MALIGNANT AND BORDERLINE EPITHELIAL OVARIAN TUMORS MORPHOLOGICAL ASPECTS AND PROGNOSTIC ASSAY

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Abstract: Tumors developing from Müllerian ducts are malignant epithelial tumors in approximately 85% of cases, borderline tumors representing only 15% of all epithelial ovarian tumors. Borderline ovarian tumors often occur in women of reproductive age (under the age of 40 years), usually nulliparous. Consequently, preservation of fertility becomes an important issue in early diagnosis and adequate therapy of borderline ovarian tumors. The adequate classification of borderline tumors, similar to their malignant counterparts, shows a morphologic spectrum composed of serous (with an incidence of 50%), mucinous (45%) and mixed types (5%) tumors and allows an improved prognosis of their behavior, as an essential issue in performing the most appropriate surgical therapy. *Study design*: Fifty seven patients with malignant and borderline epithelial ovarian tumors were included in our study. The clinical and histological data obtained from hospital records were retrospectively reviewed and statistically analyzed. *Results*: The mean age at the time of diagnosis was 33.4±2.4 years in borderline tumors *versus* 52.5±1.8 in malignant tumors. The macroscopic appearance of the tumors showed cystic ovarian masses, with diffuse papillary projections, in some cases perforating through and extending beyond the ovarian capsule, and exhibiting an associated solid component only in malignant tumors. The histopathological diagnosis of tumors was serous type (76.59%) and mucinous type (23.40%). Seven cases were diagnosed as borderline tumors (12.28%) and were classified as serous type. *Conclusions*: Accurate and complete histopathological assessment is required in ovarian epithelial tumors and is essential for prognosis and adequate therapy.

INTRODUCTION

Approximately 90% of ovarian cancers arise from the coelomic epithelium that lines the surface of the ovary, a multipotent epithelium that may subsequently differentiate into endometrial, endocervical, tubar or intestinal epithelium, histogenesis explaining the variety of epithelial ovarian tumors (1).

Depending on the intensity of cellular growth, the degree of nuclear atypia, and the degree of stromal invasion, the epithelial ovarian tumors are benign, malignant and borderline types. In 1928, Taylor described for the first time the borderline ovarian tumors (BOTs), currently known as low malignancy potential ovarian tumors (LMPOTs), subsequently included, in 1971, into FIGO (International Federation of Gynecology and Obstetrics) and in 1973, into WHO (World Health Organization) classifications. Most BOTs are diagnosed in early stages, and they represent approximately 15% of the ovarian tumors. In histopathology terms, accordingly the clinical expression and prognosis, BOTs occupy a medium position, between benign and malignant types, with the following characteristics: diagnosis in early stages (80-90% of the patients are in the 1st stage), increased survival rate, slow development of lesions, the possibility of spontaneous regression of peritoneal disseminations, diagnosis in young women (most serous borderline tumors occur before the age of 40 years, when the therapy decision is determined by fertility preservation considerations) and low recurrence incidence rate. The histopathological diagnosis involves the analysis of multiple tissue samples, to determine the invasion degree. The clinical and histopathological elements support the assumption that, in some cases, extraovarian tumors may develop multiple foci of primary serous tumor (2, 10).

Based on the experience of the 3rd Clinic of Obstetrics and Gynecology Iasi, the purpose of the hereby research was to assess the morphologic and pathological characteristics useful for the accurate diagnosis of malignant and borderline ovarian tumors originating in surface epithelia, in comparison to the available data in the literature.

MATERIALS AND METHOD

Between 1999 and 2005, a retrospective-prospective research, of a group of 57 patients diagnosed with either malignant or borderline ovarian tumors of surface epithelia, treated in the 3rd Clinic of Obstetrics and Gynecology Iasi, has been conducted. The histopathological information was collected from the patient files, upon their consent. The histopathological diagnosis was performed on resection specimens or on aspiration cytology, within the Laboratory of Pathology of 3rd Clinic of Obstetrics and Gynecology of Iasi. The specimen processing was made in the following stages: 0.5-1 cm^3 fragments of the resection specimens were collected, avoiding necrosis areas, processing and staining using routine and special techniques (HE, Alcian Blue, and PAS). After the microscopic examination, the data were analyzed and expressed in average value terms, percentages and standard deviations. The statistical processing was made using Microsoft Excel 2007.

