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A practical approach to liver metastasis from unknown primary cancer: What surgeons need to know

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The liver is a site of metastasis in 25% of metastatic cancers (Abbruzzese et al., 1995). In Western countries, metastases are the most common type of malignant neoplasms in the liver. The majority of liver metastases arise from carcinomas, but other primary tumor types should also be considered, such as lymphomas, sarcomas, melanomas, and germ cell tumors. Of primary liver malignancies, hepatocellular carcinoma is the most common (Hertz et al., 2000). The differentiation between metastatic carcinoma to the liver and primary hepatocellular carcinoma is sometimes challenging.

In the last decade, newer technologies have emerged and are being used to reinforce the existing traditional pathologic staining and immunohistochemistry techniques, thus increasing the accuracy of primary site detection, and suggesting new targeted treatment options. The purpose of this review is to present and summarize, in a practical and simplified manner, the current literature regarding the clinically challenging entity of liver metastasis from carcinomas of unknown primary.

Keywords Liver metastasis, unknown primary, carcinoma

Introduction

The liver is a site of metastasis in 25% of metastatic cancers (1). In Western countries, metastases are the most common type of malignant neoplasms in the liver. The majority of liver metastases arise from carcinomas, but other primary tumor types should also be considered, such as lymphomas, sarcomas, melanomas, and germ cell tumors. Of primary liver malignancies, hepatocellular carcinoma is the most common (2). It is the sixth most common newly diagnosed cancer worldwide and the third most common cause of death from cancer (3).

The differentiation between metastatic carcinoma to the liver and primary hepatocellular carcinoma is sometimes challenging. However, due to the different prognosis and treatment options, this discrimination should be sought by all means (4–7). After successfully differentiating hepatocellular carcinoma from metastatic carcinoma, identifying the primary site of metastatic carcinoma becomes central. However, even the most extensive clinical, laboratory, radiologic, endoscopic, and conventional pathologic investigations may fail to identify the primary carcinoma site, thus defining these cases as carcinomas of unknown primary.

Carcinomas of unknown primary comprise 2–9% of all newly diagnosed cancers, accounting for more than 30,000 cancers annually in the United States (8). They occur equally in men and women, with the median age at diagnosis being 60 years (9). In previous reports relying on autopsy confirmation of primary sites, the most common primaries were identified to be of lung, pancreas, biliary tree, and kidney origins (10). Traditionally, patients with carcinoma of unknown primary have been treated with non-targeted cytotoxic chemotherapy, frequently based on platinum and taxanes. However, the response is generally poor, with an overall survival of 11 weeks to 11 months (7,11,12).

Because of this dismal prognosis, immense efforts and wide research have been aiming to implement new techniques that can identify the primary site in carcinomas of unknown primary, and thus potentially enable oncologists and surgical oncologists to apply more tumor-specific therapies. The rationale behind this intensive search is supported by studies showing that such target directed therapies improved survival in patients with carcinoma of unknown primary (1,13).

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In the last decade, newer technologies have emerged and are being used to reinforce the existing traditional pathologic staining and immunohistochemistry techniques, thus increasing the accuracy of primary site detection, and suggesting new targeted treatment options. These new, sophisticated pathology and genetic techniques are becoming overwhelming for surgeons, as well as radiologists and oncologists and other health care providers, who are required to learn about molecular genetic profiling and implications of a plethora of findings and new information, on top of busy jobs and schedules. The purpose of this review is to present and summarize, in a practical and simplified manner, the current literature regarding the clinically challenging entity of liver metastasis from carcinomas of unknown primary.

Initial evaluation

When a patient presents with a liver mass, and a benign lesion is not likely based on clinical and radiologic parameters, a comprehensive but logical evaluation process should be undertaken in order to identify the suspected malignant mass, know its origin, and plan treatment accordingly.

The basic work-up should begin with a thorough history, emphasizing the presence of any cancer risk factors and any family or personal oncologic history. Any known primary tumors should raise the suspicion for synchronous or metachronous distant metastasis, and should be sought by means of physical examination, imaging studies, blood tests, tumor markers, and endoscopic evaluation, when appropriate.

