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MUCINOUS CARCINOMA OF THE OVARY IN PERITONEAL FLUID

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Abstract

Peritoneal cytology is crucial in the diagnosis and staging of abdominal and pelvic malignancies. Diagnostic pitfalls can be avoided by having an understanding of the different methods of sampling, a familiarity with cytomorphology of the various specimen types, adequate clinical history, and an ability to prepare cell blocks and/or review other prior or concurrent specimens. Ovarian cancer is the second most frequent type of gynecological malignancy but the most lethal. While high-grade serous carcinoma is the most common histological subtype, mucinous carcinoma of the ovary (MCO) was believed to constitute around 4% of ovarian malignancies. It is critical to diagnose these rare tumors correctly to ensure proper treatment, avoid mortality, and preserve fertility for young women.

Keywords : Mucinous carcinoma of the ovary, peritoneal fluid, cytology

INTRODUCTION

Peritoneal cytology has an important role in diagnosing and staging abdominal and gynecologic neoplasms. Morphologic evaluation and appropriate characterization of neoplastic cells in peritoneal and pelvic fluids are essential. Where peritoneal involvement by malignant tumors is extensive such as mesothelioma or high-grade abdominal or ovarian carcinomas, diagnosis can usually be confirmed by examination of cytology. However, additional procedures to assist diagnosis are required for localized tumors, less advanced disease, or treatment follow-up. This may include examination of peritoneal washings, brushings, or smears. [1,2]

If peritoneal cytology for ovarian or fallopian tube cancer is positive, the diagnosis will be moved up to stage IC by the International Federation of Obstetricians and Gynecologists (FIGO). Positive test results are linked to a worse prognosis. However, if there is no clinical or pathologic evidence of lymph node involvement, effective therapeutic results can still be achieved. Accurate pathologic evaluation and staging of the extent of the disease are essential to determine the necessity for further therapy. [1,2]

Peritoneal cytology is a specific but relatively insensitive procedure for detecting malignant cell involvement on the peritoneal surface. However, cytology is more sensitive than blind biopsy for detecting malignancy (71% and 45%, respectively), possibly because fluid gives a more representative sample. To be useful, therefore, the cytologic findings should be evaluated in conjunction with clinical and laparoscopic findings. For patients undergoing primary laparotomy for ovarian cancer, the sensitivity of peritoneal cytology for detecting malignant cells ranges from 48% to 88%. Reviewing histologic material from the primary tumor is beneficial in evaluating peritoneal fluid with abnormal cells. Cytohistologic correlation frequently assists in determining whether the cells are morphologically compatible with the primary lesion. [1,3]

LITERATURE REVIEW

Definition

The presence of cancer cells in a serous effusion, such as peritoneal fluid, indicates that the patient has cancer that is not just advanced but also virtually always incurable. Cytologic analysis of peritoneal effusions can give

information concerning inflammatory states of the serous membranes, parasite infestations, and infection with bacteria, fungi, or viruses, in addition to cancer cells. In the diagnosis and staging of abdominal and gynecological neoplasms, peritoneal cytology plays an important role. [1]

Ovarian cancer is the second most prevalent and lethal gynecological cancer. The most common histological type of ovarian cancer is epithelial. Low-grade serous carcinoma, high-grade serous carcinoma, MCO, endometrioid carcinoma, clear cell carcinoma, and others are all types of epithelial ovarian cancer defined by molecular and clinic-pathologic distinctions. Mucinous carcinoma of the ovary is an invasive mucinous neoplasm composed of gastrointestinal-type cells. [4,5]

Epidemiology

The median patient age at presentation is 55 years. Mucinous carcinoma of the ovary accounts for 3-4% of all primary ovarian carcinomas in North America but is more common in Indonesia, Singapore, and Korea. Tumors are usually localized in the ovary but may also arise in the retroperitoneum. Study from Živadinović et al., showed cytological findings obtained from patients diagnosed with ovarian carcinoma. Peritoneal cytology is highly specific (93.61 percent) but has a low sensitivity (68.92 percent), according to the findings of that study. [4,6]