RESULTS AND DISCUSSIONS

The analysis of the case mix investigated, on study years, revealed a low incidence of malignant and borderline ovarian tumors; thus 57 cases have been diagnosed in 7 years, with a variable distribution on years (between 5 and 10 years, with a peak in 2000). Out of 57 cases considered, 7 (12.28%) have been diagnosed with borderline tumor, and 50 (87.72%) with malignant tumors. The maximum incidence of malignant and borderline epithelial tumors was recorded in the 6th age decade (31.91% of the cases), followed by the 7th decade (23.91% of the cases), while the 4th decade was equal to the 3rd decade (14.89%) (fig. 1).

The patients age with borderline tumors ranged between 18 and 76 years, with a significantly reduced average compared to the malignant tumors average (33.4 ± 2.4 years *vs.* 52.5 ± 1.8 years).
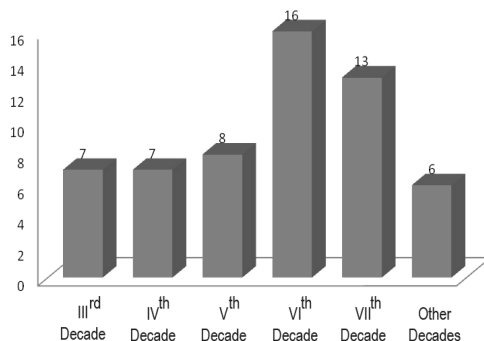

Fig. 1. Distribution on age groups of patients included in the research sample

Out of 7 patients with borderline tumors, 5 were nulliparous, and only 2 patients had an obstetrical history, unlike the patients with malignant tumors, who were equally nulliparous and multiparous (fig. 2).
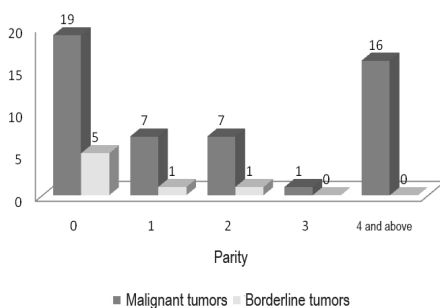

Fig. 2. Distribution of patient according to ovarian tumor types

As regarding the specificity of ovarian involvement, a unilateral dominant aspect (71.43%) was noted, while the bilateral tumors were recorded only in 28.57% of cases (2 patients).

The macroscopic appearance of borderline tumors revealed the presence of minimal vegetations on the cyst walls (fig. 3), unlike the malignant tumors, characterized by prominent, extended, internal and sometimes external proliferations, containing hemorrhage and necrosis areas, associated with solid areas.
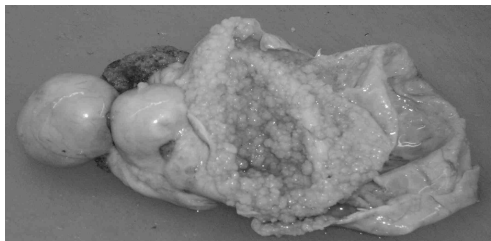

Fig. 3. Serous borderline cystadenoma- macroscopic view

The macroscopic aspect of mucinous tumors showed a gelatinous content, inside the cyst cavities, unlike the serous tumors, that presented a serous, transparent or sometimes hemorrhage contents.

The histological types registered a peak incidence of serous tumors (76.59%) compared to the mucinous tumors (23.40%). The borderline tumors (12.28%; 7 cases) were diagnosed as exclusively serous types.

The ovarian pathology incidence in our study is relatively low when compared to the reported data in literature, the cervical and uterine pathology being dominant, as a reflection of the social and economic levels in our geographical region.

The age of patients diagnosed with borderline tumors was lower in comparison to that of patients diagnosed with malignant tumors (33.4 *vs*. 52.5), thus confirming the reported data in literature; accordingly, under the age of 45, malignant ovarian lesions are relatively rare (3, 12, 15). This difference certifies the existence of a latency period during the development of malignant lesions resulted from benign and borderline lesions, with progressive accumulations of genetic mutations. *De novo* cancers, without precursor lesions, are exceptionally rare.

