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SEROMUCINOUS OVARIAN TUMORS AND ENDOMETRIOSIS IN REPRODUCTIVE-AGED WOMEN

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Endometriosis affects up to 15% of reproductive-aged women. Consideration of this nosological entity in a new aspect is impelled by the evidence that 0.5-1% of cases are complicated by endometriosis-associated ovarian neoplasms represented mainly by the endometrioid and clear-cell subtypes of tumors. This category also includes seromucinous ovarian tumors (SMOTs).

Objective. *To investigate the morphological and immunohistochemical (IHC) features of SMOTs in reproductive-aged women, including pregnant ones.*

Subjects and methods. *Ovarian tumor samples from 15 patients who had been operated on in 2012-2016 were analyzed comprehensively at the National Medical Research Center of Obstetrics, Gynecology, and Perinatology: IHC examination was conducted using the biomarkers of estrogen and progesterone receptors and Ki-67.*

Results. *Borderline SMOTs were characterized by papillary growths on the inner surface (in one case) and on the outer surface, with an adhesive process with the serous surface of the corpus uteri (FIGO Stage 1c), and mixed epithelial structures; leukocyte infiltration was observed in four cases. The epithelium of seromucinous carcinoma (n = 1) was similar to that of serous, endocervical, and endometrial types at the same time. All the samples exhibited low Ki-67 expression and high positive receptor immunoreactivity. Endometriosis diagnosed in nine women was accompanied by benign seromucinous cystadenomas (n = 4), borderline tumors (n = 4), and carcinoma (n = 1).*

Conclusion. *Most of the examined SMOTs showed the areas, covered with the endometrioid epithelium, with adjacent endometrial stroma, which indicated the development of carcinoma in the presence of endometrioid cyst. The revealed facts suggest that endometriosis plays an etiological role in developing SMOTs. When detected, most neoplasms are localized (limited to ovarian tissue, FIGO stage 1a) and characterized by a favorable prognosis as a whole.*

Keywords: *borderline ovarian tumors, reproductive age, seromucinous ovarian tumors, endometriosis-associated tumors.*

Endometriosis has been estimated to affect up to 15% of reproductive-aged women [1, 2]. The most common localizations for endometrium-like tissue (epithelial and stromal component) foci include the peritoneum and pelvic organs, as well as the ovaries [3]. Foci of endometriosis have signs typical for ovarian cancer, such as multifocal structure, genetic instability, increased proliferative activity, and the ability to invade surrounding tissues. Atypical endometriosis is the intermediate stage in the process of transformation of endometriosis into cancer. On histology, it is characterized by hypercellularity, enlarged nuclei, as well as by pleomorphism [4].

Data on the development of endometriosis-associated neoplasms (EANs) of the ovaries allow us to consider this nosology in the aspect of oncological alertness. The ovarian tumors pathogenetically associated with foci of endometriosis develop rarely but manifest a very significant complication. One study has shown that ovarian cancer is associated with endometriosis in more than 19% of cases [5]. The results of the study performed by L. Saraswat et al., in turn, also confirmed an increased risk of ovarian cancer in women with external genital endometriosis [6]. Ovarian EANs most often affect women of reproductive age and include both benign, borderline, and malignant tumors [7]. It should also be noted that primary-multiple malignant neoplasms are more common in patients with endometriosis-associated cancer [8]. However, at the time of diagnosis, the majority of tumors are localized within ovarian tissue (stage 1), and therefore, in general, have a favorable prognosis [9].

Endometrioid and clear cell carcinomas are the most common EANs among malignant tumors. Border endometrioid and clear-cell tumors are very rare. In this article, we will describe in detail seromucinous tumors

(SMTs), which are the least studied group of epithelial tumors, accounting for about 15% of all ovarian tumors with intermediate grade of malignancy [10].

SMT is a group of epithelial neoplasms, which are characterized by the combination of several cell types, therefore, the abbreviation MM / ME (Müllerian mucinous/ mixed epithelial) tumors of mixed structure can be found in the literature [1]. In 2014, the category of seromucinous ovarian neoplasms was included in the classification of the female reproductive system tumors for the first time [1, 11, 12]. It is worth noting that the prerequisites for this were formed long time ago, in particular, in 1976 Fox and Langley proposed to use this term for ovarian neoplasms consisting of endocervical and serous epithelium [13]. Later, other authors reported about borderline ovarian cystadenomas combining different types of epithelium [11, 12]. Kurman et al. described seromucinous carcinoma, which was similar to borderline SMT by histological structure, but differed in the presence of stromal invasion in the form of "merging" glands [14]. Today, SMT includes mixed-type tumors represented by several types of epithelium originating from the remnants of the Mullerian duct, namely serous, endocervical, transitional cell and flat (predominant), while the second most spread component should occupy not less than 10% of the tumor volume [1].

