

Histopathological Patterns of Microinvasion in Ovarian Serous Borderline Tumors

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ABSTRACT: Stromal microinvasion in ovarian serous borderline tumors can take various aspects, some of which are difficult to identify. Thus, the identification of stromal microinvasion is relatively simple for typical intracystic papillary proliferations such as serous borderline tumors, but may be difficult for tumors with glandular component. The study analyzed 14 cases of ovarian serous borderline tumors diagnosed in patients with mean age of 47,1 years. Histopathologically all tumors corresponded to typical forms in which we identified only two cases of stromal microinvasion. In one case, microinvasion was of eosinophilic type, and in the other case was observed a glandular and micropapillary pattern, being associated with the noninvasive peritoneal implants.

KEYWORDS: serous borderline tumors, microinvasion

Introduction

The latest WHO classification divides ovarian serous borderline tumors into typical serous borderline tumors and serous borderline tumors with non-invasive micropapillary pattern [1]. A particular aspect of typical or micropapillary serous borderline tumors is stromal microinvasion. The concept of microinvasion in serous borderline tumors has been recognized for nearly 50 years [2,3].

Currently, based on WHO criteria, microinvasion has been defined as a individual presence or as a group of neoplastic cells similar with those of noninvasive tumor component in a desmoplastic stroma [1]. In most studies, it has been shown that microinvasion has no adverse effects on prognosis, although microinvasive foci often coexist with other characteristics that may indicate a more unfavorable prognosis, such as the micropapillary pattern [4,5].

The current study aims the histopathological analysis of microinvasive component in ovarian serous borderline tumors.

Material and methods

The retrospective study was performed on 14 cases of ovarian serous borderline tumors, diagnosed over a 3-year period (2013-2015). Surgical excision pieces were obtained from the Surgery and Gynaecology Clinics of the Emergency County Hospital Craiova and processed in the Pathology Laboratory of the same hospital. The surgical specimens were fixed in 10% buffered formalin, processed by

the paraffin-embedding technique and stained with Hematoxylin-Eosin. On serial sections, we followed to identify the morphology of microinvasive foci according to WHO criteria [1] and the number of microinvasive areas. Image acquisition was performed using Nikon Eclipse E600 microscope equipped with camera and Lucia 5 software provided with morphometry software.

The study was approved by the local ethical committee (no.195/24.10.2017), and written informed consent was obtained from all the patients.

Results

This study included 14 cases of serous borderline tumors that were diagnosed in patients aged between 31 to 78 years and with a mean age of 47.1 years.

Histopathological analysis of the selected cases of serous borderline tumors has totally indicated their typical forms, associated in 5 cases with benign serous tumor areas of cystadenofibroma or serous cystadenoma. In 2 cases we found the presence of stromal microinvasion (14.2%), of which in one case was associated with the presence of the peritoneal implants (7,1%). Vascular invasion was absent in all investigated cases. All analysed cases were classified as tumors in the stage I of disease.

The tumors were characterized by the presence of numerous papillae with fibrous, edematous, myxoid or hyaline stroma, limited by cystic spaces and lined by stratified

neoplastic cells with round or oval nuclei, located at the base of the papillae, with visible nucleoli. We also noticed large hobnail cells with abundant, eosinophilic cytoplasm, and hyperchromatic nuclei, as well as cells similar to mesothelial cells or cells with clear cytoplasm. The degree of nuclear atypia ranged from mild to moderate, and the mitosis were rare, always typical, with mitotic activity comprised between 1-3 mitoses/10HPF. Due to epithelial invaginations in papillary axes, occurs a characteristic pattern of hierarchical branching which gives to the proliferation a complex aspect, and in three tumors we noticed the presence of calcified psammoma bodies. Cellular stratification was characteristic, with epithelial buds formation, which are epithelial cell groups without visible fibroconnective core due to clustering of neoplastic cells at the tip of the papillae.

In one case the stromal microinvasion was represented by five distinct foci and in another case by three distinct foci. For one of the cases the microinvasive aspect ranged from the presence of individual cells to small cellular groups, with eosinophilic cytoplasm, located at the level of papillary protrusions or in the cystic wall (Fig.1).

