Serous Borderline Tumors of the Ovary: Implants, Manifestations, Biology & New Insights in Progression

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The serous borderline tumor constitutes one of the most enigmatic of all conditions confronting gynecologic pathologists. It is enigmatic for any number of reasons. The borderline tumor as we most commonly see it is only intermittently clinically malignant, but a small number do ultimately behave aggressively. What features identify those that will behave ultimately in a clinically benign fashion from those that will become clinically malignant? Is the borderline tumor that transforms into grade 1 cancer more like its borderline parent or more like spontaneously forming grade 2 or grade 3 serous carcinoma? Are there one or more pathogenetic routes to malignancy? If a solitary lesion that is typically borderline is found in the peritoneum, what is its relation to endosalpingiosis? Does, in fact, endosalpingiosis exist as a condition? What is the relation of borderline serous tumor to mullerian inclusion cyst (MIC) found both in the peritoneum and lymph nodes? Is MIC the same as endosalpingiosis? What is its biologic significance?

Dr. Jules Berman, in his introduction and editorial overview to a workshop held in Bethesda, Maryland, on August 27-20, 2003 convened to discuss the enigmatic borderline ovarian tumor,[2] described well the "confusion, apprehension and altercations" we all have experienced with this truly perplexing family of conditions.

> Borderline ovarian tumors (BOTs) do not fall neatly into benign or malignant categories. When a tumor with BOT morphology invades its own stroma and the surrounding ovarian tissue, the tumor is not called an invasive BOT (no such lesion exists). Rather, it is called a carcinoma. Although invasive BOTs do not exist, pathologists reserve a category of microinvasive BOT (ie, a BOT can have microinvasion, but a BOT cannot have invasion). When deep invasion is present, to spare the surgeons unnecessary confusion, pathologists often omit any reference to the BOT component of the tumor. This "act of kindness" eliminates documentation of those cases in which BOT and cancer coincide, obscures our clinical understanding of tumors with mixed BOT/carcinoma morphology, and leaves us confused about the relationship between BOT and cancer.
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> Because BOTs are neither benign nor malignant, the extra-ovarian spread of BOT cannot proceed through metastasis (a property associated exclusively with malignant tumors). BOTs spread through the pelvis via "implantation." Unlike the metastatic spread of tumors (where metastasis is always bad), the clinical relevance of implants is determined by the morphological features of the implanted tumor. If the implant is invasive, then the prognosis changes. Interestingly, a patient with the diagnosis of BOT who develops a highly invasive implant (eg, an implant attaching to the colon and invading deeply into the colon wall) does not have cancer. In this case, the patient has a BOT with invasive implant. That is, the implant is invasive but the BOT is not! Remember, now, that a BOT with invasion limited to the ovary is called a carcinoma. To the best of my knowledge, BOT is the only tumor for which the diagnosis is changed not by the presence of invasion, but rather by the location in which the invasion occurs (ovary vs implantation site). Local invasion changes the diagnosis to cancer, erases the BOT, and turns any implants into metastases! A BOT with distant invasion (even if we someday learn that implantation occurs through a mechanism equivalent to metastasis) is still a BOT.

Borderline tumors not uncommonly have protracted courses, sometimes with changes in histology. As an example, a 21-year-old woman at our Institution presented with a stage IIIC ovarian serous borderline tumor. MIC was also present in a lymph node. A second-look laparoscopy performed one year later suggested regression, but a CT scan one year after that revealed carcinomatosis with soft-tissue masses in the paracolic gutters bilaterally, for which chemotherapy was begun. During the next five years she underwent periodic debulking procedures. The original histology, which was typical borderline, became grade 1 adenocarcinoma. The most recent CT scan (after 13 years) showed a 5.6 cm subcapsular calcified mass along the periphery of the liver, which had increased in size from 3.2 cm in over two years, and a 4.4 cm lesion in the falciform ligament.

