Pathologic differential diagnosis of metastatic carcinoma in the liver

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The liver is one of the most common sites to which malignancies preferentially metastasize. Although a substantial number of liver malignancies are primary tumors, including hepatocellular carcinoma and intrahepatic cholangiocarcinoma, the metastasis of carcinomas to the liver is relatively common and frequently encountered in clinical settings. Representative carcinomas that frequently metastasize to the liver include colorectal carcinoma, breast carcinoma, neuroendocrine tumors, lung carcinoma, and gastric carcinoma. The diagnostic confirmation of suspected metastatic lesions in the liver is generally achieved through a histopathologic examination of biopsy tissues. Although morphology is the most important feature for a pathologic differential diagnosis of metastatic carcinomas, immunohistochemical studies facilitate the differentiation of metastatic carcinoma origins and subtypes. Useful immunohistochemical markers for the differential diagnosis of metastatic carcinomas in the liver include cytokeratins (CK7, CK19, and CK20), neuroendocrine markers (CD56, synaptophysin, and chromogranin A), and tissue-specific markers (CDX2, SATB2, TTF-1, GCDFP-15, mammaglobin, etc.). Here, we provide a brief review about the pathologic differential diagnosis of major metastatic carcinomas in the liver. (Clin Mol Hepatol 2019;25:12-20)

Keywords: Neoplasm metastasis; Liver neoplasms; Pathology; Immunohistochemistry

INTRODUCTION

Primary liver cancer is a malignant tumor that arises from hepatocytes and intrahepatic bile ducts, or more rarely, mesenchymal cells in the liver.¹ ² Worldwide, 854 thousand new cases of liver cancer emerged and 810 thousand deaths occurred owing to liver cancer. This cancer is associated with the sixth-highest incidence and fourth-highest mortality among the different types of cancers.¹ In Korea, liver cancer is associated with the sixth-highest incidence and second-highest mortality among the different types of cancers, with 15,757 new cases and 11,311 deaths, respectively.⁴ Most primary liver cancers are hepatocellular carcinomas and intrahepatic cholangiocarcinomas.¹ ² Hepatocellular carcinoma is defined as a malignant epithelial tumor that shows hepatocellular differentiation and is the most common histologic type of primary liver cancer.¹ The incidence of hepatocellular carcinoma is highest in East Asia (including South Korea). Chronic viral infection (hepatitis B or C virus) and alcohol consumption are the leading causes...
of hepatocellular carcinoma, and most hepatocellular carcinomas arise in cirrhotic tissue. Intrahepatic cholangiocarcinoma is defined as a malignant tumor with biliary epithelial differentiation. Along with hepatocellular carcinoma, intrahepatic cholangiocarcinoma is the second most common histologic type of primary liver cancer. The incidence of intrahepatic cholangiocarcinoma is highest in Asia, including South Korea, where *Clonorchis sinensis* is endemic. Most intrahepatic cholangiocarcinomas are histologically adenocarcinomas.

Secondary liver cancer is a malignant tumor that metastasizes to the liver from an extrahepatic origin. Secondary liver cancer is much more common in Europe and North America, whereas primary liver cancer is more common in south-east Asia, including South Korea. Secondary liver cancer usually develops in non-cirrhotic liver parenchyme. Because the liver receives a dual blood supply (systemic [arterial] and portal [venous]), the liver is one of the most common hematogenous metastatic sites. Secondary liver cancers are most commonly carcinomas, followed by melanoma, sarcoma, and lymphoma. Among carcinomas, adenocarcinoma comprises 70% of carcinomas, and squamous cell carcinoma follows. The major primary cancers that metastasize to the liver are colorectal carcinoma, breast carcinoma, neuroendocrine tumors, lung carcinoma, and gastric carcinoma. In general, immunohistochemical studies and histomorphologic examinations are very useful for the pathologic differential diagnosis of metastatic tumors.

