Clin Oncol Cancer Res (2009) 6: 169-173
DOI 10.1007/s11805-009-0169-9

Research Developments on the Histopathology and Prognostic Predictors of Serous Borderline Tumor of Ovary

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Received March 12, 2009; accepted June 1, 2009.

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ABSTRACT Serous borderline tumor of ovary (SBT) includes two subtypes of typical serous borderline tumor and micropapillary variant, which have different histopathology features. Although SBTs behave in either way of the benign counterparts or malignant serous carcinomas, microinvasion, peritoneal implants, and nodal involvement are all very common in both subtypes of typical SBT and the micropapillary variant. The prognosis of the patients with serous borderline tumor of ovary and the mechanism of the microinvasion, peritoneal implantation and nodal involvement are still being debated, nor is there universal agreement about the management of SBT. To identify the histopathologic features, prognostic predictors of the SBT, and its association with ovarian serous carcinomas, we reviewed the majority of the relevant papers published in recent literature.

KEY WORDS: serous borderline tumor, histopathology, prognostic predictor.

Introduction

The ovarian tumors characterized by a degree of epithelial proliferation with nuclear atypia in the absence of destructive growth and stromal invasion were defined as ovarian borderline tumor by the World Health Organization (WHO), which account for 10% to 20% of the ovarian tumors. They were first described by Taylor in 1929. In the classification of the Cancer Committee of the International Federation of Gynecology and Obstetrics (FIGO) in 1970, it was called cystadenoma with proliferating activity of the epithelial cells and nuclear abnormalities, but with no infiltrating destructive growth (low potential malignancy). WHO applied the designation 'tumor of borderline malignancy' and added the synonym "carcinoma of low malignant potential" (LMP) in their 1973 classification of ovarian tumors. "Borderline tumor" is the term used in the recently published 2003 WHO classification and it seems to be the most commonly used by gynecological pathologists and gynecological oncologists. The usual type of ovarian borderline tumor is SBT. According to the WHO criteria, those serous tumors with the presence of epithelial hyperplasia forming papillae, micropapillae, and mild to moderate nuclear atypia, but lacking destructive stromal invasion are diagnosed as SBT. Hence, SBTs represent a conundrum as they display atypical nuclear structures and metastatic behavior, yet they are considerably less aggressive than high-grade serous carcinomas. To identify the histopathologic features, prognostic predictors, and the association

with ovarian serous carcinomas, we reviewed most of the recent relevant literature.

The histopathology of ovarian serous borderline tumor

SBT accounts for 9%-15% of all serous neoplasms, and the patients tend to be relatively youthful with a mean age of 42-44.3 years[1,2]. According to the FIGO staging system, 59% are stage I, 11% stage II, and 30% stage III[1]. Histologically, SBT consists of two subtypes of typical serous borderline tumor and a micropapillary variant. The majority is the typical subtype, and the minority is the micropapillary variant, which just accounts for less than 6% of all SBTs[3]. The typical subtype is noninvasive proliferative neoplasm characterized by multiple fibrous papillae with extensive and complex hierarchical branching. The diagnostic criteria for the typical subtype are as follows: (a) stratification of the epithelial lining of the papillae with tufting and cell detachment; (b) the absence of marked nuclear atypia; and (c) the absence of obvious stromal invasion. The micropapillary variant is characterized by a vigorous cellular proliferation that emanates from the surfaces of fibrous papillae, without a hierarchical branching pattern, or directly from cystic wall. As a result, the proliferating cells form long, delicate projections with a complex filigree pattern or thick cribriform formations. The diagnostic criteria for the micropapillary subtype are as follows: (a) thin, elongated epithelial micropapillae with minimal or no fibrovascular support arising directly from thicker papillae; (b) the micropapillae are at least 5 times as long as wide; (c) the foci of micropapillary or cribriform epithelial proliferation is at least 5 mm at its greatest dimension. In other words, a continuous 5mm micropapillary or cribriform growth pattern in a single slide is generally required for the diagnosis of micropapillary serous borderline tumor; and (d) for the cribriform pattern a proliferation of cells lining the stalks or cyst walls, producing a cribriform "lace-like" architectural pattern. Although SBTs can behave as benign counterparts, or malignant serous carcinomas, microinvasion, peritoneal implants, and nodal involvement are all very common features in both of the typical subtypes and the micropapillary variant. Compared with typical SBT, micropapillary SBT takes a more aggressive clinical course, with more invasive implants, and significantly decreased progressive-free survival (PFS)[4].

The association between SBT and low grade ovarian serous carcinoma

The role of SBT in the development of ovarian serous adenocarcinoma needs further definition. One histopathological study[1] found cases with microinvasion, invasive implantation, and recurrences were similar in characteristics to grade 1 serous carcinoma. Moreover, 31% (5/16)-60% of the cases with grade 1 serous carcinoma had the areas of SBT[1,5]. These morphological evidences suggest that SBT is strongly related with low-grade invasive carcinoma. Moreover, the age at diagnosis, progression-free survival time, and overall survival time associated with newly diagnosed stages II-IV of low grade serous carcinoma (LGSC) of the ovary are similar to those of SBT that recur as LGSC. This provides further evidence of a relationship between these two types of tumor[6]. Molecular evidences also support the concept that grade 1 serous carcinoma and SBT are closely related, because the gene expression profiles associated with low grade serous carcinoma are remarkably similar to SBT[7].

