Commentary (Trimble/Trimble): Update on Low Malignant Potential Ovarian Tumors

June 01, 2000
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Ovarian tumors of low malignant potential (LMP) would benefit from a new name, not to mention a deeper understanding of their biology, effective treatment, and a framework within which they can be studied. Fortunately, for a pathologic entity that is poorly understood and also is unresponsive to current therapy, most LMP ovarian tumors carry a benign prognosis.

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Nomenclature
Various names have been applied to this entity. These include “ovarian tumors of low malignant potential,” “borderline ovarian tumors,” “atypical proliferating ovarian tumors,” and even “borderline ovarian carcinomas.” Each of these terms has its drawbacks.

“Low malignant potential” suggests that these tumors have a certain propensity to become malignant. In fact, as Kurman and Trimble illustrated, the rate of malignant transformation for LMP ovarian tumors is lower than that for uterine leiomyomata, which undergo malignant transformation to leiomyosarcoma (0.1%).[1]

The name “borderline ovarian tumors” suggests that these tumors represent an intermediate biological stage between benign ovarian cysts and invasive carcinoma. In fact, various molecular biology studies have demonstrated that LMP tumors are not precursors to cancer.[2]

“Atypical proliferating tumors” is a histologic characterization that has not yet gained widespread acceptance among either pathologists or gynecologists. “Borderline carcinoma” suggests that tumors are invasive carcinomas warranting aggressive surgical treatment, followed by adjuvant chemotherapy. However, the natural history of LMP ovarian tumors suggests that conservative surgery without cytotoxic chemotherapy will suffice for most women.

Histology
Should the histologic subtypes of LMP ovarian tumors be made more specific? As Menzin explains, the subtypes that have been reported include serous, mucinous, endometrioid, clear cell, and Brenner. Many series and case reports fail to distinguish between these subtypes, however, or to state the histologic criteria used to subtype or provide photomicrographs that would allow the reader to confirm the subtype.[2] Endometrioid, clear cell, and Brenner ovarian tumors of LMP are exceedingly rare. Serous LMP ovarian tumors are the most common subtype.

Furthermore, some authors fail to distinguish between primary peritoneal carcinoma with LMP-type implants in the ovaries and ovarian tumors of LMP with LMP-type implants elsewhere in the abdomen.[2] In the past, pseudomyxoma peritonei (“jelly belly”) was classified as a mucinous LMP tumor. More recently, Ronnett and others have shown that the vast majority of these cases arise from gastrointestinal primary tumors, usually in the appendix.[3] Most true mucinous tumors of LMP are confined to one or both ovaries.

Epidemiology
Ovarian tumors of LMP tend to occur in women at younger ages than does invasive ovarian cancer. Most series of ovarian tumors reported in adolescents, young adults, or pregnant women contain a large proportion of ovarian tumors of LMP.

As Menzin points out, pregnancy, lactation, and oral contraceptives reduce the risk of ovarian tumors of LMP just as they reduce the risk of invasive ovarian cancer. Women with BRCA1 and BRCA2 mutations, who are at increased risk for ovarian cancer, do not appear to be at greater risk for ovarian tumors of LMP. The use of fertility drugs appears to increase the incidence of LMP tumors but not ovarian cancer.

Screening
Menzin does not address the impact of LMP tumors upon the outcome of screening trials for ovarian cancer. Current imaging techniques cannot distinguish between ovarian tumors of LMP and ovarian carcinomas.

In addition, serous tumors of LMP produce CA-125. In large screening trials reported from the University of Kentucky and the United Kingdom, a large proportion of the ovarian tumors identified were tumors of LMP.[4-6]

Treatment
Women found to have LMP tumors confined to one ovary are adequately treated with unilateral oophorectomy in addition to appropriate surgical staging. Women with more advanced disease should undergo surgical cytoreduction.

As Menzin discusses, some case reports and retrospective series have documented instances in which suboptimal cytoreduction was performed to preserve fertility. These women are at increased risk for persistent disease, but their risk for progressive disease appears to be low.

Among younger patients who may wish to preserve fertility, intraoperative decision-making can be challenging, however. The operative findings may be consistent with epithelial ovarian cancer, but the pathologist may report the frozen section as “benign” or “at least LMP.” In such cases, the clinician must choose between conservative surgery, which may be inadequate primary treatment for ovarian carcinoma, or debulking surgery including hysterectomy and bilateral salpingo-oophorectomy, which may be unnecessary for an ovarian tumor of LMP.

As mentioned above, some women experience intra-abdominal progression of disease. In most cases, this appears histologically as islands of epithelium pushing, rather than invading, into adjacent tissues. Unlike epithelial ovarian carcinoma, LMP tumors that have progressed within the abdomen rarely, if ever, metastasize outside of the peritoneal cavity. In addition, unlike epithelial ovarian carcinoma, these tumors show little response to standard cytotoxic chemotherapy, probably because of their low proliferative activity.

Several groups of investigators have attempted to define the subset of women with LMP tumors who are at highest risk of progression. The Johns Hopkins group has proposed “micropapillary architecture” and “microinvasion” as predictors of progression; the M. D. Anderson and Harvard groups, p53 mutations; the Harvard group, “invasive implants”; and the Norwegian Radium Hospital, DNA ploidy.[7-11] To date, however, none of these histopathologic diagnoses—“micropapillary architecture,” “microinvasion,” or “invasive implants”—has been found to be consistently reproducible or consistently predictive of bad outcome. Similarly, the presence of p53 mutations or DNA ploidy in LMP tumors has not been a consistent predictor of poor outcome.

Future Research
Comprehensive explorations into the molecular genetics of benign ovarian epithelium, ovarian tumors of LMP, and ovarian carcinoma are necessary in order to expand our understanding of these tumors. Such explorations may also point to effective biological therapy for LMP tumors that progress.

In addition, we need to determine how best to study the clinical behavior of these tumors. Most of them are cured with surgery. As recurrences and progression can occur over decades, we need to follow patients for many years, as well as to bank tumor specimens for correlative laboratory studies. Finally, we need a multi-institutional commitment to pool data and tissue resources. We must develop effective therapy and counsel our patients appropriately based on multi-institutional prospective studies that use widely accepted pathologic criteria, rather than the retrospective, single-institution series that currently dominate the literature on LMP ovarian tumors.

References:


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