Etiopathogenesis

Mucinous carcinoma of the ovary is usually a heterogeneous tumor. Many mucinous carcinomas develop from mucinous borderline tumors. It has benign, borderline, and cancer components, indicating a sequential development to carcinoma. Although some may arise from a mature cystic teratoma or a Brenner tumor. The most common molecular alterations are copy-number loss of CDKN2A (76%) and KRAS mutations (64%), both considered to be an early event because they have been identified in precursor lesions at similar frequencies. Mutations TP53 occur in 64% of these tumors, a higher frequency than in mucinous borderline tumors. This implicates TP53 mutation in the progression from mucinous borderline tumor to mucinous carcinoma. Amplifications of HER2 are detected in 15-26% of tumors and occur almost exclusively in a 7P53-mutated background. [4,5]

One of the theories to explain the development of MCO is the adenocarcinoma sequence stepwise pattern. This theory is supported by the presence of mucinous cystadenoma and mucinous borderline components with carcinoma. From benign epithelium through borderline tumor to invasive carcinoma, cancer develops. Early in the process, KRAS mutation occurs, but TP53 mutation and HER2 amplification occur later since they are exclusively detected in mucinous carcinoma. [5,7]

Different types of cancer cells invade the peritoneal cavity, but the frequency and mechanisms by which malignant cells reach and colonize the peritoneum vary greatly. Ovarian, colorectal, pancreatic, and gastric tumors are the most common tumors seen in the peritoneum. The peritoneum's large area is one of the most important characteristics that make it an ideal location for the formation of secondary tumors. The presence and flow of peritoneal fluid are another. When the fluid accumulates, the flow collects tumor cells and distributes them throughout the cavity to some extent. [8]

Clinical Features

Clinical signs and symptoms of a large pelvic mass are common in MCO. The average size at presentation is 18 cm. However, these tumors can become very large and fill the entire abdominopelvic cavity. Pain, abdominal or pelvic fullness, or a palpable mass are some of the signs and symptoms that might occur as a result of the huge size of the tumor. [4,9]

Macroscopic Features

Mucinous carcinomas of the ovary are usually large (8-40 cm, mean 16–19 cm in greatest dimension), unilateral, multilocular or unilocular cystic masses containing mucinous fluid with an intact and smooth outer surface. However, some tumors may rupture and be associated with adhesions. Mucinous carcinomas of the ovary often exhibit papillary and solid areas that may be soft and mucoid or firm with hemorrhagic and necrotic. Extensive sampling of MCO, especially the more solid areas, is critical, as benign, borderline, and malignant components may coexist within a single specimen and the malignant areas may involve only a small portion of the tumor. The tumors are bilateral in only 5% of cases. Bilateral mucinous carcinomas or unilateral carcinomas under 10 cm in the greatest dimension should raise the suspicion of metastases. [4,10,11]

RESULTS

Microscopic Features

Cytology

Peritoneal cavities are lined by a single layer of flat mesothelial cells called the serosa. Normally, these cavities contain only a small amount of fluid, enough to lubricate the adjacent surfaces. In disease states, a greater amount of fluid accumulates, called an effusion. Effusions are classified clinically as transudative or exudative. Transudates result from an imbalance of hydrostatic and oncotic pressures. Transudates have low lactate dehydrogenase (LDH) and low total protein concentration. Exudates result from injury to the mesothelium, as occurs with malignancy or trauma. Malignant tumors are a common cause of exudate formation because the serosal surfaces are a frequent site of metastasis for many tumors. [3]

If there is no peritoneal involvement by the tumor on gross inspection, any accumulated fluid should be aspirated and sent for cytologic evaluation. Otherwise, saline washings are submitted unfixed to the laboratory for processing as soon as possible, the specimen is well mixed, and an aliquot is resuspended in cytology fixative for preparation of cytocentrifuge or liquid-based preparations. Cytologic smears may also be prepared from surfaces such as the diaphragm, pelvic sidewall, and solid viscera using a wooden spatula or cytobrush and spray fixed in 95% ethanol. The technique is convenient and cost-effective and enables a relatively large surface area of the peritoneum to be sampled. Cell block preparations are useful in the workup of patients with suspicious lesions in cytocentrifuge or liquid-based preparations as they may provide optimal assessments of preserved architectural features and as a medium for multiple immunohistochemistry staining procedures.[1]