Typical serous tumors of borderline malignancy microscopically show bulbous, but sometimes, fine to coarse papillary fronds in which atypical, stratified neoplastic cells cover a thick core of fibrovascular stroma. Commonly, a small to moderate proportion of the papillae exhibit clusters of cells that appear as solid cellular buds that, because of tangential sectioning, appear detached from the epithelial lining. The degree of nuclear atypia as well as the number of mitotic figures is variable. Ciliated cells are common, as are psammoma bodies. The diagnosis of a borderline tumor requires that no area contain frank stromal invasion. The presence of small foci of microinvasive tumor does not alter the patient's otherwise excellent prognosis.

“Micropapillary carcinoma” is a variant of borderline serous tumor that was described initially in 1996, but with disputed significance.[3,9,16,20] This tumor was thought to act in a more aggressive and clinically malignant fashion than the usually indolent, clinically benign, and more common form of borderline tumor, even when it had spread throughout peritoneal cavity. The fibrovascular fronds of the typical borderline serous tumors display a mantle of epithelial cells on the surface that appear focally as a multilayered shell with irregular zones of filiform micropapillarity. In the variant form, the micropapillarity is diffuse and uniformly covers all of the fibrovascular cores. While the authors who described this lesion suggested it be classified as an adenocarcinoma, subsequent studies have shown that unless associated with invasive implants, it behaves as ordinary borderline tumor, suggesting it remain in the borderline category.[4,7,8,12,13,15] Within the original description of micropapillarity was a second form of abnormality, i.e., foci with a cribriform pattern, but many pathologists would interpret this as grade 1 invasive cancer.

Destructive invasion in a borderline tumor indicates the presence of a serous carcinoma. The finding of tumor with irregular, angulated margins in the stroma reflects dissection along stromal planes. When papillae invade into the stroma, the stromal margins may appear retracted and display relatively pointed contours in relief. Solid clusters of cells may exhibit a cribriform pattern (intraglandular bridging) indicative of autonomous growth and hence, adenocarcinoma. Usually, invasion is accompanied by a fibrous stromal reaction (“desmoplasia”).

During the past several years, Kurman and his associates have further explored the transformation of borderline serous tumors to frank adenocarcinoma.[17,20-22] Significantly, consistent genetic changes were found in the grade 1 type adenocarcinomas that arose in cases of borderline serous tumor, and were significantly different from the spontaneous type of high-grade invasive adenocarcinoma commonly encountered in the more usual form of ovarian

cancer. In 61% of borderline serous tumors and 68% of invasive borderlines or grade 1 adenocarcinomas, BRAF mutations were found in codon 599 and/or k-ras mutations were found in codon 12/13. This contrasted with 0% mutations of the same type in the typical high-grade invasive cancer found in the more usual form of ovarian cancer, indicating that there are probably two different pathogeneses for serous tumors, one being associated with borderline serous tumors and its transformation to grade 1 serous adenocarcinoma, and the other for the more typical form of high-grade cancer

During recent years, patients with ovarian borderline tumors have been meticulously staged and peritoneal biopsies obtained both at primary surgery and at second look laparotomies. This has led to a better understanding of the types of serous lesions that can arise de novo in the peritoneum. The peritoneum, like the ovarian surface epithelium, is of mesothelial origin and, therefore, subject to the same disease processes. The implication of this hypothesis is that tumors arising in the peritoneum may be multicentric and independent of ovarian tumors.[10]

Borderline tumors found in the peritoneum including the broad ligament are similar to those arising in the ovary, which questions what is primary and metastatic (implants). Like the borderline lesion arising in the ovary, the features characterizing the serous borderline tumor primary in the peritoneum are papillary processes, small clusters of cells, cell stratification, detached cellular clusters, nuclear atypia, and mitotic activity. However, most borderline tumors in the peritoneum are associated with a similar type of ovarian tumor and are most likely metastases to the peritoneum.[14]

In evaluating peritoneal biopsies, tumor must be distinguished from reactive peritoneal hyperplasia and benign epithelial inclusions. Reactive mesothelial proliferations commonly simulate serous differentiation. A particularly difficult differential diagnosis about which there is still considerable debate is where only few glands are found in the peritoneal biopsy. The epithelium is extremely well differentiated and psammoma bodies may be conspicuous. Some proponents consider these as benign serous growths that are reactive and non-neoplastic, while others have shown that many may be borderline tumors.[11] The term "endosalpingiosis" or "atypical endosalpingiosis" is often used to describe this lesion, but this name is arguably inappropriate since the roots of the words themselves refer to a lesion that is benign ("osis") and arising from epithelium related to the fallopian tube ("-salping-"). If the neoplasms present in the peritoneal cavity are to be considered as borderline or malignant serous neoplasms, then the reactive forms should also probably be considered as serous, and given a name such as serous metaplasia, or borderline serous tumor or even serous adenocarcinoma to achieve continuity of nomenclature.