About the relation of SBT with high-grade serous carcinoma, ample data support the concept that SBT is completely separate from high-grade serous carcinoma. Evidence in support of this include the high frequency of KRAS or BRAF mutations in SBT and low-grade serous carcinoma that are not often found in high-grade serous carcinoma[8,9] as well as the wild-type p53 status in SBT and low-grade serous carcinoma, which is often mutated in high-grade serous carcinoma[7,10]. However, some results[11] suggest that the majority of high-grade and low-grade carcinomas develop independently, but in rare cases, a high-grade serous carcinoma may arise from an SBT.

The association between the treatment and prognosis

Like the treatment for malignant ovarian tumors, the treatment for borderline ovarian tumors has traditionally been radical surgery (hysterectomy with bilateral salpingo-oophorectomy) so as to reduce the risk of recurrence. However, because borderline ovarian tumors occur commonly in women of reproductive age, usually found at an early stage, and have a favorable prognosis, conservative surgery is preferred in order to preserve the fertility. Conservative treatment is defined as a surgical procedure including removal of cystectomy and unilateral salpingo-oophorectomy with conservation of the uterus and salvage of at least one ovary. Tinelli et al.[12] concluded that unilateral salpingo-oophorectomy must be considered as the first choice of conservative treatment, which can be performed laparoscopically.

Laurent et al.[13] retrospectively studied 15 cases of conservative treatment of ovarian SBT with micropapillary patterns. After a median interval of 63 months (range, 18-120 months), 11 recurrences were observed. Moreover, compared with the recurrences for patients with radical surgery, the recurrences for patients with conservative surgery were more common[14,15]. Ren et al.[14] compared the incidence of recurrence between the

patients treated by conservative treatment with those by radical treatment, and found 20 of 119 patients (16.8%) in conservative surgery group developed recurrence, which was much higher than that (5.2%) in the radical group. Relapses occurred in the same ovary, in the other ovary, or in both ovaries, and in the peritoneal cavity. Another study[15] also indicated that conservative treatment is one of the individual factors associated with an increased risk of local relapse. Nevertheless, conservative treatment is not the exclusive factor associated with recurrence. Several studies[14,16] found tumor recurrence, as well as poor disease-free survival, was significantly associated with cyst rupture, bilateral disease, advanced stage, microinvasion, and peritoneal implants.

Although conservative surgery is one of risk factors of recurrence, it doesn't affect overall survival. The higher risk of local relapses is not associated with a reduction in the overall survival, although PFS in the conservative group is lower than that in the radical group[15]. For stage II/III ovarian SBT with noninvasive implants, the incidence of recurrence may be as high as 25%. However, carefully staged patients have a good prognosis without adjuvant therapy. Follow-up, 60.7 months later, found 81% of patients alive without evidence of disease[2].

In respect to a surgical approach for SBT, there are also two approaches, laparotomy and laparoscopic management. However, which is preferred? Is laparoscopic management as safe as laparotomy? These questions are currently debated. Clinically, the laparotomic approach is generally reserved for larger tumors, and the possibly easy manipulation for the mass by laparotomy may reduce the risk of tumor spilling[15,17]. Laparoscopic management is an appropriate and safe therapeutic option for young women with low-stage disease who wish to preserve their childbearing potential, because the reserved fertility are encouraging[18,19]. De et al.[15] found the rate of recurrences did not differ significantly in the approaches: 14% for the laparoscopic group and 17% for the laparotomic group ($P > 0.05$). Moreover, the recurrences may be detected by close follow-up and treated accordingly.

The frequency and prognostic significance of microinvasion

On the basis of the WHO criteria, microinvasion was defined as the presence of individual or clusters of neoplastic cells cytologically similar to those of the noninvasive tumor in desmoplastic stroma. One or more foci can be present, but none should exceed 10 mm^2. Although ovarian SBT is characterized by the lack of destructive stromal invasion, microinvasion is very common, and the incidence is from 12.9%-26% [1,14]. Tumors in pregnant patients apparently have an especially high frequency of stromal microinvasion, occurring in 80% of 10 pregnant patients in one series[20].

To date, the research results show that the association between microinvasion and prognosis is controversial. Some authors[1] found that the presence of microinvasion didn't appear to adversely affect prognosis, but most[14,21,22] found that microinvasion was strongly associated with adverse outcome such as decreased survival and recurrence. Disease progression was most strongly linked to the presence of micropapillae in the subepithelial stroma, but the majority of patients with adverse outcome had the patterns associated with microinvasion (i.e., individual cells, cell clusters, and simple papillae)[21]. Significantly, the cases with microinvasion, invasive implantation and recurrences all showed qualitative histologic features resembling grade 1 serous carcinoma[1]. The histologic similarity of microinvasion to grade 1 serous carcinoma suggests that microinvasion truly represents invasion rather than another appearance of SBT. Moreover, there certainly were patients with high-stage SBT coming from stage I microinvasive tumors, and microinvasion may be a risk factor for patients with high-stage disease[23].