In this review, we focus on the pathologic differential diagnosis of metastatic carcinomas in the liver. We summarize the pathologic features of major extrahepatic carcinomas that frequently metastasize to the liver, including colorectal carcinoma, breast carcinoma, neuroendocrine tumors, lung carcinoma, and gastric carcinoma, with emphasis on their immunohistochemical features.

**PATHOLOGIC FEATURES OF MAJOR METASTATIC CARCINOMAS IN THE LIVER**

**Metastatic colorectal carcinoma**

Adenocarcinoma accounts for more than 90% of colorectal carcinomas. Adenocarcinoma is a malignant epithelial tumor that shows gland formation, and based on the degree of gland formation, adenocarcinomas can be graded as one of the three differentiation types: well differentiated, moderately differentiated, and poorly differentiated. According to a study conducted in the Netherlands, approximately 20% of patients with colorectal carcinoma present metastatic lesions at diagnosis, and a Swiss group revealed that the overall metastasis rate of colorectal carcinoma was approximately 30%. The liver is the most common metastatic site of colorectal carcinoma, and the main differential diagnosis of a liver metastatic lesion of colorectal carcinoma is primary intrahepatic cholangiocarcinoma, as colorectal carcinoma is mostly adenocarcinoma. Histologically, colorectal adenocarcinoma is composed of atypical epithelial cells with various degrees of glandular differentiation and invasion (Fig. 1A). Histologic variants of colorectal adenocarcinomas include mucinous, signet ring cell, medullary, micropapillary, serrated, and cribriform-comedo subtypes, according to the latest World Health Organization (WHO) classification of tumors of the digestive system. Desmoplastic stroma, a type of fibrous proliferation, can be seen around invasive carcinoma cells. Another frequent characteristic is “dirty necrosis,” which is a form of necrotic debris, in glandular lumen. Immunohistochemically, cytokeratin 7 (CK7) negative, cytokeratin 20 (CK20) positive, and caudal-type homeobox 2 (CDX2) positive are the most common immunophenotypes of colorectal carcinoma (Fig. 2A, Table 1). CDX2 is a highly sensitive and specific marker for the detection of intestinal-origin or intestinal-type epithelial cells, and >90% of adenocarcinomas of the colorectum show diffuse and strong nuclear expression. In addition to CDX2, Special AT-rich sequence-binding protein 2 (SATB2) is also a specific immunohistochemical marker for epithelial tumors of the small and large intestines and the appendix. Thus, the combination of CDX2 and SATB2 can be used as a specific marker panel for the diagnosis of metastatic colorectal carcinoma in the liver. A small subset of poorly differentiated carcinomas of the colorectum can show loss of CDX2 and/or CK20 expression. Therefore, it should be noted that CDX2/CK20-negative colorectal carcinoma can occasionally metastasize to the liver.

**Metastatic breast carcinoma**

Breast cancer is a malignant tumor that arises in the breast, and most breast cancers are invasive breast carcinomas. Among the histologic types of breast carcinoma, invasive carcinoma of no special type (NST) is the largest group and is commonly known as invasive ductal carcinoma. Metastasis of breast cancer occurs in about 20-30% of patients, and approximately 10-15% of patients develop distant metastasis within three years of primary cancer detection. The common metastatic sites are bone, lung, and liver. As >90% of breast cancers are diagnosed as NST in-
Invasive carcinoma, which is characterized by frequent tubule formation that resembles adenocarcinoma, the main differential diagnosis of metastatic breast carcinoma in the liver is primary intrahepatic cholangiocarcinoma. Histologically, breast carcinoma is composed of atypical epithelial cells with uniform or highly pleomorphic nuclei, and tubular, glandular, cribriform, or solid structures can be observed (Fig. 1B). The tumor border shows infiltrative or pushing margins, and the stromal component shows extreme variability. Invasive lobular carcinoma is the second most common histologic type of breast carcinoma, following ductal-type (usually NST) invasive carcinoma. Invasive lobular carcinoma is morphologically characterized by single-cell or single-file type infiltration of poorly cohesive atypical epithelial cells, which show relatively monotonous nuclei. Immunohistochemically, CK7-positivity and CK20-negativity are the most common breast carcinoma immunophenotypes (Fig. 2B, Table 1). A comparison of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 immuno-profiles between primary breast carcinoma and metastatic carcinoma in the liver aids the differential diagnosis. In addition, immunohistochemical studies for tissue-specific markers, such as gross cystic disease fluid protein 15 (GCDFP-15) and mammaglobin, will be helpful. However, it should be noted that GCDFP-15 and mammaglobin are highly specific but less sensitive markers for breast-origin carcinomas. The loss of E-cadherin expression in tumor cells is a useful immunohistochemical feature for the confirmation of lobular carcinoma.