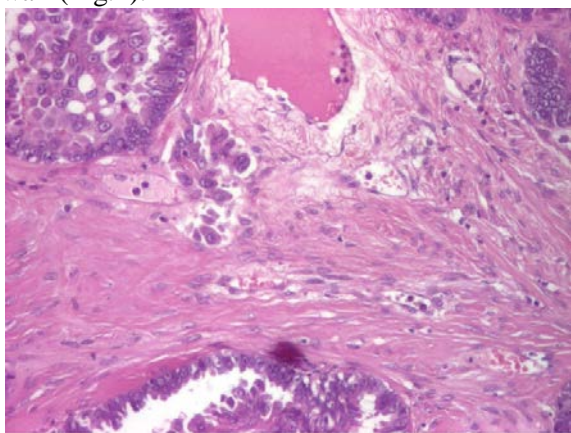


Fig.1. Microinvasion with eosinophilic pattern, HE staining, x40

Cell nuclei from the microinvasive areas were slightly enlarged and with low atypia, sometimes with prominent nucleoli. Cells or microinvasive groups were surrounded by optically empty spaces. The surrounding stroma was unchanged without edema or desmoplastic reaction.

In the second case, the microinvasive foci had granular or stromal micropapillae, adjacent to the tumor. We observed the presence of isolated glandular structures or micropapillae surrounded by a clear optical space associated

with low stromal desmoplastic reaction (Fig.2, Fig.3).

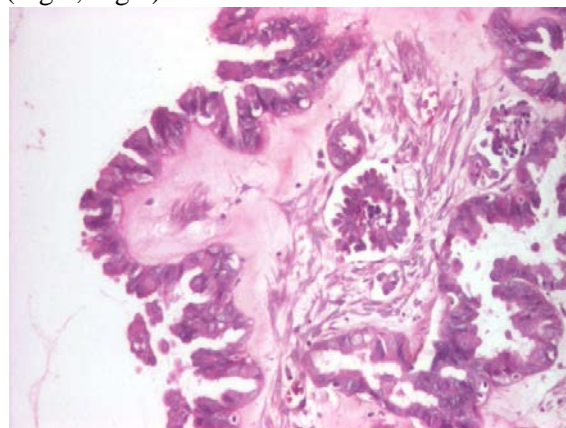


Fig.2. Microinvasion with micropapillary pattern, HE staining, x100

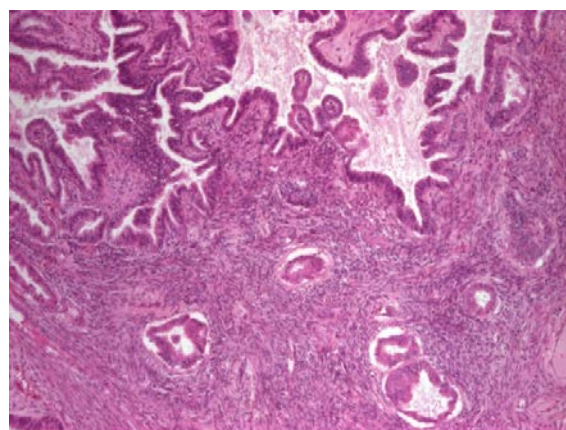


Fig.3. Microinvasion with glandular pattern, HE staining, x40

In addition, this case associated the presence of a noninvasive peritoneal implant with serous epithelia which have formed branched papillary proliferations and epithelial buds, without the invasion of the underlying tissues and without stromal desmoplastic response (Fig.4).

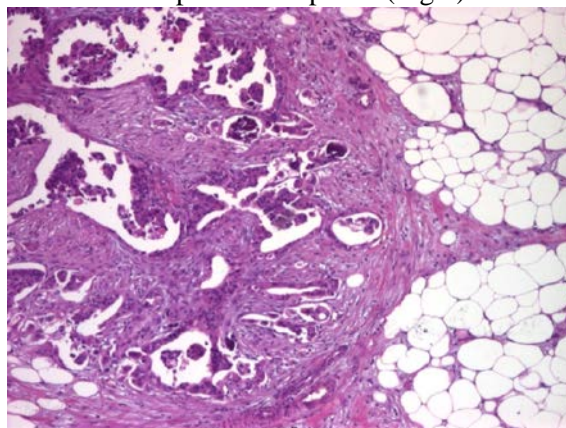


Fig. 4. Noninvasive peritoneal implant, HE staining, x40

The epithelial cell nuclei had mild atypia and the mitotic activity was absent.