SMTs are subdivided into benign, borderline and malignant in a similar way to other nosological subgroups of epithelial tumors (Table 1).

According to different authors, SMTs are associated with endometriosis in 30-50% of cases. Benign SMTs amount to not more than 1% of ovarian tumors and usually have a favorable prognosis [2].

Borderline SMTs can be difficult to diagnose until a certain time, since the emerging cellular atypia can be masked by papillary structure [11]. Borderline SMTs were previously classified as endocervical variant of borderline mucinous ovarian tumors. At present, SMT, endometrioid and clear-cell carcinomas form a group of tumors, which are pathogenetically associated with the foci of endometriosis [14].

The emergence of these tumors is associated with a somatic mutation of the ARID1A (AT rich interactive domain 1A) tumor suppressor gene encoding the BAF250a protein of the SWI-SNF-A complex involved in chromatin remodeling [15]. Interaction of ARID1A with p53 suppresses cell proliferation by p53-dependent transcriptional regulation of some tumor suppressors. Inactivating mutations of ARID1A and p53 are functional synonyms, because any of them stops the transcription of targeted tumor suppressors and leads to uncontrolled cell proliferation in ovarian neoplasias, which are associated with endometriosis. The specific microenvironment of the epithelium of endometrioid cysts, rich in oxygen free radicals (the result of iron oxidation), is considered as the mutation cause. It is proved that inactivation of a gene due to its somatic mutation is an early molecular event preceding the progression of endometrioid cysts into aggressive clear-cell or endometrial ovarian cancer. This event is one of the early stages of carcinogenesis and the development of tumors from the foci of endometriosis. Probably it demonstrates a new genetic pattern of ovarian tumors. ARID1A mutations were found in 41—57% of cases of the ovarian clear-cell carcinoma, in 30—48% of endome-

trioid cancer cases, in approximately 40% of cases with endometriosis and in 15-20% of patients with a benign endometrial cyst. Wu et al. have found a loss of ARID1A gene expression in a third of all SMTs [16]. Molecular genetic studies, as well as immunohistochemical studies, show the loss of ARID1A gene expression in the foci of endometriosis adjacent to the primary malignant foci, but there is no somatic mutation of this oncosuppressor gene in the other foci of endometriosis. This fact allows us to assume that edometriosis is the source of type I ovarian tumors. The article by E. Nakamura et al. described the case of detectining clear-cell cancer and borderline SMT of the ovaries, which is thought to originate from the foci of endometriosis. At the same time, mutations of the ARID1A gene were detected neither in the foci of endometriosis, nor in borderline SMT and clear-cell carcinoma [17].

It should be noted that only one mutation of the gene responsible for carcinogenesis is not sufficient for the malignant transformation of endometriosis. Other genetic mutations playing an important role in the processes of carcinogenesis are mutations in the genes PIK3CA, PPP2R1A, KRAS, CTNNB-1, PTEN, RUNX3, PTCH2, ERBB2, FOXM1B, FOLR1, etc. [10].

When describing the morphology of borderline SMT, their similarity to borderline serous tumors is emphasized: there may be areas of the micropapillary structure, intraepithelial carcinoma; stromal microinvasion can be found in 10—20%, but it, however, does not affect the prognosis. It is worth noting that borderline SMTs are characterized by bilateral involvement (20—30% of cases), stromal neutrophil infiltration, confirmation of the connection with endometriosis, and the absence of ring-shaped, neuroendocrine and Panet cells. Immunohistochemical examination shows negative staining to detect the expression of CK20 and CDX2 markers [11, 12].

Seromucinous carcinomas are relatively rare, and their development is often associated with borderline tumors. The authors of the appropriate section in the new WHO classification refer to the only paper published by H. Shappell et al., which described 7 seromucinous carcinomas including predominately papillary tumors with an expansive type of invasion [12]. It should be noted that the authors admit the classification of mixed tumors by the predominant component, for example, low-differentiated serous ovarian carcinoma with endometrial differentiation.

