

Ovarian metastases from the biliary tract, pancreas and liver carcinomas

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ABSTRACT Tumors metastatic to the ovary account for 5-10% of all ovarian cancers. Ovarian metastasis precede the detection in the primary site in 38% of tumors metastatic to the ovaries. Biliary tract carcinoma usually presents with symptoms of cystic duct obstruction and only less than 6% will have metastasis to the ovary, but ovarian metastases or recurrence may happen even up to two years after surgery. Pancreatic cancer metastatic to the ovary is most commonly a ductal adenocarcinoma, and accounts for 11% of all cases of ovarian metastasis. This tumor can be easily mistaken for primary mucinous adenocarcinoma of the ovary. Bilaterality of the tumor as well as extensive intraperitoneal spread and several microscopic features may suggest metastatic rather than primary ovarian tumor. Immunohistochemical staining may also aid with that distinction. Liver cancer metastasis to the ovaries are very rare and need to be distinguished from the primary hepatoid yolk sac tumor of the ovary. A benefit of prophylactic oophorectomy with hepatic, biliary of pancreatic cancer have never been shown.

Key words cancer, ovary, metastases, liver cancer, pancreatic cancer, biliary tract

INTRODUCTION Altogether, surface epithelial carcinomas of the ovary account for about 60% of all ovarian neoplasms and 80-90% of the primary ovarian malignancies (1-2). Tumors metastatic to the ovary are relatively rare and ac-

count for approximately 5-10% of all ovarian cancers (3). All metastatic adenocarcinomas to the ovary can be divided into Krukenberg and non-Krukenberg type cancers. *Novak and Grey* (4-5) in 1938 proposed the following criteria for diagnosing Krukenberg tumors. They are 1) cancer in the ovary, 2) intracellular mucin production by neoplastic signet cells and 3) diffuse sarcomatoid proliferation of the ovarian stroma. These criteria were adopted by WHO. The most common primary sites that metastasize to the ovaries are colorectum, breast, endometrium, stomach, cervix, pancreas, appendix, and biliary tract (6). Most of the tumors discussed in this chapter are of non-Krukenberg type.

Despite the uncommon occurrence, metastatic cancers to the ovary are a significant group of cancers for multiple reasons. Ovarian metastases that are of non-Krukenberg type may be difficult to distinguish from the primary ovarian carcinoma. Also, most of the tumors that metastasize to the ovary usually have poor prognosis and they need to be aggressively treated.

When patient presents with a suspected malignant mass, but her symptoms are not consistent with a primary ovarian carcinoma it is very important to search for a primary carcinoma outside the ovaries. *Petru* (7) has reported that ovarian metastasis precede the detection in the primary site in 38% of tumors metastatic to the ovaries. If primary tumor site is not diagnosed prior to the ovarian cancer debulking, patients may need additional surgery at the later time. Also, chemotherapy may be different than for primary ovarian cancer. Therefore prognosis and appropriate treatment will be dependent upon identifying the site of origin of the metastasis.

BILIARY TRACT Biliary tract carcinoma metastatic to the ovary presents as a signet-ring cell adenocarcinoma, which is consistent with Krukenberg type tumor. Patients with carcinoma of the cystic duct usually present with symptoms referable to the biliary tract (8), and only less than 6% will ever have metastasis to the ovary. Two cases published demonstrate that patients with biliary carcinoma can have recurrences in the ovaries as late as two years from the initial diagnosis.

PANCREATIC CARCINOMA Pancreatic tumors metastatic to the ovary are most commonly a ductal adenocarcinoma, mucinous cystadenocarcinoma (9) or islet cell carcinoma. Pancreatic ductal carcinoma has a prominent mucinous character and closely simulates mucinous tumors of the ovary. In the study from Japan, approximately 11% of all cancers metastatic to the ovary come from the pancreas, and approximately 19% of the patients with pancreatic cancer have ovarian involvement (10). *Young* (9) reported that in five of seven patients with pancreatic cancer metastatic to the ovary both the primary tumor and the ovarian metastasis were found at the same time. Of these, three presented with abdominal pain, and

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were found to have palpable adnexal masses. Two patients had ovarian metastasis diagnosed after their pancreatic cancer (9). Majority of the pancreatic tumors metastatic to the ovary are cystic and measure on average 12 cm in greatest dimension (9).

