microinvasion in borderline tumors by the presence of individual cells or groups of cells present in the stroma, surrounded by a free space with optical slot empty aspect [15, 16]. Literature shows that the incidence of these outbreaks of microinvasion is presented variable by different authors from 25% [16] to even 50% in the tumor [17]. Other studies using epithelial markers to identify the microinvasion determined that they occur only in 13% of cases [18]. Based on the appearance of microinvasion, there were described two morphological forms, the one described and the micropapillary one [19]. Recently, there were described in the borderline tumor a micropapillary pattern or cribriform based on epithelium tumoral proliferation and not the microinvasive one [20]. WHO recognized two forms of serous borderline tumors: typical form and micropapillary form [12]. Clinically, the diagnosed patients are between the ages of 40–50 years with an average of 46 years [21]. Our patient was 38 years old, during fertile period, at the age of diagnosis. Patients with such tumors are generally asymptomatic or as shown in our case with abdominal discomfort, hypogastric pain, dysmenorrhea or abdominal pressure, fullness [22]. Borderline tumors of all histological subtypes, namely serous, mucinous, endometroid type, with clear cells, Brenner or sero-

mucinous represent only 15% of all ovarian tumors [21]. Of all borderline tumors, the serous ones are the most numerous. Histologically, the serous borderline tumors are characterized by epithelial stratification by nuclear atypia with papillary aspect, epithelial bud formation that usually appears at the top of papillae. Stroma of papillae varies from fibrous, edematous, hyaline or myxoid as it appears in our case. There may be present polymorphonuclear neutrophils and inflammatory infiltrates of lymphocytes, plasma cells [7]. It can be identified in this type of tumors a growth as in the case presented. Literature shows that some borderline tumors may present exophytic development, some being reported in more than 70% of cases [23]. Usually, this type of tumors is associated with peritoneal implants according to Longacre's studies [22]. Currently, it is recognized the microinvasion in these types of tumors without stromal destruction with two morphological patterns [14, 24]. The most common form of microinvasion is characterized by the presence of atypical cells with eosinophilic cytoplasm arranged single or in small groups but located in a space with an empty slot aspect. In our case, there were identified eosinophils cells in the epithelial proliferation of micropapillary type there appear no microinvasive outbreaks. Usually, around these outbreaks, there is no desmoplastic stromal reaction, necrosis or inflammation. The second type of microinvasion within these tumors is the micropapillary aspect or the cribriform pattern. The micropapillary one is considered by some authors (McKenney) as aggressive and often presents invasive peritoneal implants [8]. Generally, the microinvasive stromal tumors show also lymphovascular space invasion at high risk of lymph node involvement and tumor dissemination to multiple organs. The incidence of this nodal involvement is insufficiently studied in the literature and there are many controversies [25]. Although the clinical examination is not suggestive for ovarian cancer, currently it is supplemented by additional tests. In terms of paraclinical investigations, they are not specific for distinguishing between a benign ovarian tumor or a malignant one. The most important investigations are the imaging investigations. In addition, in our case, the imaging investigation was suggestive for an ovarian tumor that raised issues and the diagnosis was crucial for the therapeutic attitude. To complement these imaging exams, there is often necessary to conduct computer-scanner or magnetic resonance imaging. MRI morphological analysis is suggestive for differentiation borderline tumors of other ovarian carcinomas showing that in other carcinomas, the septa are thicker and the solid tumor components are more common. However, these morphological elements cannot make a safe differentiation from these tumor types [26]. The histopathological diagnosis is most often completed by the immunohistochemical one, which often offers the certain one [27]. The immunohistochemical evaluation includes the expression for ER, PR, epithelial markers type CK7 strongly positive in serous borderline tumors, respectively CK20 negative for this type of tumors. WT1 is a nuclear necessary marker, in more than 80% of serous ovarian carcinoma cases, present in over 80% of cases. P53 and Ki-67 are markers of tumor aggressiveness [28]. Ki-67 is strongly positive in borderline tumors and p53 negative in the same type of tumors, necessary markers to differentiate benign ovarian tumors of the borderline ones. In our case, the immunohistochemistry was categorical for the diagnostic. The genetic diagnosis has been involved in the progression of tumors of borderline serous type and in the diagnosis of high-grade serous ovarian carcinomas. The relationship between the borderline ovarian tumors and the mutations of BRCA1 and BRCA2 genes are still uncertain. However, it appears that the mutations of the BRCA genes show a smaller percentage of cases of borderline tumors than the invasive ovarian carcinoma [29, 30]. The treatment for this type of tumor is surgical intervention type and the method depends on several factors: patient age, associated diseases, laboratory test results including imaging. In our case, the tumor being a single size tumor, the tumor's dimensions and the imaging morphological aspect, and not the patient age, caused a laparoscopic intervention of the left appendix, with preserving the contralateral appendix and the uterus. The diagnosis of certainty was subsequently a histopathological and immunohistochemistry one. The therapeutic management is different. For the woman who wishes to preserve fertility or to avoid the effects of premature menopause the conservative surgery is practiced – unilateral ovariectomy – when the tumor is confined to one ovary and no peritoneal dissemination is present [31]. After this type of treatment, unilateral ovariectomy, the patients require regular monitoring every six months, clinical and imaging over a period of about five years for a tumor recurrence or onset nature of malignancy [32].

Conclusions

Ovarian tumors often show diagnosis problems by their histological frequency. The tendency for benign, borderline or current malignancy is suggested by morphological appearance and less by the clinical one. Thus, diagnosis becomes a certainty by the pathological diagnosis associated with the immunohistochemical one and in recent years with the genetic one. The surgical treatment is the therapeutic appropriate conduct, the type of management elected conservative or radically depends on several factors including the details of imaging, histological subtype, associated diseases and not least if allowed by patient age, fertility preservation.

Conflict of interests

The authors declare that they have no conflict of interests.

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Received: January 24, 2016

Accepted: December 10, 2016