Cytology detection rates of peritoneal spread in ovarian cancers vary in different studies. Fadare et al. reported 25% and Rubin et al. reported a 30% detection rate, while Colgan et al. revealed a 50% detection rate. As much as 90% positive cytology detection rate has also been reported in a study. This is due to the inclusion of ascitic fluid along with peritoneal washings, as the ascitic fluid has a much higher rate of detecting malignant cells. [12]

Using more than one preparation method for effusions improves sensitivity for the detection of malignancy. A common preparation combination is one thin layer slide and a cell block. Cell block sections are especially useful for immunohistochemistry staining because of the ease with which multiple duplicate slides can be prepared and the relative absence of obscuring background staining. Cell blocks also make excellent morphologic comparison with histopathologic sections because they are fixed and stained in an identical manner. [3]

Depending on the degree of differentiation, it may be difficult to distinguish one epithelial type from another cytologically. Nuclear features of malignancy, including hyperchromasia, prominent nucleoli, and irregular nuclear borders, are present in

most carcinomas, although MCO can sometimes be deceptively bland. In MCO, extracellular mucin, intracytoplasmic vacuoles, and a foamy cytoplasm can be helpful cytologic clues to the diagnosis. Aspirates from MCO are cellular, composed of isolated cells and cells in sheets or grouped in irregular clusters (Figure 1). [1,3]

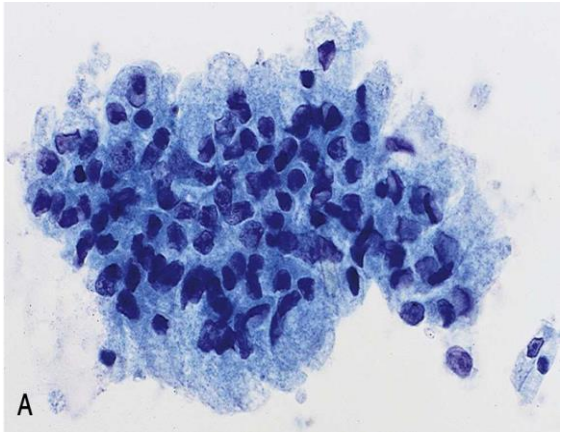

Figure 1. Cytology features of mucinous carcinoma of the ovary. Some sheets of mucinous cells show only mild atypia.[3]
Source : Cibas, 2014

Serous carcinoma is the most frequent type of ovarian cancer and the type that most often produces positive cytologic findings. Less common than the serous tumors are the mucinous, endometrioid, clear cell, and transitional cell tumors of the ovary. There is a significant overlap in the morphologic features of these tumors when they appear in peritoneal washings. It is sufficient to report results as **"**positive for malignant cells, consistent with adenocarcinoma." Alternatively, if one holds reporting of the washings until the concurrent ovarian tumor resection has been examined and subtyped (e.g., as a clear adenocarcinoma), one can report the washings as "positive for malignant cells, consistent with clear cell adenocarcinoma." [3]

Histopathology

Over 80% of MCO show components of mucinous borderline tumor or mucinous cystadenoma, or both, suggesting a progression from benign to borderline and from borderline to malignant mucinous carcinoma. The remaining 20% of carcinomas appear exclusively malignant. According to their pattern of invasion, mucinous carcinomas of the ovary are divided into two categories: expansile/ confluent and infiltrative/ destructive, each measuring at least 5 mm in linear extent. [4,11]

In expansile/confluent invasive pattern displays marked glandular crowding. Glands and cysts are lined by malignant-appearing cells with little or no intervening stroma, creating a labyrinthine appearance (Figure 2). Mucinous carcinoma of the ovary appears to have invaded by expanding into and replacing the stroma across a broad, sharply demarcated front. The invasive areas may be composed of back-to-back glands, ramifying channels lined by epithelial cells, or cystic spaces lined by complex papillae and containing eosinophilic material and nuclear debris. Papillary and cribriform areas may be present. The epithelial cells are columnar or polygonal with eosinophilic or mucinous cytoplasm, sometimes with goblet cells. In some cases, the nuclei are highly stratified, resembling those of endometrioid carcinoma, but in contrast to endometrioid carcinoma, the nuclei are characteristically long and narrow and there is slight residual cytoplasmic mucin. [4,13]