**Metastatic neuroendocrine tumor**

Neuroendocrine tumors are defined as neoplasms that are composed of atypical epithelial cells with neuroendocrine differentiation. Neuroendocrine tumors are usually found in the small intestine, appendix, rectum, pancreas, and lung. Neuroendocrine tumors have a site-specific staging system and can be graded as grade 1, 2, or 3 based on mitotic count or Ki-67 labelling index. Gastroenteropancreatic neuroendocrine tumors are divided into neuroendocrine tumor grades 1 or 2 and neuroendocrine carcinoma. Neuroendocrine tumors grades 1 and 2 show relatively well-differentiated neoplasm and are composed of atypical epithelial cells that resemble normal endocrine cells (Fig. 1C). Neuroendocrine carcinomas are poorly differentiated malignant neoplasms that are composed of small or large cells with high mitotic activity and marked nuclear atypia. Neuroendocrine tumor grade 1, formerly called carcinoid tumor, can also metastasize. The metastases of neuroendocrine tumors have been observed in about 20-25% of patients, and the liver is the most common metastatic

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**Figure 1.** Histopathologic features of metastatic carcinomas in the liver (Hematoxylin and Eosin stain, original magnification ×200). (A) Metastatic colorectal carcinoma (adenocarcinoma). (B) Metastatic breast carcinoma (invasive carcinoma of no special type). (C) A metastatic neuroendocrine tumor. (D) Metastatic non-small cell lung carcinoma (adenocarcinoma). (E) Metastatic small cell lung carcinoma. (F) Metastatic gastric carcinoma (adenocarcinoma).
site. Small intestinal neuroendocrine tumors encompass more than half of the liver metastases of all neuroendocrine tumors. Histologically, neuroendocrine tumors are composed of uniform cells with light eosinophilic cytoplasm, and the tumor cells are arranged in trabeculae and/or pseudorosette patterns. Both hepatocellular carcinoma and intrahepatic cholangiocarcinoma are considered in the differential diagnoses of metastatic neuroendocrine tumors in the liver. Immunohistochemically, neuroendocrine tumors show variable CK7 and CK20 positivity, based on anatomical site (Table 1). Characteristically, neuroendocrine tumors show immunoreactivity for neuroendocrine markers, including chromogranin A, synaptophysin, and cluster of differentiation molecule 56 (CD56) (Fig. 2C). Tissue specific markers, such as HepPar1 and Arginase-1 for hepatocellular carcinoma, along with CK7 and CK20 immunophenotypes facilitate the differentiation of metastatic neuroendocrine tumors from hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Primary hepatic neuroendocrine tumors and hepatocellular carcinomas with neuroendocrine differentiation have been reported; however, both cases are extremely rare.

