Mucinous Cancer of the Ovary

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Contributor: ABDULAZIZ BABAIER

Mucinous ovarian cancer (MOC) is a rare subtype of epithelial ovarian carcinoma (EOC). Whereas all EOC subtypes are addressed in the same way, MOC is a distinct entity. Appreciating the pathological features and genomic profile of MOC may result in the improvement in management and, hence, the prognosis. Distinguishing primary MOC from metastatic mucinous carcinoma can be challenging but is essential. Early-stage MOC carries an excellent prognosis, with advanced disease having a poor outcome. Surgical management plays an essential role in the early stage and in metastatic disease. Chemotherapy is usually administered for stage II MOC and beyond. The standard gynecology protocol is frequently used, but gastrointestinal regimens have also been administered. As MOC is associated with multiple molecular alterations, targeted therapy could be the answer to treat this disease.

Keywords: mucinous ovarian carcinoma ; metastatic mucinous carcinoma ; genomic profile ; surgery ; chemotherapy ; targeted therapy

1. Background[1]

Ovarian cancer is the second most common gynecological malignancy, but the most lethal [2]. Epithelial ovarian cancer (EOC) is the most common histological type. EOC is classified, based on molecular and clinic-pathologic differences, into Type 1 tumors, which include low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, and mucinous ovarian carcinoma (MOC), and Type 2 tumors, which include high-grade serous carcinoma (HGSC) [3][4]. While HGSC is the most frequent histological subtype, mucinous carcinoma of the ovary is sporadic. MOC was believed to constitute around 12% of ovarian malignancies. However, recent estimations show the true incidence to be at around 3% [5][6]. The two main reasons for this drop in incidence are the identification criteria, which separate benign mucinous tumors from invasive mucinous carcinoma, and better recognition of clinical and pathological features to differentiate between primary mucinous carcinoma and metastatic carcinoma of the ovary [7].

It is clearly understood that MOC is a separate entity from all other EOCs. It has a distinct natural history, molecular profile, chemo-sensitivity, and prognosis in comparison to HGSC. A comprehensive report on the genomic profile of HGSC by the Cancer Genome Atlas Research Network in 2011 revealed a distinct mutation spectrum among high-grade serous tumors and opened the door for potential targeted therapies [8].

MOC is the most frequent histological subtype in women under the age of 40 [9]. The well-known risk factors for HGSC, such as nulliparity, early menarche, late menopause, lack of breastfeeding, *BRCA* (Breast Cancer Gene) mutation, are not associated with MOC. The only possible risk factor correlated with MOC is tobacco smoking [10]. Most HGSCs present at an advanced stage, while MOC is diagnosed as stage 1 in 80% of the cases [11]. Prognosis is better in early disease, but worse in the advanced stage, compared to HGSC, which is mainly due to inadequate response to platinum-based chemotherapy [12][13].

2. Pathological Aspects

Around 80% of mucinous carcinomas of the ovary are metastatic, with approximately 80% of primary tumors being stage I. The most frequent primary sites that metastasize to the ovary are: 45% from the gastrointestinal tract, 20% from the pancreas, 18% from the cervix and endometrium, and 8% from the breast [14][15]. It is agreed that diagnosing primary MOC requires careful pathological assessment as it is histologically very similar to other mucinous carcinomas, especially colorectal carcinoma (CRC). Recognizing the microscopic features and understanding the immunohistochemistry (IHC) profile of MOC are essential to reach a definitive diagnosis, which results in delivering proper treatment and an accurate prognosis.

MOC is usually a heterogeneous tumor. It encompasses benign, borderline, and carcinoma components, which indicate a stepwise progression to carcinoma. The diagnosis of an invasive carcinoma requires the detection of stromal invasion of

more than 5 mm or more than 10 mm^2. Invasion less than these measurements is classified as “micro-invasion” with a borderline mucinous tumor. MOC is typically the intestinal type, but the endocervical type may develop infrequently [16][17][18]. According to the growth and invasion pattern, Lee and Schully classified MOC into expansile and infiltrative subtypes [19]. The expansile subtype has no destructive stromal invasion, but exhibits confluent or complex malignant glands (back to back glands) with or without minimal intervening stroma exceeding a 10 mm^2 area or >3 mm each of two linear dimensions. The infiltrative type has stromal invasion in the form of glands, cell clusters, or individual cells, unsystematically infiltrating the stroma and often associated with a desmoplastic stromal reaction [17][18][19][20]. In 2014, the World Health Organization (WHO) adopted Lee and Schully’s classification for MOC.