Late recurrences (16 yr mean duration) have been reported in some patients with stage IA or IB borderline serous tumors of the ovary and of these, about 2/3^{rds} of the patients have succumbed to the disease.[19] Curiously, many of these women initially had "endosalpingiosis" found in the peritoneum, one interpretation being that what was initially considered as endosalpingiosis might in reality have been implanted tumor from ovarian borderline tumors.

Mullerian inclusion cyst (MIC) involving the omentum and/or lymph nodes is another finding sometimes encountered when dealing with borderline serous tumors of the ovary. These occur in the form of individual round-to-oval glands with an obvious lumen. A peripheral basement membrane is present and cilia may be prominent. The epithelium is usually only

one cell layer thick, and stratification, if present, is minimal. The nuclei are basally situated, mitotic activity is absent, and there is no nuclear atypia. Their resemblance to fallopian tube epithelium has led to the use of the term "endosalpingiosis" if the lesion is in the peritoneal cavity and "mullerian inclusion cyst" if in a lymph node. These names should probably also be changed to "serous inclusion cyst" to reflect the nature of the tissue present. Although most reports have labeled these as benign inclusion cysts, many in fact may be metastases, even though their presence seems to have no impact on prognosis.[11] Many cases are associated with borderline serous tumors of the ovary and in some cases the same lymph node may disclose areas of typical borderline tumor adjacent to areas of mullerian inclusion cysts. Gene rearrangement studies performed in a small number of cases have shown the identical k-ras mutation in codon 12 in both the mullerian inclusion cyst in the lymph node as well as in the ovarian tumor.[1]

In addition to the above lesions, borderline serous tumors of the ovary can give rise to forms of more obvious metastases/implants to the peritoneum. They are 1) non-invasive with or without reactive desmoplasia, or 2) invasive. The definition of non-invasive "implants" is controversial,[18] as is the relation of this entity to long term prognosis.[19] Tumors with non-invasive implants progress slowly, if at all, and are associated with very low death rates. Non-invasive implants are superficially located on peritoneal structures and lack irregular infiltrative margins. The epithelium of non-invasive implants exhibits clusters of slightly atypical serous cells often admixed with variable numbers of psammoma bodies. They often have papillae filling smoothly contoured cystic invaginations, lying on the peritoneal surface or between folds in the omentum.

The presence of desmoplasia in the peritoneum, per se, is not considered a sign of invasive malignancy. A desmoplastic response to tumor, if present in the form of sharply circumscribed plaques, may represent implants that have plastered onto the peritoneal surface or even extended into septa between the lobules of omentum.[6] The implants are not considered to be invasive until they are solid or invade irregularly as jagged, disordered nests of tumor cells. In some cases, this distinction can be very difficult, if not impossible to make. The distinction is important, however, as the prognosis with invasive implants is significantly worse.

Some borderline tumors may show signs of invasion, but only in the peritoneal implants.[18] Although classified as "borderline" because of the microscopic findings in the ovarian primary,[5] tumors with "invasive implants" commonly act in a clinically aggressive manner and have been associated with a worse prognosis. We prefer to name these lesions as adenocarcinoma that has arisen in borderline tumor. Microscopically, invasive implants disclose an irregular, aggressive-appearing infiltration into the underlying tissue. The tumor glands show extensive intraglandular bridging or irregularly shaped solid nests of cells resembling tumors of low-grade serous adenocarcinoma. Severe cytologic atypia is present in some.