Metastatic lung carcinoma

Lung carcinoma is a malignant epithelial tumor that originates in the lungs. Lung carcinomas are largely classified into two main categories: non-small cell lung carcinoma and small cell lung carcinoma. Non-small cell lung carcinomas are further classified into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma based on histologic features. Metastases of small cell lung carcinomas can occur in about 60% of patients, and the liver is the most common metastatic site, after pleural and/or pericardial fluids. In patients with non-small cell lung carcinoma, metastases occur in approximately 40-50% of cases, and liver metastases account for 10-14% of the total metastases. Adenocarcinoma and squamous cell carcinoma account for most non-small cell lung carcinomas. Adenocarcinoma shows acinar, papillary, micropapillary, lepidic, or solid growth patterns. Intrahepatic cholangiocarcinoma is the main differential diagnosis of metastatic pulmonary adenocarcinoma of the liver (Fig. 1D). Squamous cell carcinoma shows keratinization and/or intercellular bridges, and hepatocellular carcinoma can be included as a differential diagnosis of metastatic squamous cell carcinoma in the liver. Small cell lung carcinoma is composed of atypical, small, and round...

Figure 2. Immunohistochemical features of metastatic carcinomas in the liver (original magnification ×200). (A) CDX2 positivity in metastatic colorectal carcinoma. (B) GCDFP-15 positivity in metastatic breast carcinoma. (C) CD56 positivity in a metastatic neuroendocrine tumor. (D) TTF-1 positivity in metastatic pulmonary adenocarcinoma. (E) CD56 positivity in metastatic small cell lung carcinoma. (F) MUC5AC positivity in metastatic gastric carcinoma. CDX2, caudal type homeobox 2; GCDFP-15, gross cystic disease fluid protein 15; CD56, cluster of differentiation molecule 56; TTF-1, thyroid transcription factor 1; MUC5AC, mucin SAC.
### Table 1. Useful immunohistochemical markers for differential diagnosis of metastatic carcinomas in the liver

| Antibody | Metastatic colorectal carcinoma | Metastatic breast carcinoma | Metastatic neuroendocrine tumor | Metastatic lung carcinoma (non-small cell carcinoma including adenocarcinoma) | Metastatic lung carcinoma (small cell lung carcinoma) | Metastatic gastric carcinoma |
|----------|-------------------------------|-----------------------------|--------------------------------|---------------------------------------------------------|-----------------------------------------------|-----------------------------|
| CD56     | −/+(+ in 14.1%)
13
16       | − (+ in 14.1%)
65       | − (+ in 46–83.3%)
66
65       | − (+ in 109%)
16       | + (80–90%)
35       | − (+ in 46–83.3%)
66
65       |
| CDX2     | (+ in 99–100%)
13
16       | Variable, depending on tumor origin
9,47     | − (+ in <5%)
16       | − (+ in ~9.5%)
66
68       | − (+ in 36–70%)
13,64
55       |
| CK7      | − (+ in 5–16%)
2,10     | (+96–97%)
12,13    | +/− (+ in 56%)
12,12
32       | + (~10%)
66       | + (~9.5%)
12,13    |
| CK19     | (+ in 93.5%)
66       | + (87.7–98.4%)
55
68
70       | +/− (+ in 35–91.7%)
55
71       | + (~100%)
66       | + (80.5%)
66       |
| CK20     | (+ in 85–100%)
12,13    | − (+ in <6%)
12,13    | − (+ in ≤5%)
66
12,12
32       | − (+ in ≤10%)
66
12,12
32       | − (+ in ≤5%)
66
12,12
32       |
| GCDFP-15 | NA                            | −/+(+ in 2.31–74%)
24,26     | −/+(+ in <10%)
13,16     | −/+(+ in ~15%)
73
75       | −/+(+ in ~25%)
78,89     |
| MUC5AC   | −/+(+ in 6–26%)
61,74     | −/+(+ in 5–37%)
55
27,29     | −/+(+ in 23.1–74%)
24,26     | −/+(+ in 14–26.2%)
20,40     | −/+(+ in 53–85%)
55,64     |
| TTF-1    | − (+ in <10%)
55,84     | − (+ in 2.4%)
55,86     | −/+(+ in <10%)
55,84     | − (+ in ~25%)
88,89     | − (+ in 36–70%)
13,64
55       |

CD56, cluster of differentiation molecule 56; CDX2, caudal type homeobox 2; CK7, cytokeratin 7; CK19, cytokeratin 19; CK20, cytokeratin 20; GCDFP-15, gross cystic disease fluid protein 15; MUC5AC, mucin 5AC; TTF-1, thyroid transcription factor 1; NA, not assessed; +, positive; −, negative.