Pancreatic tumors metastatic to the ovary pose a great diagnostic problem to the pathologist. Microscopically, metastatic pancreatic tumors can easily be mistaken for primary mucinous tumor, because they contain areas indistinguishable from those seen in mucinous cystadenomas, mucinous cystadenocarcinomas and mucinous borderline tumors. Several factors point to the tumor being metastatic, rather than primary ovarian. If there is an extensive intraabdominal spread and the ovarian tumor is a well-differentiated mucinous cystadenocarcinoma, the ovarian tumor is most likely metastatic from a pancreatic primary. It would be very unusual for well-differentiated mucinous ovarian tumor to cause extensive intraabdominal spread. The nature of the intraperitoneal spread is also very important especially in cases where the ovarian tumor mimics an atypically proliferating (borderline, of low malignant potential) ovarian mucinous tumor. The vast majority (85%) of atypically proliferating (borderline) mucinous tumors do not present with spread beyond the ovaries. Most important macroscopic factor that suggests metastatic, rather than primary ovarian cancer, is bilaterality of the tumor. Only about 15% of primary mucinous ovarian carcinomas are bilateral, and only 5% have extended beyond the ovaries at the time of diagnosis (3). Microscopically, metastatic tumors are likely to have desmoplastic implants of carcinoma on the surface and in the superficial cortex of the ovary. Those implants are typically focal, often project above the surface of the adjacent cortex, and characteristically are embedded in the extremely desmoplastic or hyalinized fibrous tissue. Lymphatic or vascular invasion at the periphery of the tumor is characteristic of tumor metastatic to the ovary as well as multinodular pattern of growth.

Pancreatic islet cell carcinoma is a very rare tumor with the incidence less than 1/100,000 people (11). Several cases of metastasis of this rare tumor to the ovary have been reported, however (12). Characteristically, this disease behaves like a typical carcinoma spreading by local extension or lymphatic drainage. Pancreatic islet carcinomas respond well to treatment with streptozotocin. In a study by Broder (13-14), 38% of the patients had complete remission or partial response to this treatment.

LIVER CARCINOMA Primary hepatic cancer is a relatively uncommon neoplasm in the United States, representing only 0.7% of all cancers (15). Incidence of this cancer is 2.7/100,000 and is recently increasing, almost tripling in California in the last 20 years. Because hepatic carcinoma tends to invade the

hepatic and portal veins, the tumor frequently metastasizes to the heart and then to the lungs. Metastases to ovaries are exceedingly rare with only a few cases reported. In one of the cases, patient was diagnosed with ovarian metastases six months after the resection of the primary hepatic tumor. In patients with hepatic tumor, AFP may be used as a marker for recurrence.

Since carcinoma of the liver is usually a rapidly growing and fatal cancer with mean longevity of 3.2 months from initial symptoms, metastasis to the ovary do not significantly affect the outcome.

The major differential diagnosis of the hepatocellular tumor metastatic to the ovary is the primary hepatoid yolk sac tumor of the ovary (16). In the latter, finding of the foci of more typical yolk sac neoplasia or of other germ cell elements exclude the diagnosis of metastatic hepatocellular carcinoma. The young age of the patient will argue against the diagnosis hepatocellular carcinoma. Hepatoid tumors may also arise outside the ovary, for example in the stomach or lung, and may metastasize to the ovary (17).

ROUTES OF SPREAD Tumors metastatic from the liver, gallbladder or pancreas most likely reach the ovary by transperitoneal spread. This is based on the finding that usually in early metastatic cancers, small discrete foci are present on the external surface of the ovary without deep invasion of the tumor. From the frequent presence of the positive lymph nodes in the location of primary cancer, it was concluded that another possible route for the spread of gastrointestinal origin tumors to the ovary is a retrograde lymphatic spread (18).

