Journal of Mind and Medical Sciences

Volume 8 | Issue 1 Article 7

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Recommended Citation

Georgescu, Tiberiu-Augustin; Bohiltea, Roxana; Munteanu, Octavian; Grigoriu, Corina; Paunica, Ioana; and Sajin, Maria () "A mini-review regarding the carcinogenesis and morphology of serous tumors of the ovary, fallopian tube and peritoneum," *Journal of Mind and Medical Sciences*: Vol. 8 : Iss. 1 , Article 7.
DOI: 10.22543/7674.81.P4452
Available at: https://scholar.valpo.edu/jmms/vol8/iss1/7

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https://scholar.valpo.edu/jmms/
https://proscholar.org/jmms/

ISSN: 2392-7674

A mini-review regarding the carcinogenesis and morphology of serous tumors of the ovary, fallopian tube and peritoneum

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ABSTRACT

Similar to the already well-recognized adenoma-carcinoma sequence in colorectal cancer pathogenesis, it has been believed for many decades that the progression of ovarian epithelial tumors occurs from benign serous cystadenomas to borderline tumors, to well-differentiated carcinomas, and ultimately, to poorly differentiated carcinomas. However, it is currently accepted that low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC) are fundamentally different tumor types and, consequently, different diseases. In fact, whereas the benign-borderline-malignant sequence seems to apply quite well to low-grade serous carcinoma, the sequence of genetic alterations in high-grade serous carcinoma is substantially different.

In this mini-review, we included the current consensus regarding the morphological and etiopathogenic results regarding serous tumors of the ovary, fallopian tube and peritoneum. It also briefly describes the history of benign, borderline and malignant serous tumors, discussing multiple types of dichotomies in serous carcinomas of the female genital tract and summarizing the current molecular classification.

Category: Review

Received: January 17, 2021
Accepted: March 03, 2021

Keywords:

serous carcinoma, borderline tumor, ovary, fallopian tube, peritoneum

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Introduction

Epithelial tumors of the ovary account for approximately two-thirds of all ovarian tumors in the Western world. They encompass a heterogeneous group of neoplasms that are primary classified based on the cell type into serous, mucinous, endometrioid, clear cell, transitional and squamous cell tumors. Based on the fact that the histologically normal counterparts of these cells are not usually present in the ovary, their neoplastic presence has previously been associated with müllerian neometaplasia of the ovarian surface epithelium (mesothelium), which evolves from celomic epithelium. Recently, several scientific studies have provided compelling evidence that multiple tumors, which were believed to be primary ovarian cancers, actually originate in other pelvic organs and involve the ovary as a secondary effect. As a matter of fact, novel molecular developments demonstrated that high-grade serous carcinomas might arise from precursor lesions in the epithelial lining of the distal fimbria of the fallopian tube, while endometrioid and clear cell carcinomas originate from ovarian endometriosis [1-3].

The difference between borderline tumors and carcinomas is one of the most common problems in ovarian tumor pathology, yet the literature on borderline tumors is confusing, particularly with regard to their diagnostic features and treatment. Although the World Health Organization recommends the presence of “obvious invasion” of the stroma as a mandatory criterion for carcinoma, most pathologists do not require obvious stromal invasion for the diagnosis if the epithelial cells feature malignant cytology. In order to address this issue, the World Health Organization has proposed that such tumors be classified as borderline serous tumors with intraepithelial carcinoma. However, the heterogeneity of ovarian tumors and high inter-observer variability remain a difficult aspect in gynecological pathology [4-6].