This paper presented morphological and immunohistochemical features of benign, borderline and malignant SMTs in women of reproductive age, including pregnant ones.

Materials and methods

The material for the present study included histological specimens and paraffin blocks of 15 patients with ovarian SMT, selected among 1179 specimens of ovarian tumors, which were further analyzed in Pathology and Anatomy Department of the National Medical Research Center of Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov from 2012 to 2016. The histological specimens were re-examined, additional sections were prepared from the preserved paraffin blocks (some of them were irretrievably given to patients for consultation and further observation in the outpatient

oncology clinic) and the immunohistochemical study was performed using the biomarkers of estrogen receptors (ER) (clone 1D5, DAKO), progesterone receptors (PR) (clone 636, DAKO) and Ki-67 cell proliferation marker (30—9, VENTANA). Ki-67 expression was evaluated by counting positively stained nuclei of 3000 cells, the evaluation of the expression of steroid hormones was performed using the formula H-score = 3a + 2b + 3c, where *a* is the percentage of intensively stained cell nuclei, *b* is the percentage of moderately stained, and *c* is the percentage of slightly stained nuclei. Marked expression was noted when the value of H-score was at least 200 points. The nuclear expression of ER and PR was considered as positive, there were more than 45% of stained cells. The immunoreactivity of ER and PR, as well as the proliferative activity of SMT epithelium, was calculated on the basis of the number of epithelium nuclei with the expression of these biomarkers per 100 cells (with at least 500 cells counted) and were expressed as a percentage. A low level of expression corresponded to the presence of 5—25% of stained cells, an intermediate level to 25—75% of cells, and high level to more than 75% of cells.

Results

Benign SMTs were found in seven patients aged 29.8±6.3 years, two of them had bilateral tumors. Two patients were 37—38 and 15—16 weeks pregnant by the time of surgery. Borderline SMT were diagnosed in six women aged 35.1 ± 4.6 years; all of them were unilateral. Seromucinous carcinoma was revealed in one patient aged 31 years.

Benign tumors were represented by cystadenomas. The diameter of these tumors in non-pregnant patients ranged from 1.5 to 6 cm, and wall thickness was up to 0.5 cm. Neoplasms were characterized by smooth outer surface, the inner surface was velvety, covered with mucus, with dark plaque in one patient, another patient manifesting barely noticeable papillary vegetations. In one pregnant woman, the tumor was 13x15 cm in size with papillary vegetations on the inner surface 0.2 cm in height located on the 0.5 cm area; another woman had 3×4 cm cystadenoma with numerous edematic papillary vegetations on the inner surface, 0.8 cm in height (Figure A). Microscopic examination revealed that the wall was characterized by ovarian tissue with fibrous changes, areas of edema, calcification foci, single-row lining epithelium (in one case it was of exclusively endocervical type, in others it was of endocervical type with areas of serous one).

Borderline tumors were cystic formations, 2—8 cm in diameter, with a variable amount of 1—2 cm papillary vegetations on the inner surface. In one patient, papillary vegetations of 0.4 cm in diameter were detected on the

external surface of the tumor and were united to the serous surface of the uterine body. Microscopic examination showed papillary vegetations similar to papillae of serous borderline neoplasms, single- or multiple-row surface epithelium of endocervical, serous or clear-cell type with mild nuclear atypia, fibrous-edematous stroma, as well as isolated complexes of atypical epithelial cells. One patient aged 44 years had borderline adenofibroma focus with numerous glands located unevenly and surrounded by fibrous stroma; predominantly single-row flattened glandular epithelium; at the same time, sites of epithelial proliferation and isolated complexes of atypical eosinophilic cells in the lumen of the glands were found (Figure B). In four women, leukocyte infiltration was observed in the tumor samples (Figure B); necrosis was revealed in individual small papillae in one of them. Outside the papillary vegetations, the tumor wall resembled benign seromucinous cystadenoma.

Seromucinous carcinoma turned out to be a cystic tumor with a diameter of 4 cm and papillary vegetations on the inner surface, 1.2 cm in diameter and 0.5 cm in height. Morphological examination showed that papillary vegetations had cribriform structure with a small number of "glands"; outside the papillary vegetations, gland-like structures from atypical epithelium were found, there were sites covered with endometrioid epithelium with adjacent endometrial stroma, which indicated the development of carcinoma associated with endometrioid cyst. The epithelium forming the carcinoma differed in moderate and severe dyskaryosis, resembling serous, endocervical and endometrial epithelium. Severe leukocyte infiltration was observed throughout the entire wall of the neoplasm (Figure D).