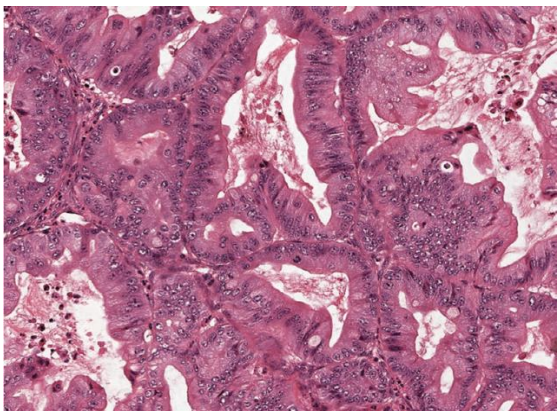

Figure 2. Mucinous carcinoma of the ovary with expansile invasion. There is minimal stroma between the closely packed glands. [14]
Source: Goldblum, 2017

In infiltrative/destructive pattern is characterized by irregular glands, sheets, or single epithelial cells haphazardly invading the

stroma (Figure 3). The invasive cells may appear intestinal but usually have a nondescript eosinophilic cytoplasm. Signet ring cells may be present, but abundant signet ring cells should raise the question of metastasis. The stroma may be desmoplastic with or without inflammatory cells. In the latter instance, MCO may be mistaken for a borderline tumor, especially if the infiltrative glands are large and evenly distributed. However, in carcinomas, the glands are entirely lined by malignant cells rather than the mixture of benign, atypical, and malignant-appearing cells seen in borderline tumors. Tumors with infiltrative invasion are biologically more aggressive and spread beyond the ovary more readily than those with purely expansile invasion. [4,13]

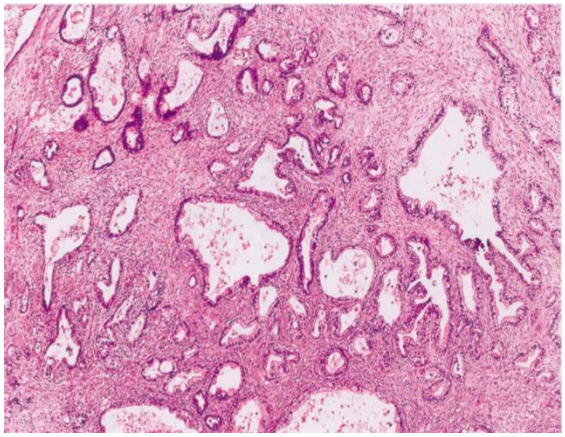

Figure 3. Mucinous carcinoma of the ovary with the infiltrative pattern. The tumor exhibits infiltrative/destructive growth with irregularly shaped glands, arranged haphazardly within altered stroma. [4]
Source: Vang, 2020

The stromal invasion must exceed 5 mm in linear extent in order to be classified as carcinoma. Otherwise, a diagnosis of micro invasion is warranted. An infiltrative pattern, in particular in the setting of bilateral ovarian involvement, should raise suspicion for metastatic mucinous carcinoma and prompt evaluation for an extra ovarian source. Currently, there is no standardized grading system for primary MCO. The expansile/confluent pattern is more common. Both patterns may coexist in a single tumor. [4,11]

Differential Diagnosis

The most important differential diagnosis of mucinous carcinoma of the ovary is with metastatic mucinous carcinoma that may present clinically as a primary ovarian tumor. Most of these originate in the large intestine, appendix, pancreas, biliary tract or stomach. Common features that favor a primary mucinous carcinoma are an expansile pattern of invasion and a complex papillary architecture. A borderline or benign-appearing component is commonly found. [11]

Features favoring a metastatic mucinous carcinoma are bilaterality, small size (<10 cm), a multinodular growth pattern, signet-ring cell component, vascular space invasion, and presence of extra ovarian disease. The finding of abundant extracellular mucin should always raise the suspicion of metastatic carcinoma. Most primary MCO is unilateral. Nevertheless, metastatic mucinous adenocarcinomas, particularly colorectal carcinomas, may be large (≥10 cm) and unilateral in approximately 40% of cases. [3,10,11]