REFERENCES

1. Alvarez AA, Moore WF, Robboy SJ, et al.: *K-ras mutations in Mullerian inclusion cysts associated with serous borderline tumors of the ovary.* Gynecol Oncol 2001, 80:201-6
2. Berman JJ: *Borderline Ovarian Tumor Workshop, Bethesda, Maryland, August 27-28, 2003*. Human Pathol 2004, 35:907
3. Burks RT, Sherman ME, Kurman RJ: *Micropapillary serous carcinoma of the ovary: A distinctive low-grade carcinoma related to serous borderline tumors.* Am J Surg Pathol 1996, 20:1319-30
4. Deavers MT, Gershenson DM, Tortolero-Luna G, et al.: *Micropapillary and cribriform patterns in ovarian serous tumors of low malignant potential - A study of 99 advanced stage cases*. Amer J Surg Pathol 2002, 26:1129-41
5. Gershenson DM, Silva EG, Levy L, et al.: *Ovarian serous borderline tumors with invasive peritoneal implants*. Cancer 1998, 82:1096-103
6. Gershenson DM, Silva EG, TortoleroLuna G, et al.: *Serous borderline tumors of the ovary with noninvasive peritoneal implants*. Cancer 1998, 83:2157-63
7. Gilks CB, Alkushi A, Yue JJW, et al.: *Advanced-stage serous borderline tumors of the ovary: A clinicopathological study of 49 cases*. Int J Gynecol Pathol 2003, 22:29-36
8. Goldstein NS, Ceniza N: *Ovarian micropapillary serous borderline tumors - Clinicopathologic features and outcome of seven surgically staged patients*. Amer J Clin Pathol 2000, 114:380-6
9. Kempson RL, Hendrickson MR: *Ovarian serous borderline tumors: The citadel defended*. Hum Pathol 2000, 31:525-6
10. Lauchlan SC: *The secondary mullerian system revisited.* Int J Gynecol Pathol 1994, 13:73-9
11. Moore WF, Bentley RC, Berchuck A, et al.: *Some mullerian inclusion cysts in lymph nodes may sometimes be metastases from serous borderline tumors of the ovary.* Amer J Surg Pathol 2000, 24:710-8
12. Prat J: *Serous tumors of the ovary (borderline tumors and carcinomas) with and without micropapillary features*. Int J Gynecol Pathol 2003, 22:25-8
13. Prat J, de Nictolis M: *Serous borderline tumors of the ovary - A long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion.* Amer J Surg Pathol 2002, 26:1111-28
14. Segal GH, Hart WR: *Ovarian serous tumors of low malignant potential (serous borderline tumors). The relationship of exophytic surface tumor to peritoneal "implants"*. Am J Surg Pathol 1992, 16:577-83
15. Sehdev AES, Sehdev PS, Kurman RJ: *Noninvasive and invasive micropapillary (low-grade) serous carcinoma of the ovary - A clinicopathologic analysis of 135 cases*. Amer J Surg Pathol 2003, 27:725-36
16. Seidman JD, Kurman RJ: *Ovarian serous borderline tumors: A critical review of the literature with emphasis on prognostic indicators*. Hum Pathol 2000, 31:539-57
17. Shih IM, Kurman RJ: *Ovarian tumorigenesis - A proposed model based on morphological and molecular genetic analysis*. Amer J Pathol 2004, 164:1511-8
18. Silva EG, Kurman RJ, Russell P, et al.: *Symposium: Ovarian tumors of borderline malignancy*. Int J Gynecol Pathol 1996, 15:281-302
19. Silva EG, Tornos C, Zhuang ZP, et al.: *Tumor recurrence in stage I ovarian serous neoplasms of low malignant potential.* Int J Gynecol Pathol 1998, 17:1-6
20. Singer G, Kurman RJ, Chang HW, et al.: *Diverse tumorigenic pathways in ovarian serous carcinoma*. Am J Pathol 2002, 160:1223-8
21. Singer G, Oldt R, 3rd, Cohen Y, et al.: *Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma*. J Natl Cancer Inst 2003, 95:484-6
22. Singer G, Shih IM, Truskinovsky A, et al.: *Mutational analysis of K-ras segregates ovarian serous carcinomas into two types: Invasive MPSC (low-grade tumor) and conventional serous carcinoma (high-grade tumor).* Int J Gynecol Pathol 2003, 22:37-41