Endometriosis, diagnosed in nine women, accompanied benign seromucinous cystadenomas (n = 4), borderline tumors (n = 4), and carcinoma (n = 1). All neoplasms were delivered open, while the surgeons reported that 1 benign cystadenoma and 2 borderline tumors had thick brownish contents. In one of the four patients with benign SMT, endometriotic heterotopies were detected in adjacent ovarian tissue, the other two had tumor development against the background of the endometrioid cyst, and one of them showed pseudodyscaryosis representing reactive changes in epithelium in the form of its flattening, the appearance of the enlarged cells with polymorphic, somewhat hyperchromic nuclei with uniformly distributed chromatin and without mitosis; the fourth woman was pregnant, she had decidual changes in the tumor wall. In four women with borderline SMT and the patient with seromucinous carcinoma, neoplasms developed against the background of endometrioid cysts, two of them had pseudodyscaryosis of endometrioid epithelium similar to the above-described changes in benign cystadenomas.

Table 1. SMT subgroup according to the classification of the female reproductive system tumors (2014) (WHO Classification of Tumors)	
Benign	seromucinous cystadenoma; 8474/0 seromucinous cystadenofibroma; 9014/0
Borderline	Seromucinous borderline tumour/Atypical proliferative seromucinous tumour; 8474/1
Malignant	seromucinous carcinoma; 8474/3

Immunophenotype of SMT was characterized by low Ki-67 expression, ranging from 1 to 15% (samples of seromucinous carcinoma were not subjected to immunohistochemical examination), high positive immunoreactivity of ER, from 250 to 280 points (Figure D), and PR (Figure E).

All patients with borderline tumors underwent an urgent intraoperative histological examination, on the basis of which the surgery was performed including adnexectomy on the side of the lesion with the resection of the large omentum, biopsy of the opposite ovary, and removal of the washings from the peritoneum. In the patient with carcinoma, organ-preserving surgery was performed to let her realize reproductive function in future. Histological examination showed no tumor implants or metastases in the material of patients with borderline tumors and carcinoma, which indicated Stage 1a according to the

FIGO classification in all patients, except the woman with a borderline tumor of the ovary surface adhered to the uterus, who had Stage 1c.

Discussion

This study has established that benign SMT is characterized by a smooth internal surface, papillary vegetations covered with single-row epithelium. These tumors were found in 3 women, 2 of them were pregnant. Similar morphological features have been described by Massicot et al. [18], investigating SMT in 23 girls with mean age of 11.5 years. The investigators found papillary structures inside cystadenomas in only 4 girls in puberty, suggesting the need for hormonal stimulation. Despite the tumor recurrence in 4 girls in 1—3.5 years after total