13% of those with biliary cancers. Both carcinomas are AFP-positive, but CK19 positivity is more frequent in metastatic hepatoid adenocarcinoma than in primary hepatocellular carcinoma. As MUC5AC is usually not assessed, it may be difficult to differentiate between the two carcinomas. Histologically, tubular adenocarcinoma is the most common histological subtype of gastric carcinoma (Fig. 1F). Other common histological subtypes of gastric carcinoma include poorly cohesive gastric carcinoma (including signet ring cell carcinoma), papillary adenocarcinoma, and mucinous adenocarcinoma. As adenocarcinoma of the esophagus (esophageal gastroesophageal junction adenocarcinoma) can be considered as a differential diagnosis, immunohistochemically, the most common differential diagnosis of gastric carcinoma is the most common histological subtype of gastric carcinoma (including signet ring cell carcinoma). Papillary adenocarcinoma of the esophagus is characterized by the presence of papillae composed of a single layer of columnar cells. In contrast, poorly cohesive gastric carcinoma (including signet ring cell carcinoma) is characterized by the presence of sheets of neoplastic cells with round, hyperchromatic nuclei and a high mitotic rate. The differentiation of poorly cohesive gastric carcinoma from metastatic gastric carcinoma can be challenging.

Metastatic gastric carcinoma

Metastatic gastric carcinoma is defined as a malignant epithelial neoplasm that arises in the stomach. According to a study of Swedish patients, 26% of gastric carcinomas develop distant metastases, and the liver is the most common distant site for metastasis. The metastasis of hepatoid adenocarcinoma to the liver needs to be differentiated from hepatocellular carcinoma. The metachronous development of hepatoid adenocarcinoma in the liver occurs less frequently than in the stomach, and the pathological diagnosis of hepatoid adenocarcinoma in the liver is considered as an independent entity. The metastasizing hepatoid adenocarcinoma to the liver occurs less frequently than in the stomach, and the pathological diagnosis of hepatoid adenocarcinoma in the liver is considered as an independent entity. The metastasizing hepatoid adenocarcinoma to the liver occurs less frequently than in the stomach, and the pathological diagnosis of hepatoid adenocarcinoma in the liver is considered as an independent entity. The metastasizing hepatoid adenocarcinoma to the liver occurs less frequently than in the stomach, and the pathological diagnosis of hepatoid adenocarcinoma in the liver is considered as an independent entity.
However, MUC5AC should be used with caution for the differential diagnosis of metastatic GC in the liver because MUC5AC positivity can be observed in 42-61.1% of intrahepatic cholangiocarcinomas and is rarely observed in adenocarcinomas from other sites (Table 1).

**CONCLUSION**

Metastatic carcinoma in the liver can be observed in various patients with cancer. It is important to correctly diagnose the histologic type and the primary site of the metastatic lesions to establish the optimal treatment strategy. A constellation of clinical information that includes radiologic findings and laboratory results is also important for the correct pathologic diagnosis of metastatic tumors in the liver. In a pathologic aspect, background liver pathology is helpful for the differential diagnosis between primary and secondary liver cancers. If secondary liver cancer is suspected, a pathologic review of the potential primary cancer is helpful. Immunohistochemical studies with cytokeratins, neuroendocrine markers, and tissue-specific markers are sometimes essential for the differential diagnosis of metastatic carcinomas in the liver.

**Authors’ contribution**

JHP performed a literature review and drafted the manuscript. JHK conceived the study and revised the manuscript.

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**Conflicts of Interest**

The authors have no conflicts to disclose.

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