DIAGNOSIS Distinction between primary and metastatic tumor, as well as identification of the primary source of tumor is extremely important for proper treatment of the patient. The misinterpretation of a metastatic tumor as a primary tumor may have adverse consequences for the patient, such as an unnecessarily radical operation, inappropriate chemotherapy or radiation therapy, and a delay in the identification of the primary tumor (3). With the exception of the serous and undifferentiated types, most of the ovarian tumors tend to be unilateral. When bilateral ovarian tumor is found and histology is not that of a serous tumor, metastatic tumor should be a part of the differential diagnosis. Mucinous and endometrioid type ovarian tumors are bilateral in less than 15% of cases, and bilateral tumors with endometrioid-like or mucinous epithelial features are statistically more likely to be metastatic (3). Metastatic mucinous carcinomas involving the ovary are more common than primary ovarian mucinous carcinomas. However, it should be remembered that although metastatic tumors as a group are bilateral more of-

ten than the primary tumors, many metastatic tumors could be unilateral. Ovarian metastases from colorectal adenocarcinomas tend to be unilateral and large compared to metastases from the other sites (3). If pulmonary or other distant metastases are found without significant intraperitoneal involvement, a primary neoplasm other than ovarian should be sought. On gross examination, features that suggest a metastatic lesion include bilaterality, modest enlargement of the ovaries <10-15 cm, and a nodular growth pattern involving the surface of the ovary. One gross feature of the metastatic tumors that causes them to simulate primary tumors is cyst formation. This is a common finding in metastatic tumors of many different types, even though the primary tumor is not cystic (3). Microscopically, a multi-nodular growth pattern with surrounding compressed hypercellular stroma, and isolated tumor in surface blood and lymphatic vessels are suggestive of a metastatic lesion. The presence of a hypercellular functioning stroma can produce hormonal symptoms such as virilization and have resulted in these metastatic lesions appearing as a primary ovarian stromal tumor. In addition, a haphazard pattern of dilated bland mucinous glands with foci of small infiltrative atypical glands are features that can assist in distinguishing a metastatic pancreatic carcinoma from the primary ovarian tumor. Primary mucinous ovarian carcinomas have a more regular organized confluent pattern.

IMMUNOHISTOCHEMISTRY It is best to use a panel of antibodies that can often assist in the distinction of a metastatic carcinoma from a primary ovarian tumor. Cytokeratin 7 & 20 (CK7, CK20), Cdx2 and Dpc4 have been shown to be useful in distinguishing metastatic from primary ovarian tumors especially if the pattern of staining is examined. CK 7 is positive in almost 100% of primary ovarian tumors but negative in 90% of colon adenocarcinomas (19). Dpc4 is expressed by all primary ovarian mucinous tumors but its expression is lost in about 50% of metastatic pancreatic carcinomas (19). This loss of expression appears to be specific for pancreatic carcinomas. Cdx2 can help distinguish a primary serous and endometrioid ovarian carcinoma from metastatic colorectal carcinoma (20).

TREATMENT

PROPHYLACTIC OOPHORECTOMY There are no studies showing a benefit of prophylactic oophorectomy in patients with pancreatic, liver or gallbladder carcinoma. Several studies on patients with colorectal tumors metastatic to the ovary have showed only a minor advantage on survival (21). There is a concern though that unlike other metastatic sites, ovarian metastasis may be more resistant to chemotherapy, especially in premenopausal patients.

OOPHORECTOMY IN PATIENTS WITH METASTASIS Because of the relative resistance of ovarian metastasis to chemotherapy, ovarian metastases almost certainly require surgical resection. In case of surgical procedure on pancreas or liver, ovaries can easily be removed at the time of surgery. If prophylactic oophorectomy is not done at the time of the initial surgery, and metastasis are diagnosed later on, the decision may need to be made if the oophorectomy is still warranted. Most of the patients with liver, biliary or pancreatic cancer have a poor prognosis, and oophorectomy may not improve their response to treatment or overall survival.

CHEMOTHERAPY After surgical removal of the primary tumor and tumor metastatic to the ovaries, most patients will require chemotherapy. It should be tailored to the site and type of the primary cancer.

CONCLUSIONS Metastatic lesions to the ovary from these anatomic sites can present a diagnostic dilemma. However, a complete patient evaluation with the gross and microscopic appearance, as well as the immunohistochemical features of the tumor can identify the site of origin. This usually results in a more accurate prognosis when appropriate treatment can be administered.

In the future, molecular diagnostics will allow more detail analysis of these tumors, so definitive determination of their site of origin, prognosis, and most effective treatment will be achieved.

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