OVARIAN AND PERITONEAL BORDERLINE NEOPLASMS: HISTOPATHOLOGY, DIAGNOSTIC PITFALLS, AND PROGNOSTICATION

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Introduction
Ovarian epithelial cancer affects over 26,000 American women annually, and it accounts for approximately 5% of all cancers exclusive of cutaneous epithelial malignancies and many in situ carcinomas except bladder.[1] Over 80% of ovarian carcinomas are of surface epithelial origin.[2] Ovarian surface epithelial cancer represents approximately 50% of all pelvic malignancies and kills annually more than 14,500 women compared with 5,900 and 4,800 deaths related to endometrial and cervical cancer, respectively.[2] Clinical discovery of ovarian surface epithelial cancer is often late[3] and the relative five-year survival for ovarian surface epithelial cancer of 42% contrasts with survival figures of 70% for cervical cancer and 85% for endometrial cancer.[1] These statistics reflect our limited comprehension of the natural history of ovarian surface epithelial cancer.

Low malignant potential (LMP) or borderline neoplasms derive from the so-called surface epithelium of the human ovary, a modified mesothelium in continuity with the adjacent extra-ovarian peritoneum. These neoplasms represent an important category of ovarian common epithelial tumors usually associated with an excellent prognosis but, rarely, with a more aggressive and unpredictable behavior characterized by intraperitoneal seeding and frank malignant transformation.

Two areas of current clinicopathologic relevance in the evaluation of ovarian epithelial cancer are addressed[4,5]: (1) the histologic diagnosis of borderline or low malignant potential (LMP) epithelial neoplasms and (2) the difficulty in distinguishing metastatic implants from endosalpingiosis, florid mesothelial hyperplasia, and peritoneal serous borderline tumors. The application of ancillary laboratory studies in the diagnosis and prognostication of such lesions also is discussed on this article.

LMP Ovarian Neoplasms
The diagnostic challenge associated with LMP ovarian neoplasms begins at the exploratory laparotomy.[6] At this time, the gynecologic surgeon must assess several issues, including (1) ovarian or paraovarian location and extent of the neoplasm, (2) presence of adhesions between the ovary and surrounding structures, (3) indication for staging omentectomy, subdiaphragmatic smears, and peritoneal washings, (4) involvement of the contralateral ovary, and (5) preservation of fertility. For accurate sampling, the surgeon should indicate to the pathologist the location of any adhesions. Methodical sampling of the omentum may reveal small implants not visible to the unassisted eye that would influence staging and treatment. Fertility preservation should be considered before surgery, since almost 30% of LMP ovarian neoplasms are seen in women during the childbearing years.[7] If the exact degree of malignancy cannot be established intraoperatively, these women may be best treated conservatively, with more extensive surgery carried out after a thorough study of the removed neoplasm, omentum, and peritoneal washings. This approach appears justified in view of a reported lower rate of malignant transformation than previously thought.[8]

Russell[6] described that LMP ovarian neoplasms represented 15% of all ovarian surface epithelial tumors. LMP potential forms occur at a younger age than frankly malignant neoplasms. However, their clinical presentation and epidemiologic pattern are not otherwise distinctive.[7] For the purposes in this article, the histology of LMP neoplasms focuses on serous and mucinous forms only.

Most surface epithelial neoplasms are believed to develop from inclusion cysts,[9] although some may originate from nonencysted surface mesothelium.[10] Cysts appear to result from invagination of the ovarian mesothelium, either as a consequence of aging or as a result of intraperitoneal irritation. Tissue injury secondary to such events may predispose to surface mesothelial reactions and formation of papillary lesions.[2] The entrapped or reactive mesothelium may then undergo Müllerian-oriented metaplasia and may proliferate and form papillae in response to a number of stimuli, including intraovarian growth factors.[11-14] Dividing ovarian mesothelial cells would be susceptible to environmental transforming agents, and this hypothetical chain of events may lead to surface epithelial neoplasia.[2,11] A reaction may occur for mesothelial cells at extra-ovarian sites.

Histopathologic Features of LMP Neoplasms
Most serous and mucinous neoplasms of LMP are cystic.[6,15] Bilaterality occurs in 10% to 40% of patients. A distinction between LMP neoplasms and well-differentiated carcinomas based on gross examination alone is difficult, if not impossible, since both neoplasms usually contain grape-like structures arising from the cyst wall.