To cite this article: Tiberiu-Augustin Georgescu, Roxana Bohiltea, Octavian Munteanu, Corina Grigoriu, Ioana Paunica, Maria Sajin. A mini-review regarding the carcinogenesis and morphology of serous tumors of the ovary, fallopian tube and peritoneum. *J Mind Med Sci*. 2021; 8(1): 44-52. DOI: 10.22543/7674.81.P4452

A thorough search on PubMed using various combinations of the following headings: "ovarian serous tumor", "fallopian serous tumor", "peritoneal serous tumor", "serous borderline tumor", "low-grade serous tumor" and "high-grade serous tumor" revealed a total of 94 meta-analyses and systematic reviews published in the past 10 years. After thoroughly covering these publications, we have established a mini-review including the current consensus regarding the morphological and etiopathogenic results regarding serous tumors of the ovary, fallopian tubes and peritoneum [5].

Discussions

Benign serous tumors of the ovary and fallopian tube

Benign serous tumors are typically unilateral tumors, histologically composed of varying amounts of ovarian-type stroma and benign tubal-type epithelium. Based on the predominant histological component, they can be classified into: serous cystadenoma (predominantly cystic, with minimal stromal component), serous cystadenofibroma (predominantly cystic, with abundant stromal component), serous adenofibroma (predominant stromal component admixed with small glands) and surface papilloma (adenofibroma variant with prominent papillae involving the ovarian surface) [1-3].

Benign serous tumors have a wide age distribution, usually being diagnosed in the 4th decade. They can be asymptomatic or present with pelvic pressure and pain, urinary bladder symptoms or change in bowel habits due to secondary compression [2]. They can be treated by cystectomy or oophorectomy and have excellent prognoses.

The ultrasound examination of the ovarian serous cystadenoma usually reveals a unilocular cystic or anechoic adnexal lesion, with no papillary projections. If any wall irregularity is present, it is thin, with regular surface and forms an acute angle with the cyst wall. Some lesions may contain ultrasonographically detectable septations, but with no flow on color Doppler. Almost all cystadenofibromas are predominantly cystic with septations seen in approximately 30% of the cases. Papillary projections or solid nodules have been ultrasonographically reported in just over 50% of the cases [1-4]. Vascularization can be present in less than 50% of cases, with a typical pattern of peripheral vascularization, with scattered vessels of high blood flow impedance.

The gross features of benign serous tumors can vary widely, based on the morphological subtype. Most of them are unilateral, with a mean size of 8-9 cm. Serous cystadenomas are more frequently unilocular rather than multilocular, with clear to straw-colored fluid, minimal stromal component and smooth inner and outer surfaces. Some cysts have thick walls and may show internal folds when the cyst is collapsed. Serous cystadenofibromas present as variably sized cysts with white-to-gray, firm, solid areas, containing clear fluid. Firm papillary excrescences may sometimes be present on the surface. Serous adenofibromas are predominantly solid, firm, with white-to-grey homogenous cut surface and scattered small cysts filled with serous and/or serosanguineous fluid. Occasionally, serous adenofibromas only involve the ovarian surface as firm, nodular excrescences (surface serous papilloma) [5].

Histologically, benign serous tumors are composed of varying amounts of cysts, glands or papillae lined by a single layer of serous-type epithelium (cuboidal, columnar or flattened cells with variable amounts of cilia). Cystadenofibromas have variably cellular fibromatous stroma, which may feature areas of edema or hyalinization. Rarely, psammoma bodies, minor sex cord-like elements, signet ring stromal elements or ulceration with histiocytes may be present [6,7].

Immunohistochemically, PAX8, WT1 and ER are positive in the epithelial component and genetic testing may reveal copy number changes (trisomy 12) in stromal cells [8].

The differential diagnosis of benign serous tumors includes serous borderline tumors, endometriosis, peritoneal inclusion cysts, hydrosalpinx, cystic struma ovarii and rete cystadenoma [9].

Serous borderline tumors of the ovary and fallopian tubes

There are two histological types of serous borderline tumors: conventional and micro-papillary. Conventional serous borderline tumors are epithelial neoplasms composed of papillae with hierarchical branching lined by fallopian tube-type epithelium showing stratification, detached cell clusters, and low-grade nuclear atypia without evidence of frank stromal invasion [10]. Micro-papillary serous borderline tumors are epithelial neoplasms in which papillae show abrupt transition from central fibrovascular cores to long, slender papillae which are usually five-times longer than wider, lined by cuboidal tubal-type epithelium without evidence of frank stromal invasion [11-13].

