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Editorial and Overview

Borderline Ovarian Tumor Workshop, Bethesda, Maryland, August 27-28, 2003

Borderline ovarian tumors (BOTs) are enigmatic neoplasms that have inspired confusion, apprehension, and altercation disproportionate to their incidence. As a general pathologist with no expertise in gynecologic pathology, I was baffled by this tumor that ignores the common rules of tumor biology. Here are some of my impressions.

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.

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.

When Dr. Steven Silverberg approached me with the idea of co-organizing a BOT Workshop, I jumped at the opportunity. Such a workshop seemed like an excellent way to learn from the masters while participating in an effort to bring clarity to general pathologists who may share some of my confusion.

PURPOSE

In the 30-plus years since BOTs were officially "invented," BOTs have been mired in controversy. In the past several years, pathologists have urged a BOT Workshop, expressing the opinion that agreement could be reached on some issues that will help pathologists diagnose BOTs with higher consistency and that will guide clinicians toward treatments commensurate with the expected clinical behavior of BOTs. For those areas in which there is no agreement, a group would seek to develop a commonly accepted way of describing the basis of disagreement. By providing a thoughtful discussion of areas that lack agreement, new areas for future BOT research could be developed.

SPONSORS AND ORGANIZATION

The BOT Workshop was sponsored by the National Institutes of Health Office of Rare Diseases, the

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National Cancer Institute's (NCI) Office of Women's Health, and the NCI Cancer Diagnosis Program. Drs. Jules Berman and Steven Silverberg were the workshop organizers.

Because the area of BOT pathology is so contentious, the Workshop organizers took extraordinary measures to ensure fairness and objectivity. A planning committee composed of 4 eminent gynecologic pathologists (Drs. Steven Silverberg, Elvio Silva, Robert Kurman, and Robert H. Young) suggested the list of attendees and the meeting agenda. Every prospective attendee named by the advisory panel was invited, regardless of geographic location. In addition, registrants were encouraged to submit additional names for attendance. Every person who asked to attend the Workshop was registered, and funds were provided for transportation and lodging to all nonlocal registrants.

ATTENDEES

Workshop participants included pathologists, oncologists, surgeons, gynecologists, and research scientists. The 39 attendees, listed here in alphabetical order, were Andre Kajdacsy-Balla, Debra Bell, David Berman, Jules Berman, Michael Birrer, Jeff Boyd, Kathleen Cho, Larry Copeland, Ben Davidson, Michael Deavers, Lora Hedrick Ellenson, Elizabeth Garner, Blake Gilks, Fred Gorstein, Thomas Hamilton, Elise Kohn, Robert Kurman, Anna Levy, Rebecca Liddell, Teri Longacre, Tracy Lugo, Anais Malpica, Maria Merino, Samuel Mok, Alexander Nikitin, Esther Oliva, Jaime Prat, Brigitte Ronnettt, Robert Scully, Jeffrey Seidman, Mark Sherman, Ie-Ming Shih, Elvio Silva, Steven Silverberg, Robert Soslow, Mark Stoler, Sheila Taube, Bruce Werness, and Robert H. Young.

AGENDA

Day 1 of the Workshop was given over to a review of the major issues in BOT pathology. Dr. Larry Copeland (Ohio State University) provided a clinical overview of BOTs from the perspective of an oncologic surgeon and clinical trialist. Drs. Kathleen Cho (University of Michigan) and Michael Birrer (NCI) described the tools and approaches used by molecular biologists to characterize BOTs and to answer questions on fundamental issues of BOT biology. Dr. Mark Sherman (NCI) discussed how studies might be designed that address the still-unresolved issues of BOT incidence and survival. Dr. Jeff Seidman (Washington Hospital Center) discussed the pathological features of the controversial micropapillary variant of BOT. Drs. Debra Bell (Massachusetts General Hospital) and Robert Kurman (Johns Hopkins Hospital) discussed the pathology and clinical significance of implants in BOT. Dr. Brigitte Ronnett (Johns Hopkins Hospital) led discussion on the special category of mucinous tumors of the ovary.

Day 2 consisted of an open discussion of issues raised on day 1 of the Workshop. As might be expected, 2 half-day sessions were insufficient to resolve all of the BOT issues raised in the Workshop. There was approval for a plan to continue Workshop activities through list-server participation. Group e-mails permitted an extended period of discussion, during which a collection of BOT manuscripts were written and reviewed.

WORKSHOP ARTICLES

The following BOT Workshop articles appear in this issue of HUMAN PATHOLOGY:

- Borderline Ovarian Tumors: Key Points and Workshop Summary, by Steven Silverberg et al.
- Borderline Ovarian Tumors: Diverse Contemporary Viewpoints on Terminology and Diagnostic Criteria, With Illustrative Images, by Jeffrey Seidman et al.
- Serous Borderline Ovarian Tumors: Workshop Perspectives, by Debra Bell et al.
- Mucinous Borderline Ovarian Tumors: Points of General Agreement and Persistent Controversies Regarding Nomenclature, Diagnostic Criteria, and Behavior, by Brigitte Ronnett et al.
- Current Challenges and Opportunities for Research on Borderline Ovarian Tumors, by Mark Sherman et al.

REVIEW PROCESS

To ensure that all opinions are represented in the conference articles, a tiered review process was established. A National Institutes of Health–supervised list server was created for workshop participants. The list server was used over the ensuing 6 months to collect and share comments, to resolve remaining issues, and to exchange manuscript revisions. Each article was assigned a primary author and a group of coauthors. The primary author was responsible for writing a first draft of the article; coauthors were responsible for revising the draft and supplying sufficient commentary to give readers a useful perspective on the range of opinions represented at the Workshop. All coauthors were required to make substantial intellectual input and to approve the final manuscript, in compliance with the rules for authorship proposed by the International Committee of Medical Journal Editors.[1] Once the author and coauthors were satisfied with the manuscript, it was circulated to the list server, where all of the Workshop participants were given an opportunity to comment on the draft. The primary author and coauthors for each article were required to modify their article in response to comments received through the list server. At the end of this review and revision process, participants were given a final opportunity to add dissenting comments to the articles, if they so desired. In addition, all participants were given the option of quitting the group process and submitting their own manuscripts for peer review. The Workshop organizers,

the planning committee, and the primary authors of each article were responsible for ensuring compliance with the review process. The final result of this process is a series of up-to-date discussions of issues. The articles were written with the intent of representing multiple expert opinions, and were not intended as clinical guidelines. The following disclaimer applies to all of the Workshop articles:

> Disclaimer: The Borderline Ovarian Tumor Workshop manuscripts contain statements that include suggestions and recommendations from many different participants. In view of the wide range of expressed opinions, no statements contained in these manuscripts should be used as a "standard of care."

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REFERENCE

1. International Committee of Medical Journal Editors: Uniform requirements for manuscripts submitted to biomedical journals. Ann Intern Med 126:36-47, 1997