Oncology

Metastatic urothelial carcinoma to the liver with unknown primary tumor

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ABSTRACT

Cancer of unknown primary (CUP), a rare and aggressive clinical entity, accounts for approximately 3% of all malignancies. CUP with urothelial origin is even more unusual, with no other cases reported in the current literature. As imaging and other studies often do not reveal the tumor origin, the approach to CUP involves a focused search for the primary tumor, relying on guidance from immunohistochemical staining of biopsy specimens. Treatment consists of standard therapies directed at the most likely tumor origin.

Introduction

Cancer of unknown primary (CUP) is a rare diagnosis and accounts for approximately 3% of all malignancies. Initial evaluation requires a battery of standard cancer screening tests such as colonoscopy and mammography as well as immunohistochemical tests of biopsy specimens to determine the tumor origin. Metastatic urothelial carcinoma with an unidentified primary tumor is rare, and to our knowledge, no other cases have been reported in the literature. Herein, we present a case of a patient with metastatic urothelial carcinoma to the liver with an unknown primary tumor.

Case presentation

The patient is a 50 year old male with a 7.5 pack year smoking history, who presented with intermittent right upper quadrant pain of one month's duration. Abdominal ultrasound findings were consistent with acute cholecystitis, and he underwent urgent cholecystectomy. Three months postoperatively, he presented with one month of intermittent fever, malaise, and persistent right upper quadrant pain. A computed tomography scan of the chest, abdomen and pelvis with intravenous and oral contrast revealed several liver masses (Fig. 1). Additionally, an enlarged lymph node adjacent to the stomach was identified; however, no abnormality was present in the kidneys, ureters or bladder. Fine needle aspiration of one of the liver masses was performed. Immunohistochemistry demonstrated positivity for CK7, GATA3 (Fig. 2), p63, H&E (Fig. 3), CK5/6, and S100p, consistent with a diagnosis of metastatic urothelial carcinoma. Further urological work-up included flexible cystoscopy, which was negative for bladder erythema or masses. His insurance would not cover upper tract imaging, procedures or PET scan despite peer to peer review. Voided urine and bladder barbotage cytology were benign.

Further immunohistochemistry studies were performed on the liver biopsy and ruled out breast, salivary gland and intrahepatic bile duct carcinomas. After confirmation of metastatic urothelial carcinoma, the patient elected to begin chemotherapy. However, after his first cycle of gemcitabine and cisplatin, he had two hospital admissions for worsening liver failure. Ultimately, the patient died, approximately 6 weeks after initial diagnosis.

Discussion

CUP is rare and aggressive with median survival of 6–12 months. The initial evaluation requires a battery of immunohistochemical studies as well as general imaging and procedural testing (e.g. mammogram, colonoscopy) to rule out common primary sites, as well as targeted evaluation based on immunohistochemistry. In this case, the immunostains pointed towards a urothelial carcinoma primary, though no clear tumor could be identified with imaging, cystoscopy, or urine cytologies. Treatment of carcinoma of unknown primary is based on the standard therapy for the most likely primary tumor; however, prognosis remains poor.
Bladder cancer is the sixth most common cancer in the United States with 80,470 new cases predicted for 2019. One-third of patients with bladder cancer present with muscle invasive disease (pT2-T4). Autopsy studies show that metastasis are present in 68% of patients with muscle invasive bladder cancer. The most common sites of metastasis are lymph node, lung, liver and bones. The pattern of metastasis does not differ between the different histological subtypes or urothelial carcinoma variants. Additionally, more locally advanced disease (higher T stage) is associated with shorter metastasis-free interval.

CUP is a clinically recognized entity, comprising 3–5% of all epithelial tumors. It is characterized by an aggressive clinical course, early metastases, and poor prognosis. Histologically, most cases are adenocarcinoma (>60%) and are poorly differentiated in appearance (30–35%). Autopsy studies have found that the most common primary sites were lung (27%) and pancreatic (24%), followed by liver or bile duct, kidney or adrenals, colon or rectum, genitourinary system, and stomach.

The approach to CUP involves a focused search for the primary guided by immunohistochemistry staining of biopsy specimens. Imaging studies, serum tumor markers, and cytogenetic studies are not particularly helpful in identifying the source. Pavlidis and Pentheroudakis delineated three rules with regards to the histological diagnosis of CUP. First, the biopsy or cytology specimen sent for pathologic analysis should be adequate and properly processed. Second, immunohistochemical staining should be applied in a stepwise fashion, to determine the broad type of cancer, the subtype, and the origin if it is adenocarcinoma. Third, the clinical oncologist and the pathologist should maintain close communication regarding relevant laboratory and clinical information. No specific chromosomal or molecular characteristics have been identified that are unique to CUP. However, one assay that uses tissue-specific gene expression profiling to identify tissue origin (Pathwork Tissue of Origin Test) is currently approved and may assist with diagnosis.

Patients with CUP are divided into two prognostic subsets: favorable and unfavorable, with 80% of patients belonging to the unfavorable subset. Unfavorable subset includes adenocarcinoma that is either metastatic to the liver or other organs or causing malignant ascites, multiple cerebral metastases of adenocarcinoma or squamous carcinoma, and squamous cell carcinoma of the abdominopelvic cavity. The patient presented in this case, with urothelial carcinoma metastatic to the liver, does not fall into either the favorable or unfavorable subset by the defined criteria. CUP is traditionally treated with cisplatin-based combination chemotherapy. Median response rate is approximately 45% for patients in the favorable subset, and less than 20% for those in the unfavorable subset. For most patients presenting with CUP and disseminated liver or multi-organ metastasis, no chemotherapy regimen has been found to be effective. Median survival with disseminated CUP is approximately 6–10 months.

**Conclusions**

Metastatic urothelial carcinoma to the liver of unknown primary is a rare and aggressive disease. Diagnosis of the primary tumor is often difficult to determine, and treatment is generally directed towards the most likely source based on immunohistochemistry of biopsy specimens. Large metastatic burden in the liver indicates visceral crisis, with extremely poor prognosis. Systemic chemotherapy should be initiated as soon as possible.

**Conflicts of interest**

None.

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Appendix A. Supplementary data

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