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Benign ovarian serous tumors: a re-evaluation and proposed reclassification of serous "cystadenomas" and "cystadenofibromas"

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Abstract

Objective. Serous cystadenomas and cystadenofibromas of the ovaries are currently regarded as neoplasms and are considered the most common ovarian neoplasms. The purpose of this study is to determine what proportion of benign serous tumors contain an epithelial proliferation (the hallmark of a neoplastic process in nearly all other sites) that can be considered neoplastic as opposed to reactive in nature.

Methods. An unselected series of 113 ovarian serous tumors (76 serous cystadenomas and 37 serous cystadenofibromas) were histologically evaluated. A 1-mm in diameter area of epithelial proliferation was considered potentially neoplastic.

Results. Eight tumors (7%) displayed at least 1 mm of epithelial proliferation (1% of serous cystadenomas and 19% of serous cystadenofibromas).

Conclusion. The vast majority of benign serous tumors may not be bona fide epithelial neoplasms, but rather, may represent cystically dilated glandular inclusions (cystadenomas) and fibromas with epithelial inclusions (cystadenofibromas). A recently published study evaluating clonality in serous cystadenomas found that the vast majority are polyclonal and thus supports this hypothesis. These findings have important implications for the pathogenesis of ovarian cancer, for the distribution of ovarian neoplasms, and for the interpretation of molecular biological studies of ovarian tumors.
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Introduction

The terms "ovarian tumor" and "ovarian neoplasm" are often used interchangeably. This practice is fostered by many authoritative works including the World Health Organization's *International Histological Classification of Tumours: Histological Typing of Ovarian Tumours* published in 1999 [1]. Indeed, it is now generally accepted that the terms "tumor" and "neoplasm" are synonymous: ". . .by long precedent, the non-neoplastic usage of *tumor* has passed into limbo; thus the term is now equated with neoplasm [2]. Historically, the term tumor has generally referred to an abnormal mass, while the term neoplasm has more specifically referred to "an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change" [3]. Nearly 50 years after Willis [3] stated this definition, it remains accurate but incomplete as noted by Cotran et al. [2] who added that "the abnormal mass is purposeless, preys on the host, and is virtually autonomous". Nonetheless, the latter authors recognize that it has been "surprisingly difficult" to develop an accurate definition of a neoplasm. Any current definition must recognize that all neoplastic proliferations have some abnormality in their DNA, whether it be obviously aneuploid or only slightly abnormal by virtue of a minor DNA alteration influencing the expression of an oncogene or tumor suppressor gene.

The most common ovarian epithelial "tumor" or "neoplasm" is the "serous cystadenoma." The suffix, "adenoma," has evolved over many years; at present, this

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suffix indicates an epithelial neoplasm. Serous cystadenomas have been considered neoplastic for many years and currently are generally regarded as neoplastic. It is our opinion, however, that the current use of the term "neoplasm" in this context is not based on sufficient evidence.

In addition to the features of neoplasia described above, a histologically defining feature of a neoplasm is a cellular proliferation, most often of one cell type. We have observed that those lesions that qualify for the designation, "serous cystadenoma," (as well as "serous cystadenofibroma") often display little if any *epithelial* proliferation, and therefore, we hypothesize that the suffix "adenoma" may be inappropriate. This would have significant implications for our understanding of ovarian epithelial neoplasms. In order to examine critically the histopathological framework on which the classification of these tumors is based, we evaluated a consecutive series of serous cystadenomas and serous cystadenofibromas. The first aim was to determine what proportion of these tumors contain epithelial proliferations that could possibly be regarded as neoplastic. Then, we examine the consequences of reclassifying these lesions.

Materials and methods

Consecutive surgical pathology accessions with diagnoses coded as serous cyst, serous cystadenoma, and serous cystadenofibroma of the ovary were identified. At the Washington Hospital Center, 57 cases were prospectively accrued, and 31 cases were retrospectively identified. At Georgetown University Hospital, 25 cases were identified retrospectively. Patient age was recorded. The gross description and microscopic slides were reviewed for all cases. Lesions smaller than 1.0 cm in diameter were excluded. From the gross description, tumor size and locularity (unilocular or multilocular) were recorded. On review of the gross description in conjunction with the histologic slides, tumors were subclassified into unilocular serous cysts, multilocular serous cysts, and serous cystadenofibromas. Then, the presence or absence of an epithelial proliferation that could possibly be considered neoplastic was evaluated using the following arbitrary criteria. Unilocular or multilocular cysts lined by a single layer of epithelium lacking stratification or papillae with thin fibrovascular cores were considered to lack proliferation. In cystadenofibromas, a single nonstratified epithelial layer lining clefts or covering fibrous papillae was considered to lack epithelial proliferation. Epithelial stratification and/or papillary proliferation with thin fibrovascular cores or without fibrovascular cores over a distance of 1 mm or greater was considered evidence of proliferation in unilocular/multilocular cysts and cystadenofibromas. A hobnail-cell morphology alone was not considered evidence of epithelial proliferation. Care was taken to avoid misinterpreting tangentially sectioned areas as evidence of proliferation. In addition, glandular elements in the fibrous stroma of a cystadenofibroma were considered to be proliferating if any 1 mm in diameter field contained 10 or more glandular structures, and lacking proliferation if nine or fewer glands were present. These criteria were set arbitrarily and have not been tested or used by other investigators.

Noninvasive serous tumors displaying cytologic atypia, papillary epithelial proliferation with tufting, and detachment of cell clusters, were classified as atypical proliferative serous tumor (APST) (serous borderline tumor (SBT)) if the proliferative area involved greater than 10% of the tumor, and thus were excluded from the study. Morphologically similar tumors were classified as serous cystadenoma if the proliferative area involved less than 10% of the tumor. These criteria are in accordance with the recent NCI Borderline Ovarian Tumor Consensus Workshop [4].

Results

There were 96 patients among whom 113 tumors were evaluated. The mean patient age was 60 years and the mean tumor size was 5.7 cm. Eighteen percent of patients had bilateral tumors. A total of eight tumors (7%) displayed epithelial proliferation. No case had an epithelial proliferation of the degree usually seen in APST (SBT).

There were 36 unilocular serous cysts (32%), 40 multilocular serous cysts (35%), and 37 cystadenofibromas (33%). The mean patient ages were 60, 58, and 61, respectively. Among eight tumors (7%) that displayed epithelial proliferation, there were seven cystadenofibromas (19% of cystadenofibromas) (Fig. 1) and one unilocular serous cyst (1% of unilocular/multilocular serous cysts) (Fig. 2).

Discussion

Serous tumours are defined by the World Health Organization (WHO) [1] as "tumours composed of epithelium resembling that of the fallopian tube or in some cases the surface epithelium of the ovary." The phrases "neoplastic epithelium" and "neoplastic cells" are used throughout the description of all types of serous tumors, clearly indicating that serous cystadenomas are regarded as neoplasms. All such lesions that are 1.0 cm or greater are generally considered by experts to qualify for the designation [5]. However, the following observations must be considered. First, benign glandular epithelial inclusions (germinal or cortical inclusions) lined by serous epithelium are very commonly found in the ovarian cortex [6]. Second, these inclusions are often clustered (Fig. 3). Third, these inclusions may become cystic, individually (Fig. 4) or as a group (Fig. 5), presumably due to the accumulation of secretions that cannot escape. Finally, a single layer of serous epithelium lining an inclusion may proliferate in response to cystic enlargement simply as a

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