The clear correlation of unilateral involvement preponderance in borderline ovarian tumors (71.43%) corresponds to the literature data (1, 3, 13, 15).

Macroscopically, it is difficult to differentiate borderline tumors from benign counterparts (cystadenomas) or malignant counterparts (adenocarcinoma), the size and extension degree of vegetations being approximately useful, while diagnosis may be achieved only by microscopic examination.

According to the diagnosis data in the literature (1, 4, 11), the following morphological criteria have been useful to differentiate between malignant and borderline tumors: the degree of complexity and uniformity of the histological architecture, the variable association of solid areas, stromal characteristics (myxomatous, hyaline or desmoplastic areas) around invasive aspects (considered those exceeding 10 mm^2), psammoma bodies (in serous type), the aspect of micropapillary epithelial hyperplasia, with layers (usually, not more than three layers but sometimes with four or more layers), the presence of a minimal stromal support, detached cell groups, the degree of nuclear irregularity and mitotic index (14).

BOTs have been defined due to the presence of a nuclear pleomorphism, with epithelial layers and development of microscopic papillary extensions, in the absence of stromal invasion. There are certain common histopathological characteristics present in both borderline and

malignant ovarian tumors, such as the epithelial tissue layers covering the papillae, the formation of microscopic papillary extensions at the epithelial surface of papillae, the epithelial pleomorphism, cellular irregularities and the presence of mitotic activity (5). The absence of an identified destructive stroma invasion and the presence of minimum two of the abovementioned characteristics are sufficient in the diagnosis of a borderline ovarian tumor (fig. 4).
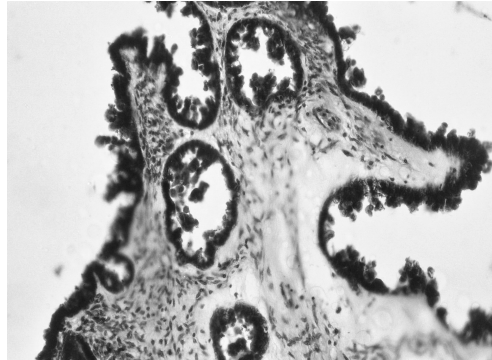

Fig. 4. Serous borderline ovarian tumor with complex papillary aspect, atypia, and minimal stratification (HE x 20).

Borderline tumors present two histopathological types (1, 3):
1. Serous borderline tumors (55%) classified using WHO criteria, as S-BOTs
Macroscopically, BOTs consist of one or more cystic structures, with polypoid projections based on an endophytic and/or exophytic growth pattern. Microscopically, the tumors present complex intracystic papillary arborizations, as commonly observed in our study. Micropapillary S-BOTs may be defined as tumor growths with minimum one permanent micropapillary growing area exceeding 5 mm^2 and the absence of stromal invasion. The lymphatic invasion is represented by lymph node containing borderline epithelial tumor (serous, mucinous or mixed), increasing the tumor stage, in accordance with FIGO classification.

S-BOT presents the following histopathological types:
a. The micropapillary S-BOT presents a fibro-vascular core surrounded either by "jellyfish head" shaped villous micropapillae, or by cribriform epithelium, or, sometimes, by a combination of these two patterns. Tumors contain minimum one continuous area of micropapillary growth, with more than 5 mm in diameter. This cellular pattern is associated to a variable prognostic, and its poor prognosis is determined by the simultaneous presence of several invasive peritoneal disseminations (6).

b. The microinvasive S-BOT is defined by the presence of an invasive area of maximum 10 mm^2, for each invasive center. These areas consist of a single epithelial lining and microcellular masses (that do not exceed 3 mm in length) and polymorphous disseminations; these tumors are associated to extra-ovarian exophytic growths, billaterality and diagnosis in advanced stages. A recent study, using the inactivation of X chromosome in patients with borderline ovarian tumors and peritoneal disseminations, showed that peritoneal tumors and BOTs develop independently but simultaneously, in accordance to the polyclonal and multifocal origins of peritoneal carcinomas (6).