Certain histological features are suggestive for metastatic mucinous carcinoma. In general, mucinous carcinomas are categorized into cystic and colloid type, based on intracellular or extracellular mucin localization. Ovarian and pancreatic cystic mucinous carcinomas contain a large amount of intracellular mucin (>50%) in at least 90% of tumor cells. On the other hand, colloid mucinous carcinomas arising from the gastrointestinal tract, lung, breast, and skin are associated with abundant extracellular mucin accounting for 50% or more tumor volume [7]. Seidman et al. proposed an algorithm based on tumor size and laterality to distinguish between MOC and metastatic mucinous carcinoma. Tumors that were ≥10 cm and unilateral were primary MOCs 82% of the time. Unilateral tumors <10 cm were metastatic 87% of the time. Bilateral tumors <10 cm were metastatic in 92% of cases and when bilateral and ≥10 cm they were metastatic in 95% of cases [5][21]. Therefore, the possibility of metastatic mucinous carcinoma should always be considered, even in the case of a unilateral tumor. Moreover, features that suggest that metastatic disease is more likely are [22][23][24]:

- Bilateral disease;
- Ovarian surface involvement;
- Extracellular mucin localization;
- Destructive stromal invasion;
- Nodular growth pattern;
- Hilar involvement;
- Vascular invasion;
- Signet ring cells;
- Extensive necrosis.

In addition to the microscopic features, IHC staining plays an essential role in distinguishing MOC from other possible diagnoses. MOC typically shares positive IHC patterns for CK20, CEA, Ca19-9, and CDX2 with metastatic CRC. Nevertheless, CK7 is mostly positive in MOC and negative in CRC. **Table 1** summarizes the IHC profile for MOC and metastatic mucinous carcinoma [12][16][25][26]. The standard IHC profile for MOC is CK7 +, CK20 +/−, CDX2 +/−, PAX8 −, WT1 −, ER −, PR −, and SATB2 – [26].

Table 1. Summary of the IHC expression of MOC and metastatic mucinous carcinoma.

	MOC Intestinal Type	MOC Endocervical Type	CRC	Pancreatic	Biliary	Gastric	Cervical
CK7	+	+	−	+/−	+/−	+/−	+
CK20	+/−	−	+	−/+	−/+	−/+	−/+
CDX2	+/−	−	+	+/−	+/-	+/−	−/+
CEA	+/−	−	+	+/−	+/-	+/−	+/−
CA 125	−	+	−	+/−	+/-	−	+
CA 19-9	+	−/+	+	+	+	+	-
ER	−	+	−	−	−	−	−/+
DPC4	+	+	+	+ or −	+ or −	+	+
P16	−	−	−/+	−	-	−	+

MOC: Mucinous Ovarian carcinoma; CRC: Colorectal carcinoma; +: diffusely positive; −: diffusely negative; +/−: diffusely positive or focally negative; −/+: diffusely negative or focally positive.

3. Genomic Profile

Advancement in pathology and molecular data has allowed for consideration of MOC as a separate entity from other EOC subtypes. Cheasley et al. recently reported a comprehensive analysis of the MOC genetic profile in comparison to many histological types and proved that MOC is a genetically-unique entity [27]. **Table 2** compares the frequency of molecular mutations in MOC, HGSC, and mucinous and non-mucinous CRC [7][12]. *KRAS* mutation is the most frequent molecular alteration in MOCs, with 46% having this mutation. While *TP53* mutation is typically associated with HGSC, about 25% of MOCs harbor this alteration as well. The amplification of *HER2* is also observed in 18% of MOCs. Moreover, high microsatellite instability (MSI-H) has been reported in MOCs [28]. Aberrant signaling in the wingless (WTN) pathway in the form of a mutation in *CTNNB1* or *APC* gene has also been documented. It is believed that the *KRAS* mutation develops as a first event, as the mutation is detected in the surrounding borderline and benign lesions, and *HER2* amplification or *TP53* mutation occurs at a later stage during malignant transformation, as this is observed exclusively in carcinomas [7][12][13].

Table 2. Frequency of molecular alterations in MOC, HGSC, mucinous, and non-mucinous CRC.

Molecular Alteration	MOC	HGSC	Mucinous CRC	Non-Mucinous CRC
***KRAS* mutation**	**33–46%**	**10–22%**	**31–48%**	**24–33%**
***BRAF* mutation**	**0–9%**	**0%**	**15–27%**	**6–12%**
***TP53* mutation**	**26–55%**	**96%**	**31–41%**	**41%**
***HER2* amplification**	**18–35%**	**-**	**<1%**	**2%**
MSI-H	**22%**	**13.8%**	**25–36%**	**3–6%**
***APC*/*CTNNB1* mutation**	**9%**	**-**	**24%**	**88%**

MOC: mucinous ovarian carcinoma; HGSC; high-grade serous carcinoma; CRC: colorectal carcinoma; MSI-H: high microsatellite instability.

To explore the molecular alterations in MOC, Friedlander et al. extensively evaluated the molecular profile of 304 cases of MOCs to investigate potential therapeutic targets. Alterations in MAP kinase pathway were the most common (49% mutations in *KRAS* and 3.5% in *BRAF*). mTOR pathway alterations were less likely (*PIK3CA* in 12% and *PTEN* in 6%). cMET overexpression was observed in 33% of cases, but no *cMET* gene amplification was seen. *p53* mutation was documented in 37% of cases and *EGFR* (epidermal growth factor receptor) gene amplification was seen in 50%. *HER2* gene amplification was found in 11% of cases. PD-1 positivity was detected in tumor-infiltrating lymphocytes in 43% of cases and PD-L1 was positive in 14% cases [29]. At the molecular level, MOC is a heterogeneous disease and its molecular landscape still poorly understood.

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