Figure. Seromucinous tumor of the ovary. A – benign papillary cystadenoma in the pregnant patient x5, hematoxylin – eosin. B – border adenofibroma x20, hematoxylin – eosin. C – border papillary tumor with leukocyte infiltration in subepithelial tissue x20, hematoxylin – eosin. D – seromucinous carcinoma x20, hematoxylin – eosin. E – ER expression in the epithelium of the borderline x40 tumor. F – PR expression in the epithelium of the x40 border tumor
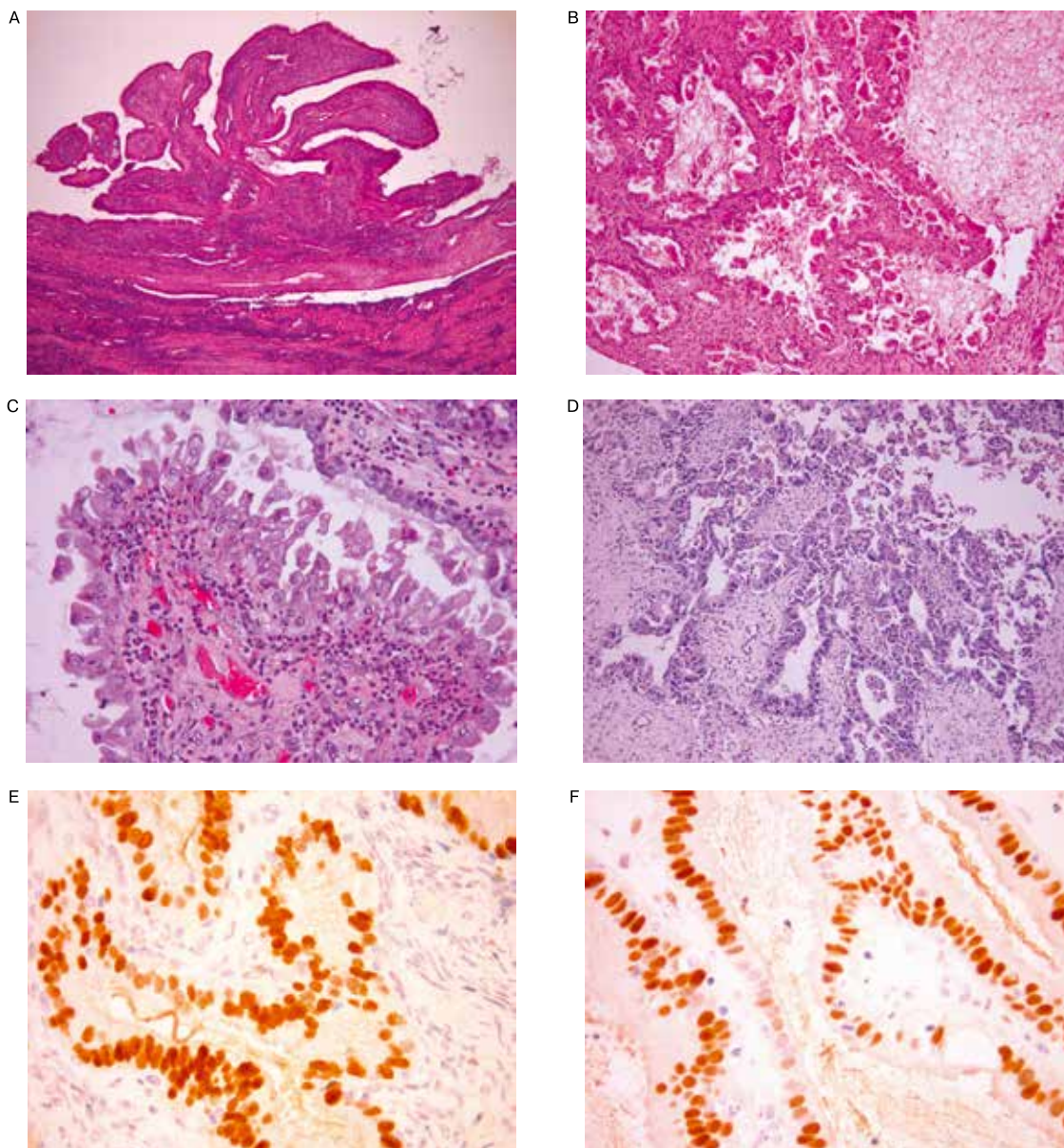
resection of cystic formation, the authors concluded that the outcomes were favorable [19].

The revealed morphological features of borderline SMT and seromucinous carcinoma are similar to the literature data. Shappell et al. [20] have studied the clinical morphological features of borderline SMT in 34 women, intraepithelial carcinoma in 5 patients, microinvasive carcinoma with stromal invasion less than 5 mm in 7 patients, and carcinoma in 8 women. They found a characteristic papillary structure resembling serous tumors and heterogeneity of the epithelial cells population, including not only serous (ciliated) and endocervical, but also endometrioid, clear-cell and undifferentiated cells with eosinophilic cytoplasm. Occasionally, there were tumors lined with epithelium of the endocervical type only [20]. It should be noted that borderline tumors also consisted of different types of epithelial cells in this paper, in contrast to benign cystadenomas represented mainly by epithelium of endocervical type with some serous cells.

Immunohistochemical examination of tumor specimens revealed high expression of ER and PR in all patients. Vang et al. compared the immunoprofilets of intestinal mucinous tumors and seromucinous (endocervical type) ovarian neoplasms and established high expression of ER and PR in serocumcus tumors, in contrast to intestinal mucinous cystadenomas [16]. In addition to these markers, SMT also shows positive staining for CK7, PAX8 and vimentin [21].