Serous borderline tumors represent 4% of all ovarian tumors and 10-15% of all ovarian serous tumors. The mean age at presentation is 42-50 years [14]. Most patients are asymptomatic, while others may present with abdominal pain, distention or ascites [15].

Serous borderline tumors are usually larger than 5 cm and frequently bilateral, especially the micro-papillary variant. They show velvety projections and/or nodularity, which are white-to-yellow, soft, friable and most of the times intracystic, with or without surface involvement. The

cystic space is filled with viscous or serous fluid and hemorrhage or necrosis are typically absent [16].

The histological architecture of conventional serous borderline tumors shows hierarchical branching of papillae with irregular contours, ending with detached cell clusters and single cells (budding/tufting). The wall of the cyst is composed of variable amounts of fibromatous stroma, which may show ulceration, hemosiderin deposition and foamy histiocytes [17]. Cytologically, the fibrovascular cores are lined by non-stratified or pseudostratified columnar or cuboidal cells, with low-grade nuclear atypia and small nucleoli. The cells may be ciliated or show clear or focal apical mucinous cytoplasm. Pregnant patients may also have variable numbers of polygonal and hobnail cells with eosinophilic cytoplasm. The histological architecture of micro-papillary serous borderline tumors is characterized by a central edematous papilla with abrupt transition to delicate, filiform micro-papillae without fibrovascular cores, which are five-times longer than wider. This structure is often referred to as "caput medusae". Sometimes, the fusion of the micro-papillae can lead to a cribriform appearance [18]. Cytologically, the cells are cuboidal, with small, uniform nuclei, often with prominent nucleoli, high nuclear to cytoplasmic ratio and typical lack of cilia.

Conventional and micro-papillary patterns may be admixed. In order to fall into the micro-papillary category, micro-papillary patterns must measure more than 5 mm in continuous extent or represent at least 10% of the tumor. If these criteria are not met, the tumor should be classified as serous borderline tumor with focal micro-papillary features [19].

Serous borderline tumors may show foci of microinvasion, noninvasive epithelial or desmoplastic implants, invasive implants and even lymph node involvement.

Microinvasion is present in 10% of all serous borderline tumors and may show multiple histological patterns, which can coexist within the same tumor. Microinvasion is characterized by single cells, clusters of cells or small papillae floating in cleft-like spaces. Sometimes, this so-called "inside-out pattern" may represent lymphatics. In this case, immunohistochemistry for D2-40 can be useful. The area of microinvasion must measure less than 10 mm2 or less than 5 mm in its greatest extent. If the area is larger, the tumor should be classified as low-grade serous carcinoma [20].

Peritoneal implants are present in 30% of all serous borderline tumors [13,21]. They are more frequent in patients who have an exophytic component than in those that do not. Non-invasive implants are confined to the surface of organs. Non-invasive epithelial implants appear on peritoneal surfaces, as papillary proliferations or detached clusters of cells resembling those in ovarian SBT, confined within well demarcated cystic spaces or invaginations, lined by a single layer of serous cells. They are frequently associated with psammomatous calcifications. Non-invasive desmoplastic implants appear on peritoneal surfaces or ovarian surface (autoimplants) as single cells, clusters of cells, small papillae, or irregularly shaped glands with mild cytologic atypia, entrapped in a desmoplastic or granulation tissue-like stroma, which is the predominant component. They are also well demarcated from the underlying tissues. Invasive implants appear as small papillae, micro-papillae, small and large irregular glands, solid nests or single cells with destructive invasion of underlying tissues and desmoplastic response [22].