Endometrioid carcinoma shows a wide spectrum of appearance. Most commonly, a back-to-back arrangement of variably sized glands is seen. The nuclei are usually round to oval, with low or moderate atypia. Mucinous differentiation may be seen, and when extensive, may result in misclassification of the tumor as mucinous carcinoma. Some endometrioid carcinomas secrete large amounts of mucin into the lumens of their glands and cysts, but the mucin is present only in the glycocalyx of the tumor cells. [4,11]

In cytology features, endometrioid carcinoma shows large cohesive cell clusters, mild nuclear membrane irregularities, and may see squamous differentiation. In histopathological examination, the most common morphologic pattern is confluent glands, stromal invasion is usually by

expansion. Squamous metaplasia, cytoplasmic mucin, intracytoplasmic vacuoles, oncocytic changes, clear cell changes and cilia, and sex cord-like elements can be observed. Endometrioid carcinoma is immunoreactive for EMA, CK7, PAX8, ER, PR and negative for CDX 2. [15]

Reactive mesothelial cells demonstrate a greater spectrum of cellular cytologic changes. Reactive mesothelial cells are more often arranged in large clusters, balls, or non-branching papillae. These cells tend to be plumper with dense cytoplasm and vacuoles when compared to normal mesothelial cells. Nuclear enlargement is also frequently present, resulting in slightly higher nuclear to cytoplasmic ratios. Nucleoli may be small to prominent, binucleation and multinucleation can be seen, as well as mitotic figures. Features of mesothelial differentiation such as polygonal or round shapes and well-defined cellular borders with windows between cells can be helpful to exclude metastatic disease. [16]

Immunohistochemistry

Immunohistochemistry staining plays an essential role in distinguishing MCO from other possible diagnoses. Mucinous carcinomas of the ovary are typically diffusely and strongly positive for CK7 up to 80% cases. Mucinous carcinomas of the ovary are variably positive for CK20 (75% of cases), CEA, and CDX2. [4,5,11,17–19]

CA19-9 is often diffusely positive in MCO. CA125, WT1, napsin A, vimentin, ER, and PR are usually negative. PAX8, usually focal and weak, and p16 is usually negative or focally positive. Diffuse strong positivity for SATB2 can be seen in mucinous tumors associated with mature teratomas. [4,5,11,18]

Treatment

A staging method for early disease and cytoreductive surgery for advanced disease, followed by platinum-based chemotherapy, is the gold standard surgical management for all epithelial ovarian carcinomas, including MCO. Peritoneal fluid for cytology, hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, and multiple peritoneal biopsies are all part of the staging operation. Positive cytology and microscopic omentum involvement are both 5.7 percent and 1.7 percent in apparent confined disease, respectively. Cytoreductive surgery involves removing all measurable diseases aiming for microscopic residual disease. [5]

Preservation of future fertility may be possible in cases of malignant tumors, but this option must be evaluated on an individual basis with close follow-up owing to a higher risk of recurrence. Further research regarding the best surgical management of malignancy may benefit from a prospective evaluation of outcomes according to tumor histology, stage, and method of treatment.[5, 20]

Prognosis

Most MCO is confined to the ovary (stage I) at presentation, and the prognosis is very favorable. In a SEER analysis, the 5-year survival rate was 91% for stage I, 76% for stage II, and 17% for stage lll/IV disease. Mucinous carcinoma of the ovary with expansile/confluent invasion has a better prognosis than those displaying infiltrative/destructive stromal invasion. The infiltrative pattern is linked to a higher risk of relapse, peritoneal spread, lymph nodes involvement, and mortality. Recurrences tend to occur within three years of diagnosis and have low rates of response to chemotherapy. [4,5,10]

CONCLUSION

The objective of peritoneal cytology is to confirm malignancy; an abdominal/pelvic mass has already been identified. Review of histologic material from the primary tumor is very useful in evaluating peritoneal cytology with abnormal cells. Cytohistologic correlation

frequently assists in determining whether the cells are morphologically compatible with the primary lesion. Accurate pathologic evaluation and staging of the extent of the disease are important to determine the necessity for further therapy.

Conflict of Interest

The authors have no conflict of interest.

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