Discussions

The absence of evident stromal invasion is an important criterion for the diagnosis of ovarian borderline tumors. Microinvasion associated with these tumors is defined by the presence of small stromal foci of single neoplastic cells or by small cell groups, occasional papillary, cribriform or rounded aggregates, with eosinophilic cytoplasm and minimal or absent stromal reaction [1]. The identification of stromal microinvasion is relatively simple for typical intracystic papillary proliferation, as are generally serous borderline tumors, but it can be difficult in predominantly glandular tumors.

The size of the microinvasive area used by most studies are 3mm in greatest dimension, or the surface to not exceed 10mm² [2,6,7], although some authors include foci of up to 5mm [8]. The latest WHO classification recommends the maximum microinvasive size of 5mm [1].

The incidence of stromal microinvasion is reported with quite varying values. Most authors found an incidence of approximately 10% of serous borderline tumors [2,4], similar to our data. In one study, using epithelial markers, the incidence of microinvasion was detected in 13% of cases [9]. Another study reported for pregnant women a very high frequency of stromal microinvasion, respectively 80% of patients [5,10]. On the other hand, Silva et al. reported that serous borderline tumors with microinvasive implants had stromal microinvasion in 56% of cases [11]. In a recent study, the microinvasion was identified in 22.3% of cases [12].

In our study, we identified only two cases of typical serous borderline tumors with stromal microinvasion (14.2%). In one case, the microinvasion was of eosinophil type, and in the other case it had a glandular and micropapillary pattern associated with noninvasive peritoneal implants.

The histological characteristics of stromal microinvasion in serous borderline tumors have been approached in a wide variety of studies, but controversy persists regarding the diagnostic criteria and prognostic significance, especially in patients with advanced stage disease [5].

McKenney et al. have described five different types of microinvasion (individual eosinophilic cells and clusters, simple papillae, inverted macropapillae, cribriform structures

and micropapillae) and concluded that the only type that has aggressive behavior is composed of micropapillae [5]. The most common pattern is represented by isolated cells or small cellular groups with eosinophilic cytoplasm, apparently budded from the atypical epithelium in a adjacent tumor space, called by Bell et al. as microinvasion with eosinophilic model [13]. Cell nests with cribriform, papillary or micropapillary architectural growth patterns that randomly invade the stroma and are often surrounded by a clear space represent the second type of microinvasion. Stroma of this type of microinvasion can present desmoplastic reaction. Another type of microinvasion is characterized by epithelial proliferation similar to the one present in well-differentiated carcinomas or with epithelium present in invasive peritoneal implants [14].

The microinvasion with individual eosinophilic cell pattern and clusters, simple papillae, inverted macropapillae appears to correspond to the most of the reported cases in the literature [2,3,15,16], while the cribriform and micropapillary patterns correspond to the low serous carcinoma [15-17]. As a result, some authors propose that the glandular and conglomerate cribriform pattern to be designated as a "microinvasive carcinoma" to distinguish it from the microinvasion [15,16,18]. Due to an insufficient number of cases in the literature, conclusions about the clinical significance of different microinvasive patterns have not been identified [13,1,5].

So far, the results of various studies indicate that the association between microinvasion and prognosis is controversial. Some studies conclude that serous borderline tumors with microinvasion have a similar prognosis to that of the normal serous borderline tumor [2,12,19], and conserving the contralateral ovary and uterus may be an acceptable therapy for young women who wish to maintain their fertility [2]. On the contrary, other studies consider that some patients with microinvasion may be at high risk of recurrence [20,21] and may require different treatment strategies [20]. Other studies have shown that stromal microinvasion if it is not associated with invasive extraovarian implants, has no effect on the recurrence rate or on the progression rate to invasive disease as confirmed by large metaanalyses [22,23]. In addition, the combination of microinvasion and advanced stage was also proposed as a negative prognostic factor [5].

Conclusions

Careful analysis of serous borderline tumors may reveal the microinvasive foci and their type. Since the microinvasion of micropapillary type may represent a lesion with a relatively higher risk, with similar clinical outcomes to that of low-grade serous carcinoma, pathologists should identify this specific pattern.

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