Microscopic criteria for diagnosis of LMP serous neoplasms include (1) epithelial proliferation with stratification to two to three cell layers, (2) architectural disorganization of cells, (3) complex branching papillae with cells forming long, frond-like projections, (4) free cell clusters and epithelial tufting within the cyst lumen (Fig 1A), (5) one to five mitotic figures per 10 high-power fields, (6) moderate to occasionally severe nuclear atypia (Fig 1B), and (7) absence of stromal invasion, back-to-back or solid sheets of tumor cells, small clusters or individual cells within an edematous or immature fibrous stroma, and inflammatory response adjacent to putative areas of stromal invasion. Adequate sampling is necessary to conclusively differentiate low malignant from frankly malignant forms. One to two histologic sections per centimeter of lesion should be obtained and carefully screened to determine that no foci of frank malignancy is overlooked. Search for invasion is elaborate and, at times, controversial due to the presence of only a few infiltrating cells or to a peculiar angle of sectioning. In this regard, a category of LMP serous tumors with microinvasion (Fig 2) and relatively favorable outcome also has been identified.[16,17]

In general, two or more of the histologic criteria outlined above should be met before assigning a neoplasm to the category of LMP tumors. LMP serous neoplasms may exhibit papillae on the outer surface of the cyst, and surface papillomas or papillomatosis of LMP also may exist on the ovarian surface in the absence of a grossly cystic mass.[4,7] Atypical cells may be shed directly into the peritoneal cavity from both such lesions. While these criteria are useful in identifying LMP neoplasms, the best indicator of clinical outcome is the presence of neoplastic cells beyond the ovaries. Fortunately, up to 85% of patients with LMP ovarian neoplasms present with stage I tumors.[18] The 10- and 20-year survival rates for these patients may be as high as 90% and 80%, respectively. Extra-ovarian disease is present at the time of diagnosis in 15% to 30% of patients and is equally distributed between stage II and stage III (stage IV neoplasms are rare). Although tumor-related deaths occur in patients with stage II and stage III neoplasms, more than 50% of these patients die many years after the initial diagnosis and usually after an initially incomplete resection. These figures differ from those of frankly malignant neoplasms, for which the five-year survival rate is no better than 40%, with most deaths occurring within the first few years after the initial diagnosis.[18]

Evaluation of LMP Ovarian Neoplasms
Approximately 10% of patients with stage I LMP ovarian neoplasms may die within 10 years after diagnosis. However, a recent analysis indicates that survival for patients with stage I neoplasms is 99%, while survival for advanced-stage disease without invasive implants is 92%.[8] Frank malignant transformation appears to occur in less than 1% of LMP neoplasms.[8] Therefore, conservative treatment of these lesions may be justified even if in 20% to 30% of cases, multiple small foci of benign-appearing serous proliferations may be found throughout the abdomen.[8]
Investigators have been searching for histologic prognosticators of tumor behavior in "unfavorable" LMP neoplasms but have found no conclusive evidence. For instance, little correlation is present between cytoplasmic atypia and tumor behavior.[19] Using flow cytometric DNA analysis, Friedlander et al.[20] discovered aneuploidy in two of 44 LMP ovarian neoplasms. Both patients displayed omental and peritoneal implants; one died seven months after the initial diagnosis. Feulgen-based cytometric determination of nuclear DNA also revealed an increased level of aneuploidy in LMP neoplasms of progressively higher stage. However, in this and subsequent studies,[21] no obvious correlation between aneuploidy and clinical outcome was apparent. In frankly malignant ovarian neoplasms, the simultaneous evaluation of DNA aneuploidy, S-phase cell fraction, and quantitation of silver-stained nucleolar organizer regions (AgNORs) may provide more powerful prognostic information than the determination of tumor ploidy alone.[21,22] More recent studies suggest that such an approach may identify a subpopulation of more aggressive tumors within the general category of LMP neoplasms. For instance, the demonstration of DNA aneuploidy or diploidy with high ras p21 expression[23] or high p53 expression[24] may identify LMP neoplasms at high risk for aggressive behavior. Similarly, high counts of AgNORs may help to distinguish LMP neoplasms from frankly malignant carcinomas[25] and more aggressive LMP neoplasms.

[26] Mountford et al.[27] used high-resolution proton magnetic resonance spectroscopy to identify this category of neoplasms and found five of six LMP neoplasms with a population of tumor cells capable of metastasizing and not identifiable by light microscopy.