Lymph node involvement in patients with ovarian serous borderline tumors varies between 20% to 30%. However, most clinical studies with follow-up data indicate that the lymph node status is not an independent prognostic factor for the patient's survival [23].

Serous borderline tumors show positive immunoreaction for CK7, PAX8, CA125, WT1, ER and PR [24]. Calretinin and p16 can be patchy positive or negative and p53 shows a wild-type pattern of expression (scattered positive cells) [25,26]. Genetic testing reveals BRAF and KRAS mutations with 95% concordance in serous borderline tumors and associated implants [27,28].

The differential diagnosis includes serous cystadenoma with focal epithelial proliferation, low-grade serous carcinoma, high-grade serous carcinoma, seromucinous borderline tumor, endometrioid borderline tumor, clear cell carcinoma, retiform variant of Sertoli-Leydig cell tumor, peritoneal low-grade serous carcinoma and endosalpingiosis [28-31].

The serous borderline tumor of the peritoneum

The serous borderline tumor of the peritoneum is a low-grade epithelial neoplasm of tubal-type cells with cellular proliferation and stratification, without underlying tissue invasion. For a serous borderline tumor to be designated as primary peritoneal, the ovaries must be grossly and microscopically normal or enlarged only by benign processes [32].

Serous borderline tumors of the peritoneum are rare, with a peak incidence between the 4th and the 5th decades of life, have no association with BRCA1 or BRCA2 mutations and most commonly affect the pelvis or both the pelvis and the abdominal cavity.

Clinically, patients may present with pelvic pain, pressure, discomfort, ascites, vaginal bleeding or infertility, but most serous borderline tumors are usually asymptomatic and detected incidentally. Occasionally, they can be identified upon imaging investigations due to the presence of psammoma bodies in the Papanicolau smear [33,34].

The treatment involves hysterectomy with bilateral salpingo-oophorectomy with removal of any pelvic/omental tumor. If fertility is desired, the conservative approach may be considered. At the time of writing, chemotherapy or radiation have no established role in the therapeutic management of serous borderline tumors of the peritoneum. Most tumors have a favorable prognosis, but recurrences are common. If these tumors progress to serous carcinomas, adverse outcomes are very likely and most patients die from the disease.

Grossly, serous borderline tumors of the peritoneum appear as adhesions simulating the inflammatory pelvic disease with individual nodules smaller than 1 cm.

From a histopathological point of view, serous borderline tumors resemble non-invasive or desmoplastic implants of ovarian serous borderline tumors and are composed of papillae, nests, glands, clusters of cells or single cells with tufting, budding and epithelial pseudo-stratification. The cells are uniform, cuboidal or columnar, with eosinophilic cytoplasm and round nuclei, with small nucleoli [35].

The differential diagnosis includes primary peritoneal low-grade serous carcinoma, non-invasive implants of ovarian serous borderline tumor, well-differentiated papillary mesothelioma or malignant mesothelioma and endosalpingiosis with focal atypia [36-38].

Low-grade serous carcinomas of the ovary and fallopian tubes

The low-grade serous carcinoma is a malignant epithelial neoplasm of serous cell lineage with distinctive architecture, low-grade nuclear atypia and destructive invasion.

Low-grade serous carcinoma is less frequent than high-grade serous carcinoma, accounting for 3.5% of all ovarian carcinomas and 5% of all serous carcinomas [39]. It usually affects patients in the 6th decade of life and it can be diagnosed incidentally or present with abdominal swelling or pain. Low-grade serous carcinomas are usually high stage at presentation and may be a recurrence of a previous serous borderline tumor. Most tumors tend to have an indolent course with progressive disease. The therapeutic management involves bilateral salpingo-oophorectomy and hysterectomy with debulking and staging biopsies.