The frequency and prognostic significance of peritoneal implants

The peritoneal implants were divided into noninvasive and invasive according to the WHO criteria. Noninvasive implants look as though they coated on the peritoneal surface without destructive invasion of the underlying tissue. The epithelial aggregates are similar to those of SBT in ovaries. Invasive implants show invasion of tissue by haphazardly distributed glands and small cell clusters accompanied by a dense stromal reaction. The epithelial cells exhibit marked nuclear atypia.

Lackman et al.[2] studied 16 patients with stage II/III ovarian borderline tumors and noninvasive implants, and found that the pelvic peritoneum was the most common site (69%), with rectosigmoid and small bowel the second most common sites (53%) of extraovarian disease. Although the incidence of macroscopic implants in the omentum was found in only 4 of 16 patients (25%), another 8 of 16 (50%) patients were found to have microscopic implants. Hence, the omentum is the most common site of noninvasive implants. Noninvasive implants traditionally have been considered to be nonaggressive tumors associated with an excellent prognosis. However, one study found that the recurrence and overall survival rates of these patients were time dependent. Eighty cases of advanced-stage ovarian SBT with noninvasive implants treated by total abdominal hysterectomy and bilateral or unilateral salpingo-oophorectomy were followed up for 5-31 years, and 35 patients (44%) developed recurrences[24].

Invasive implants are much less common than non-invasive implants but are usually an indication of a worse prognosis. Hogg et al.[1] found that only 1 of 19 advanced stage SBTs presented invasive implants at presentation.

Sometimes, it's very difficult to determine whether the implants are invasive or noninvasive. To a certain extent, elastin staining is useful in the subclassification and is of most value in confirming the superficial distribution of non-invasive lesions. However, evaluation is limited by the absence of a defined elastic layer in a proportion of biopsy specimens, possibly reflecting their superficial location, as well as absence of a distinct peritoneal elastic lamina in sites such as the omentum[25].

The pathogenesis of the implants is currently unknown. Two major hypotheses have been proposed: the first favors a monoclonal origin, arguing that the peritoneal lesions are derived from neoplastic cells that are shed from the primary ovarian tumor. The second hypothesis favors a polyclonal origin as a result of a field defect of susceptible Müllerian cells from which multiple independent tumors arise. Lackman et al.[2] found that the majority of patients with SBT and noninvasive implants had tumors on the ovarian surface, and patients with macroscopic extraovarian disease usually had visible implants on the pelvic peritoneum. Moreover, by genome-wide allelotype and B-RAF/K-RAS mutation analyses, genetic changes in all of the sites in 21 tumors from 8 patients were in agreement[26]. These results support the first hypothesis.

The frequency and prognostic significance of nodal involvement

The frequency of nodal involvement in patients with SBT may be as high as 41.9% (31/74), and the most common involved nodes are pelvic, peritoneal, and paraaortic nodes, although the supradiaphragmatic nodes, such as mammary and cervical nodes also may be involved[27-29]. The present studies[30-32] showed that the survival of patients having SBT with nodal involvement was not statistically different from that of patients with negative nodes. Moreover, disease-free survival is not associated with the number of involved nodes, the extent of nodal involvement (diffuse or focus), and the location of nodal involvement (sinusoidal or paranchymal). However, if the nodal involvement present as nodular aggregates of epithelium which are greater than 1 mm, the disease-free survival of patients with SBT is significantly decreased compared with other patterns of lymph node involvement.

In the patients with nodal involvement, both the 5- and 10-year overall survival, who received lymphadenectomy had also no significant difference compared with the survivals in those without lymphadenectomy[33].

By far, the mechanism of nodal involvement in the patients with SBT is unclear. The presence of benign endosalpingiosis in nodes invaded by SBT may be as high as 62%[33]. Moreover, benign endosalpingiosis is much more common in patients of SBT with lymph node involvement (58%) than those without lymph node involvement (35%)[27]. The coexistence of invasive implants with benign endosalpingiosis seems to support the hypothesis of the synchronous transformation (metaplasia) in the nodes of benign inclusions, under the influence of the same oncogenic agent, rather than that of real lymphatic metastases. Meanwhile, the phenomenon that the nodal involvement doesn't influence 5- and 10-year overall survival also supports the hypothesis of metaplasia of benign inclusions in the nodes. Furthermore, no differences in lymphatic vessel density were found between the cases with and those without nodal involvement[34]. Briefly, the above findings indicate that the mechanism of nodal involvement doesn't occur via lymphatic path of tumor, but most likely via the lymphatic vascular network of the peritoneal surfaces[35] or via synchronous transformation.

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