Lymph nodes involvement in S-BOTs presents two types of development: primary lymph node involvement (with tumor-free subcapsular sinuses) and lymph node involvement (with

tumor present inside the lymph nodes sinuses), known as metastasis. In our study, no lymph node involvement was detected in S-BOT. Recent molecular studies revealed that serous malignant tumors follow a stage based pattern, developed from atypical tumors, passing through an intraepithelial micropapillary serous carcinoma *in situ* stage, and they are frequently associated to k-RAS or b-RAF mutations, and rarely associated to p53 mutations. On the other hand, strongly invasive serous carcinomas originate in the epithelial surface of the ovary or within cystic inclusions, and its intermediate stages are characterized by the presence of p53 mutations and rarely by k-RAS or b-RAF mutations (7, 9).

2. Mucinous borderline tumors (M-BOTs)

M-BOT represent 10-15% of mucinous ovarian tumors and 40% of borderline tumors, and they are characterized by epithelial proliferation of mucinous cells and variable malignancy degrees within the same tumors, from benign to invasive behavior. In literature, M-BOT are classified into two categories: gastrointestinal and endocervical. Although no mucinous borderline tumors were diagnosed in the investigated case mix, the two mucinous cytological types have been noticed in malignant types, with a preponderance of the endocervical type tumoral cells. M-BOT has the following histopathological characteristics (1, 3, 15):

a. Gastrointestinal M-BOTs are multilocular tumors, containing mucinous fluid, and may be covered by papillae and variable several pedicle outgrowths. Microscopically, they are characterized by the presence of glands and cysts of variable size and shape. Focally, the epithelium shows complex multilayered proliferations.

b. Endocervical M-BOT is a unilocular tumor (80%) with evident intracystic papillae. Microscopically, they are characterized by complex epithelial proliferations, with a similar architecture as S-BOTs, covered by endocervical cells containing mucus, and polygonal cells, with rich eosinophilic cytoplasm.

c. M-BOTs containing intraepithelial carcinoma show multilayered, cribriform areas, and severe nuclear atypias, known as non-invasive epithelial carcinomas.

d. Microinvasive M-BOT has one or several dissemination forms. The tumor is formed by irregular glands and single or groups of cells, surrounded by a net area of invasion of 3-5 mm.

e. Ovarian pseudomyxoma and pseudomyxoma peritonei.

M-BOT is sometimes characterized (in 10% of the cases) by extraovarian disseminations in the form of pseudomyxoma peritonei. In literature, PMP (pseudomyxoma peritonei) is defined as a clinical-pathological syndrome, with mucinous ascitis associated to mucinous neoplasia, almost always derived from torn appendix mucinous tumors.

To achieve an accurate diagnosis, the presence of both invasive and noninvasive peritoneal implants must be quantified. Noninvasive implants do not significantly affect the 10 years-survival, unlike the invasive implants, associated to an unfavorable prognosis, since more than 50% of the patients develop recurrences, and the 10 years survival rate is only 33%. The peritoneal implants have been noticed only in malignant tumors in the investigated case mix, corresponding to a favorable prognosis in borderline tumors.

CONCLUSIONS

The accurate classification of borderline tumors in the current histopathological subclasses represents a crucial issue. The limited sampling of some tumor regions may determine a misdiagnosis, and consequently the lack of adequate treatment, that may be followed by the development of a malignant tumor. In order to reduce the risk of a misdiagnosis, we should collect samples from each centimeter of lesion.

Due to the fact that recent studies showed that approximately 86% of serous borderline tumors are diploid and 14% are aneuploid (1, 8), the modern diagnosis techniques should be used to improve the diagnosis accuracy and to evaluate borderline tumors prognosis.

In multicystic lesions, with multiple epithelial inclusions and penetration of tubular epithelial structures into stroma, it is difficult to ascertain the presence of stroma invasion, and thus, the malignancy.

The morphology of peritoneal implants represents the most important prognosis factor in borderline tumors.

Despite all current methods used in the diagnosis of malignant tumors, the histopathological investigation continues to be the essential investigation in the diagnosis and in the management of the optimal therapeutic strategy.

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