Imaging techniques play an important role in the diagnosis of ovarian carcinoma and in the assessment of the metastatic disease. However, surgical and histopathological examinations remain the standard of care for staging the disease [40]. Typical imaging features of ovarian serous carcinomas include: the presence of a cystic adnexal mass with substantial solid components, associated with ascites, peritoneal nodularity and lymphadenopathy. Calcification can be seen in approximately 12% of the cases, but it also appears in serous cystadenoma and other tumors [41].

Low-grade serous carcinomas are typically bilateral, solid or both solid and cystic with multiple polypoid excrescences and little, if any, necrosis. Solid areas may have gritty surfaces due to calcifications. Most tumors show a non-invasive serous borderline component, with or without a micro-papillary pattern [42].

The histological examination of low-grade serous carcinomas will reveal both non-invasive and invasive patterns [43]. Non-invasive patterns are represented by tall and slender to rounded bud-like papillae with variable cellularity as well as solid, fenestrated or cribriform areas of epithelial proliferation. Cytologically, the cells show low-grade nuclear atypia with prominent nucleoli. Invasive patterns must measure more than 5 mm in continuous extent and may be represented by micro-papillae, small papillae, small or large nests or inverted micro-papillae in cleft-like spaces. Rarely, single cells, signet cells, solid, cribriform or glandular patterns of growth may show haphazard invasion and desmoplastic stromal reaction. Psammoma bodies are common and variably numerous. Necrosis and cytological pleomorphism are rare [44].

The immunohistochemical profile of low-grade serous carcinoma is very similar to that of its high-grade counterpart [45]. The only significant differences are wild-type pattern of expression for p53 and lower Ki67 index in low-grade serous ovarian carcinomas. B-RAF and K-RAS mutations are present in 38% and 19% of cases, respectively [46]. Low-grade serous carcinomas do not show chromosomal instability and lack the complex genetic abnormalities seen in high-grade serous carcinomas. Moreover, low-grade serous carcinomas are not associated with BRCA germline mutations [47,48].

The differential diagnosis of low-grade serous ovarian carcinoma includes high-grade serous carcinoma, serous borderline tumor, endometrioid borderline tumor and malignant mesothelioma secondarily involving the ovary.

High-grade serous carcinomas of the ovary and fallopian tubes

The high-grade serous carcinoma is a malignant epithelial tumor showing serous (tubal-type) differentiation with papillary, solid and/or glandular growth and moderate to severe nuclear atypia [49].

The high-grade serous ovarian carcinoma is the most common type of ovarian cancer, accounting for approximately 70% of all ovarian carcinomas. It usually affects slightly older women than the low-grade serous ovarian carcinoma (the 6th to the 7th decade of life) [50]. Although most patients have symptoms, these are often subtle or nonspecific and easily confused with those of benign conditions of the gastrointestinal and urinary tracts. Because of this, up to 80% of the patients present with advanced stage disease and tumors confined to the ovary at diagnosis are extremely uncommon. The clinical features include pelvic pain, gastrointestinal symptoms, increased

abdominal girth due to ascites, urinary frequency, dysuria and vaginal bleeding [51].

High grade serous ovarian carcinomas range in size from microscopic to over 20 cm in diameter and are bilateral in 60% of all cases. The papillae tend to be softer and more confluent than those in serous borderline tumors. Poorly differentiated tumors are predominantly solid, multinodular masses with extensive areas of necrosis and hemorrhage [52].

Histologically, high-grade serous ovarian tumors show multiple architectural patterns, frequently admixed, including: hierarchical branching of variably sized papillae with cellular tufting and budding, bridging and fusion of papillae with formation of slit-like spaces, solid, pseudo-endometrioid, transitional cell carcinoma-like, microcystic, glandular or micro-papillary patterns [53,54]. Cytologically, the proliferation is composed of columnar to cuboidal epithelial cells with variable amounts of eosinophilic and sometimes clear cytoplasm, showing high-grade nuclear atypia, often with severe pleomorphism and more than 3-fold variation in nuclear size. Necrosis is frequent and extensive. The mitotic index is high (typically >12 mitoses / 10HPF), with mostly atypical forms. Solid, pseudo-endometrioid and transitional cell carcinoma-like morphology, as well as tumor infiltrating lymphocytes are more common in patients with BRCA1 mutation, but these features are not pathognomonic of that setting. Psammoma bodies can be present, but are less numerous than in low-grade serous ovarian carcinomas. If sampled accordingly, most high-grade serous ovarian carcinomas will reveal the association with serous tubal intraepithelial carcinoma. Although low-grade and high-grade serous ovarian carcinoma typically develops independently, in some cases, a morphologic continuum may be seen.