Multiparameter analysis of nuclear DNA and morphometry also may provide an additional prognostic tool in the evaluation of LMP ovarian neoplasms. For instance, a survival rate of 91% was reported in women with diploid tumors displaying a mitotic activity index less than 30 and a volume percentage of neoplastic epithelium less than 65.[19] In contrast, a 29% survival rate was noted in patients with FIGO stage I ovarian neoplasms exhibiting DNA aneuploidy, a mitotic activity index higher than 30, and a volume percentage of epithelium greater than 65.[19] Development of sensitive prognostic indices would be valuable to therapeutic management. Currently, standard surgical therapy for LMP ovarian serous neoplasms is total abdominal hysterectomy and bilateral salpingo-oophorectomy. In younger women, unilateral salpingo-oophorectomy or even cystectomy may be performed with careful evaluation and biopsy of the contralateral ovary.[9] Adjuvant therapy may be required for stage I neoplasms. With stage II or stage III LMP neoplasms, extra-ovarian lesions are surgically removed and patients closely followed with second-look laparotomy. Adjuvant chemotherapy also may be administered if invasive extra-ovarian lesions are identified.

LMP Mucinous Neoplasms

Atypical mucinous cystadenomas also are designated as LMP mucinous neoplasms.[28] Histopathologically, these tumors are frequently multilocular and display abnormal cellular activity and proliferation of the lining epithelium with papillary projections (Fig 3A) and cell multilayering up to, but not more than, three cell layers (Fig 3B). Invasion is difficult to establish in multilocular neoplasms and is not necessary for diagnosis of frank carcinoma.[15,29] Thus, neoplasms exhibiting more than three-cell stratification but no obvious invasion are classified as mucinous carcinomas without invasion. The mortality rate for patients with these neoplasms is approximately 30% (compared with a 94% survival rate for LMP mucinous neoplasms confined to the ovary).[6] Mucinous carcinomas with demonstrable stromal invasion are associated with an approximate 33% survival rate for all stages.[6,29] As for benign and frankly malignant mucinous tumors, pseudomyxoma peritonei can complicate LMP mucinous neoplasms.[30] Histologic or cytologic evaluation of a pseudomyxomatous peritoneum may indicate the presence of abundant mucin with or without epithelial cells and may assist in staging and confirming recurrence. Stage I LMP mucinous neoplasms are treated with conservative surgery, while more advanced neoplasms require extensive and often repetitive surgery. The finding of a pseudomyxomatous ovary may forecast the subsequent development of pseudomyxoma peritonei and/or malignant recurrence in LMP mucinous neoplasms.[30]

Endosalpingiosis, Mesothelial Hyperplasia, and Peritoneal Serous Borderline Tumors

When LMP neoplasms are excised, both pelvic and peritoneal cavities often appear free of macroscopic implants. However, if omentectomy and lymphadenectomy are performed, examination of omental and lymph nodal tissues may disclose the presence of glands, papillary, or tubulo-papillary epithelial proliferations within submesothelial invaginations. Discovery of such lesions will prompt the differential consideration of endosalpingiosis, mesothelial hyperplasia, peritoneal implants of ovarian neoplasms, peritoneal serous borderline tumors, and well-differentiated peritoneal serous carcinomas.

Endosalpingiosis

Endosalpingiosis (benign Müllerian inclusions or Müllerianosis) is a condition defined by the presence of small cysts lined by an epithelium that is usually tubal-type.[31] These structures may be present in pelvic adhesions, within or below the serosal surface of pelvic organs, in the omentum, or within lymph nodes. Developmentally, endosalpingiosis may be related to pelvic inflammatory disease, tubal surgery, tubal lavage, or metaplasia of the peritoneal mesothelium secondary to poorly characterized stimuli including steroid hormones and growth factors.[11,32] Although endosalpingiosis occurs more frequently before menopause, its sequelae can be seen in older women in the form of few or numerous subperitoneal psammoma bodies. In the latter instance, the peritoneum may appear granular and sandy, a condition described over 150 years ago as "peritonitis avara."[33]

The presence of endosalpingiosis alone does not affect patient survival, while extra-ovarian implants of LMP neoplasms represent an adverse prognostic factor. The differential diagnosis of endosalpingiologic structures and implants of low-grade serous carcinomas or LMP neoplasms can be challenging, since all three lesions may exhibit ciliated cells and form small cysts. However, diagnostic criteria have been developed to discriminate between benign and malignant cysts in the omentum.[31] Benign endosalpingiologic lesions usually are noninfiltrative, lack obvious desmoplastic reaction, are located subperitoneally, and exhibit a well-defined basement membrane, uniform nuclei, no mitoses, prominent cilia, and commonly a single layer of low columnar epithelial cells with intraepithelial lymphocytes akin to those observed in normal fallopian tubes (Figs 4A and B). In contrast, neoplastic implants are located on mesothelial surfaces as well as subperitoneally, may exhibit an infiltrative pattern or a desmoplastic reaction, lack a basement membrane, and display papillary features with detached cell clusters, rare cilia, pseudostratification of nuclei, and nuclear features of malignancy with variable numbers of mitoses.

