Ovarian Tumors of Low Malignant Potential:
Can Molecular Biology Solve This Enigma?

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Borderline tumors of the ovary, originally described by Taylor (1) in 1929, were officially recognized by the International Federation of Gynecology and Obstetrics and the World Health Organization approximately 30 years ago. Despite their longstanding recognition as a distinct entity, they remain an oncologic enigma. Borderline tumors, also referred to as ovarian tumors of low malignant potential, are defined pathologically by epithelial proliferations, multicellular layering, mitotic activity, and atypical nuclear structures similar to invasive ovarian cancer, but without evidence of stromal invasion (2). Ovarian tumors of low malignant potential are most frequently diagnosed as early-stage tumors; however, they can present with widespread metastatic intra-abdominal disease (3). On the basis of these pathologic and clinical features, investigators have suggested that ovarian tumors of low malignant potential represent a tumor that is “semimalignant,” a “low-grade noninvasive carcinoma,” or an intermediate “between clearly benign and frankly malignant tumor” (1,4,5). It is recognized, however, that, despite these biologic and clinical characteristics, the survival of these patients remains quite good, even in the presence of advanced-stage or large-volume disease (2,4,5). It is clear that ovarian tumors of low malignant potential display a unique combination of clinical and pathologic features that is essentially without parallel in clinical oncology.

Borderline ovarian tumors, therefore, represent a conundrum in which tumors with malignant-like pathologic features generally have a benign clinical course. To resolve this paradox, pathologists have attempted to subcategorize borderline tumors. Extensive pathologic evaluation has identified features that predict for recurrence of disease, poor survival, or progression to malignancy (6). The nature of peritoneal implants (microinvasive versus invasive versus noninvasive) and characteristics of the primary tumor (microinvasion or micropapillary architecture) have been suggested to impart a more aggressive phenotype (6). In fact, benign and malignant subtypes of borderline tumors have also been proposed (7). Borderline tumors without micropapillary histology or invasive implants have been described as atypical serous proliferative lesions to reflect their essentially benign clinical course. Ovarian tumors of low malignant potential with micropapillary features or invasive implants have been associated with a higher rate of recurrent and progressive disease (6,7). Although histopathologic distinctions have contributed greatly toward understanding the subtleties of borderline tumors, identifying and interpreting these pathologic subtypes have led to considerable debate among pathologists (6).

The recent application of molecular biologic techniques to the characterization of ovarian tumors of low malignant potential has yielded several important discoveries that affect this debate. One of the first clues about the unique molecular signature of tumors of low malignant potential was the analysis of the ras and p53 genes. Several groups (8,9) demonstrated that tumors of low malignant potential had a low frequency of p53 mutations but a high frequency of ras mutations, the opposite of invasive cancers. Although the lack of p53 mutations could be explained as a progression event, the higher incidence of ras mutations strongly implied that ovarian tumors of low malignant potential are different biologic entities from both benign and malignant tumors. In another report, Cheng et al. (10) concluded that ovarian tumors of low malignant potential are not precursors of low-grade ovarian carcinoma when they reported loss of heterozygosity (LOH) at chromosome Xq in borderline tumors, a genetic alteration not present in low-grade ovarian carcinoma. Furthermore, they showed LOH at multiple loci only in invasive ovarian cancer and not in borderline tumors. Finally, the multiclonal nature of some borderline tumors was first established by Lu et al. (11), who described several examples of advanced-stage ovarian tumors of low malignant potential that demonstrated multiclonality.

In this issue of the Journal, Gu et al. (12) studied the clonal origin of advanced-stage ovarian tumors of low malignant potential. They selectively evaluated the clonality of serous tumors, the most common histologic subtype of borderline tumors. They examined 18 cases, 13 of which were evaluable on the basis of normal random X inactivation seen in the control non-tumor specimen. Of interest, six cases showed random loss of the X chromosome. The meaning of this finding is unclear. Of the other seven cases, in six, the ovarian and peritoneal implants were from different clonal origin, as determined by their pattern of X-chromosome inactivation. The authors conclude that most borderline tumors are polyclonal. The study by Gu et al. (12) confirms and extends the original report of eight cases by Lu et al. (11), in which three cases were shown to be multifocal in origin by patterns of X inactivation. In the study by Lu et al. (11), two cases were limited to bilateral ovarian tumors, and only one had peritoneal implants. Thus, the present study substantially extends the multiclonal etiology of some ovarian tumors of low malignant potential to those with widespread peritoneal implants. Unfortunately, there are insufficient cases to indicate any association between clonality and pathologic features. Moreover, the lack of clinical data precludes an assessment of the impact of clonality on patient survival.

It is clear from the initial molecular analysis of ovarian tumors of low malignant potential that the majority of them are distinct from their benign and malignant counterparts (8–10). Furthermore, a subset of ovarian tumors of low malignant potential is multiclonal in origin (11,12). These results confirmed the suspicions of many clinicians and pathologists familiar with this disease, who noted that LMP tumors can present bilaterally in the ovaries without surface involvement or within an ovary and at a distant site, suggesting that a multicentric origin is present. However, critical questions concerning the etiology and...
biologic behavior of borderline tumors remain unanswered. For instance, do multiclonal borderline tumors have a different clinical course than monoclonal borderline tumors? What is the molecular abnormality(ies) that gives rise to multiclonal tumors (field effect), and how does it differ from the molecular events underlying clonal tumors? Is there any association between clonality and pathologic features associated with a more aggressive phenotype? If not, what are the molecular differences that define the pathologic subtypes?

The application of genomic techniques to ovarian tumors of low malignant potential should help unravel the mysteries of this disease. The molecular profiles of ovarian tumors of low malignant potential with micropapillary architecture and tumors with noninvasive or invasive implants will need to be determined and compared. This analysis will establish if they are indeed definable entities and, if so, determine more accurately their clinical and biologic significance. A molecular characterization will also determine any possible relationship among these subtypes, addressing such issues as tumor progression versus independent tumors. This analysis will ultimately reclassify ovarian tumors of low malignant potential into subgroups, depending on their molecular origins, which should result in a better understanding and management of this disease.

REFERENCES