The assignment of primary site for high-grade serous carcinoma (ovary vs. fallopian tube vs. peritoneum) is arbitrary and has no clinical relevance. Singh et al. proposed the following scheme for assigning the site of origin: primary ovarian for dominant ovarian masses without serous tubal intraepithelial carcinoma and primary tubal for dominant ovarian masses with serous tubal intraepithelial carcinoma [51,52].

Most high-grade serous carcinomas show either diffuse positivity or complete absence of p53 and strong and diffuse staining for p16 in approximately 60% of the cases. Ki67 is usually > 75% and Napsin-A and HNF-1β are negative [53, 54].

The differential diagnosis includes low-grade serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, endometrioid carcinoma, metastatic serous carcinoma, metastatic breast carcinoma and malignant mesothelioma [55-58].

Serous carcinomas of the peritoneum

The serous carcinoma of the peritoneum is a malignant neoplasm showing tubal-type differentiation. For a serous carcinoma to be designated as primary peritoneal, the ovaries and fallopian tubes must be grossly and microscopically normal or altered only by benign processes and no evidence of primary ovarian, tubal or uterine serous carcinoma (including serous intraepithelial carcinoma) should be found [59].

Both low-grade and high-grade serous carcinomas of the peritoneum are extremely rare, with a continuously decreasing incidence due to the increased recognition of fallopian tube primary tumors. Low-grade serous carcinomas usually affect patients in the 5th decade of life, while high-grade serous carcinomas appear 2 decades later. Symptoms, if present, can include malaise, increasing girth, changes in bowel habits and abdominal pain [60].

Low-grade serous carcinomas of the peritoneum have a relatively indolent course, but they are usually chemoresistant. On the other hand, high-grade serous carcinomas are initially chemosensitive, but recur frequently. The therapeutic management involves hysterectomy with bilateral salpingo-oophorectomy, omentectomy and the surgical removal of any macroscopically visible tumor, followed by platinum chemotherapy [61].

Conclusions

Ovarian cancer remains the most lethal neoplasm in gynecological oncological pathology and malignant epithelial tumors are the most common subtype, accounting for 90% of the cases. Although traditionally referred to as a single entity, ovarian cancer is not a homogenous disease but rather a group of diseases with variable morphology and biologic behavior. Based on the histopathological, immunohistochemical and molecular genetic analyses, there are at least five subtypes of ovarian carcinomas: high-grade serous carcinomas, endometrioid carcinomas, clear cell carcinomas, mucinous carcinomas and low-grade serous carcinomas. These tumors account for 98% of the ovarian carcinomas, can be reproducibly diagnosed by light microscopy and are inherently different diseases, as indicated by differences in epidemiologic and genetic risk factors, precursor lesions, patterns of spread, molecular events during oncogenesis, response to chemotherapy and prognosis.

In this review, we briefly described the history of benign, borderline and malignant serous tumors, discussed multiple types of dichotomies in serous carcinomas of the female genital tract and summarized the current molecular classification. Although traditionally, ovarian tumors were diagnosed based on morphology alone, the current concepts have shifted to a combination of histologic and

molecular findings. While the importance of histopathological examination in unravelling the origins of high-grade serous carcinoma is undeniable, future molecular findings could rank at the top of an integrated diagnosis system for making a decision.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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