Implants of LMP Serous Neoplasms

Implants of LMP serous neoplasms are noninvasive and invasive.[34] Noninvasive implants are sharply demarcated from underlying normal tissues and can be subdivided into epithelial or papillary (Fig 5A) and desmoplastic types with dense and reactive stroma around them (Fig 5B). Psammoma bodies and moderate epithelial atypia often are present. Invasive implants irregularly and massively infiltrate underlying normal tissues and frequently display marked cytologic atypia (Figs 5C and D). Recent data suggest that such a histologic distinction, albeit not always possible, is of prognostic significance, with invasive implants associated with a lower four- to 12-year disease-free survival rate than that of noninvasive implants (20% vs 90%, respectively).[6,10,34]

Mesothelial Hyperplasia

Mesothelial hyperplasia presents with small, solid cell clusters or irregular nests of cells with columnar morphology and delicate, eosinophilic cytoplasm without obvious nuclear atypia. Mesothelial proliferations associated with pelvic inflammatory disease, endometriosis, and a history of pelvic surgery pose no significant diagnostic problems. However, florid mesothelial proliferations can be seen in association with LMP ovarian neoplasms.[35] Particularly when presenting with papillary features, these proliferations may be interpreted as metastatic tumor intraoperatively or at initial microscopic examination. Careful evaluation usually will disclose the absence of grossly visible nodules, marked nuclear atypia, necrosis, papillary stalk microinvansion, surrounding desmoplastic reaction, and the presence of an orderly or parallel arrangement in benign mesothelial cells.[35] In contrast with cells shed from ovarian epithelial neoplasms, reactive mesothelial cells lack or weakly express an epithelial membrane antigen and do not immunostain positively with antibodies against carcinoembryonic antigen, leukocyte M1 (CD15), and B7.2.[2,36]

Peritoneal Serous Borderline Tumors

Peritoneal serous borderline tumors (PSBT) occur usually in women of reproductive age.[37] At laparotomy, the pelvic peritoneum is involved and displays adhesions or granularity. The microscopic features of PSBT include a histology similar to that of noninvasive implants of LMP serous ovarian neoplasms (Fig 6), the absence of significant desmoplastic reaction, associated peritoneal endosalpingiosis, and, less frequently, ovarian serous cystadenomas or adenofibromas. Suggested therapy for PSBT includes bilateral salpingo-oophorectomy, total abdominal hysterectomy and omentectomy, with few patients receiving chemotherapy or only limited surgical therapy. Burmeister et al.[38] found no clinical recurrences in over 85% women after a mean follow-up of more than eight years and observed recurrent tumor in three of 21 patients with continued survival after resection in two of them. However, a low-grade serous carcinoma of the peritoneum developed in the third patient seven years after initial surgery. Therefore, PSBT behavior appears similar to that of LMP ovarian neoplasm with noninvasive peritoneal implants and limited cytologic atypia when complete or near-complete resection and careful follow-up are carried out.[6,34]
Distinction between PSBT and the 4% to 14% of women presenting with endosalpingiosis may be difficult since complex endosalpingiogenic lesions can induce desmoplasia in the surrounding stroma.[37,38] There may be a developmental link between these two lesions.[39,40] Dallenbach-Hellweg[41] described a case of atypical endosalpingiosis with focal epithelial tufting and detached cell clusters. At our institution, we have observed a similar histopathology in peritoneal biopsies of women with or without concomitant ovarian neoplasms (Fig 7). LMP and frankly malignant serous neoplasms also have arisen in pelvic lymph nodes harboring endosalpingiosis.[40] The distinction between PSBT and adenocarcinomas is based on the marked atypicality and invasive nature of the latter and may be difficult to establish in the presence of implanted very low-grade serous adenocarcinomas with or without associated psammoma bodies. However, these neoplasms usually are associated with some degree of destructiveness and omental and/or extrapelvic peritoneum involvement.

Conclusions

Modern techniques should improve our ability to more accurately diagnose and provide a prognosis for patients with LMP serous neoplasms. There may be a continuum of lesions from endosalpingiosis to intraperitoneal serous carcinomas. Verification of such a possibility would reinforce the autochthonous peritoneal tumorigenesis theory championed by Woodruff.[42] Recent data indicate that approximately 86% and 14% of LMP serous neoplasms are diploid or aneuploid by DNA analysis, respectively.[20,43] Of the aneuploid tumors with or without invasive peritoneal implants, approximately one third may result in death.[46,47] Further study is needed to establish if other parameters such as proliferating cell nuclear antigens,[48] frequency of AgNORs,[25] expression of growth factor ligands or receptors[49] and tumor suppressor genes[24] as well as cytogenetic abnormalities[50] are useful to other prognostic factors independent of other parameters such as tumour grade and stage.

References