However, Rambau et al. analyzed the reproducibility of the diagnosis of seromucinous carcinoma and the molecular genetic structure of this tumor on the samples obtained from 32 women. The reproducibility of seromucinous carcinoma diagnosis was 39-56% among 4 pathologists. The combined results of morphological, immunohistochemical and genetic examinations resulted in the reclassification of seromucinous carcinoma into endometrioid carcinoma in 23 patients, serous low-grade carcinoma in 8 women, and mucinous carcinoma in 1 patient. The authors substantiated the results of their study by the non-specificity of ER and PR expression in SMT, as well as by those fact, that cells of flat, clear-cell and mucinous epithelium can be found in low-grade endometrioid and serous carcinomas [22].

It is known that marked leukocyte infiltration is present in almost all SMTs and this feature makes it possible to distinguish them from others other borderline neoplasms [22, 23]. Taylor et al. described the structural features of seromucinous carcinoma in 19 women. These authors have noted the presence of a neutrophil infiltrate in many specimens [24]. In the present study, leukocyte infiltration was revealed in the specimens of four women with a borderline tumor, one of them showed small foci of lysis, which probably do not worsen the prognosis, since they are microscopic in size. This is evidenced by data on the relationship between infarctions in papillae and microinvasion in 32 serous and seromucinous borderline ovarian tumors in 26 women (bilateral lesions in 6 patients). The authors found microinvasion in 50% of tumor specimens with infarctions compared to 7% of samples without infarctions, and concluded that the average size of the infarction observed simultaneously with the microinvasion sites is 5.9 mm; and infarctions less than 2.2 mm in diameter are not accompanied by microinvasive growth [25].

The large studies show that endometriosis occurs concomitantly with malignant neoplasms of the ovaries in 5-10% of cases. However, some authors present data on the malignant transformation of endometriosis (glands with atypia signs) in not more than 0.7—1.6% [5]. At the same time, we found no signs of atypical endometriosis in the material studied. On the other hand, Wu et al. examined borderline SMT samples and found coexisting endometriosis in 7 out of 17 women, revealing no signs of atypia [16]. Atypical endometriosis refers to the neoplastic transformation of the endometrioid cyst epithelium resulting from the accumulation of DNA damage, which is due to the formation of free radicals from iron oxidation, as well as repeated damage, inflammation, epithelial repair, and prolonged estrogenic exposure [25].

It should be noted that this study included patients of reproductive age only. Contrary to this, Wu et al. indicated that the average age of patients with borderline SMT is 51.3 years [16]. Karpathiou et al. described observations of the borderline SMT in women aged 63.2 years and seromucinous carcinoma in female patients aged 68.3 years [21]. This difference is probably related to the specific orientation of the treating activity of National Medical Research Center of Obstetrics, Gynecology and Perinatology and the Center for Family Planning and Reproduction, and confirms the possibility of the SMT development at any age. The age of the patient with seromucinous carcinoma was 31 years. It is within the age range (16-79 years) reported by Taylor and McCluggage in the study of 19 patients with seromucinous carcinoma [24].

With the exception of one patient with borderline FIGO Stage 1c SMT, all other patients had Stage 1a, which is typical for this tumor according to the literature. Dubé et al. examined 17 samples of tumors (n borderline SMTs = 12, n intraepithelial carcinomas = 2, n microinvasive carcinomas = 2 and n invasive carcinomas = 1), and found Stage 1 in 14 women, Stage2a in one patient, Stage 3c in one woman, and in one patient staging was not performed. All patients had favorable outcomes (no recurrence or death), despite high mitotic activity, signs of intraepithelial carcinoma, microinvasion, bilateral lesions, conservative treatment or advanced stage [26]. Shappell et al. concluded that most borderline SMTs diagnosed at the first stage are benign, stressing that intraepithelial carcinoma or the presence of microinvasion does not worsen the prognosis. However, the authors noted that two out of seven women who had a stromal invasion or a micropapillary structure subsequently died [20].

Conclusion

Benign SMTs are predominantly smooth-walled cystic lesions lined with endocervical epithelium with a small amount of serous, while borderline tumors are characterized by papillary structure and additionally have endometrioid, clear-cell and undifferentiated eosinophilic cells in the epithelium. Leukocyte infiltration in the tumor wall and coexistence with endometriosis are specific signs of SMT. These facts indicate the etiological role of endometriosis in the occurrence of SMT.

In the overwhelming majority of the examined patients of reproductive age, the tumor was diagnosed at FIGO Stage 1, which demonstrates a predominantly favorable course of the disease. Specific and partially similar mechanisms of molecular alteration are characteristic for EAN. This facet can be used in future to apply targeted therapy for advanced or recurrent tumors of this type.

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