After careful history taking, all patients should undergo a head to toe physical examination, with a special focus on nevi and other skin lesions, breast and pelvic examinations in women, and careful genital, anal, and rectal examinations. Any suspicious findings should be further investigated with laboratory, imaging, and/or endoscopic tests.

If initial history and physical examinations are negative, further tests should be undertaken, including complete blood count, serum chemistries, urinalysis, computed tomography (CT) of the chest, abdomen and pelvis, a pelvic examination and mammography in women, and a prostate examination and measurement of prostate specific antigen (PSA) in men.

The use of positron emission tomography (PET) in this regard is gaining popularity. It comes to reason that PET can play an important role in selected patients, as whole-body imaging may, in addition to possibly identifying the primary site, detect or exclude additional metastatic sites, which may have important therapeutic or prognostic consequences. In this regard, CT and MRI allow for the detection of anatomical abnormalities, and therefore frequently miss small lesions and non-enhancing lesions, a common scenario in patients with carcinoma of unknown primary. PET imaging usually utilizes radio-labeled fluorodeoxyglucose (FDG) as a radiotracer for metabolic activity, because the majority of malignant cancers have a high rate of glucose metabolism (Warburg effect) (14). Therefore, FDG PET offers high lesion-to-background contrast, giving it a high sensitivity for the detection of small lesions. In 1994, Rege et al. suggested a possible advantage of PET over CT in patients with carcinoma of unknown primary (15). Roh et al. have shown that the sensitivity of FDG PET/CT was significantly higher than that of CT alone in detecting primary tumors in patients presenting with cervical metastases from unknown origin (87.5% vs. 43.7%, respectively) (16). Modern PET scanners have a spatial resolution of about 4–7 mm for whole-body imaging, but can detect even smaller lesions because of the high lesion-to-background contrast (12,17,18). However, there is still no consensus as to the utility of PET in the setting of carcinoma of unknown primary; in contrast to the above retrospective studies, we found only one prospective study comparing primary site detection rates between CT and PET/CT in the setting of carcinoma of unknown primary, showing no superiority of one modality over the other (19).

Tissue sampling

When the above initial evaluation fails to identify any primary tumors that might be a source of metastasis, the focus should be pointed towards establishing a tissue diagnosis. Tissue samples are generally obtained by fine needle aspiration (FNA) or needle core biopsy (NCB), usually using either transabdominal ultrasound or CT guidance or, less commonly, endoscopic ultrasound (EUS), yielding diagnostic specimens in over 90% of cases (20). Many factors influence the choice between FNA and NCB, including lesion size, depth, location, and proximity to vital hepatic structures, the risk of complications, radiologist preference and expertise, and pathologist expertise in cytologic and histologic techniques required for the diagnosis. Usually more tissue can be obtained through NCB. However, this does not necessarily mean that it has a diagnostic advantage over FNA. On the contrary; recent studies showed that an adequate FNA sample is 2% to 24% more sensitive than NCB (21–27).

Tissue diagnosis

Once a tissue sample is obtained, the pathologist should first try to determine the tumor type, as whether it is a carcinoma, melanoma, lymphoma, sarcoma, or germ cell tumor. This determination can largely be made by morphology alone. However, sometimes additional studies are required for this discrimination, especially when the cancer is poorly differentiated. To narrow the differential diagnosis, basic testing for cytokeratins, leukocyte common antigen, and S100 can determine most carcinomas, lymphomas, and melanomas, respectively. In the following sections we bring a brief description of the main histologic and immunohistochemical features of each of these tumors.

Melanomas

Melanomas comprise only 2.2% of all liver metastases (28). Diagnosis is made when cytoplasmic melanin pigment is demonstrated on FNA smears. However, this is not seen when the melanoma is amelanotic. Using immunohistochemistry, the vast majority of melanomas can be diagnosed. Melanomas are positive for S100, HMB45, and MelanA (29).

Lymphomas

The appearance on FNA slides depends on the specific type of lymphoma. The most common lymphoma to metastasize to the liver is large-cell lymphoma, which is usually identified