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Unique morphologic and clinical features of liver predominant/primary small cell carcinoma—autopsy and biopsy case series

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ABSTRACT

Liver predominant small cell carcinoma is rare but often presents as hyperacute liver failure with unknown primary and is a medical emergency. We present 2 autopsy and 7 biopsy cases of liver predominant small cell carcinoma and demonstrate that these patients present with liver failure and identifiable hepatomegaly but lack discrete lesions on imaging as well as no mass lesions identified in other organs including lung. Compared with the multiple nodules of metastatic small cell carcinoma in the liver, unique morphologic feature of liver predominant/primary small cell carcinoma in autopsy and biopsy specimens was a diffuse infiltration of small blue neoplastic cells predominantly in the sinusoidal space in the liver parenchyma. Before diagnosing liver predominant/primary small cell carcinoma, other infiltrating small blue cell neoplasms including lymphoma and peripheral neuroectodermal tumor need to be ruled out through immunohistochemistry. We, therefore, demonstrate that liver biopsy together with a rapid panel of immunostains is necessary to firmly establish a diagnosis of liver predominant small cell carcinoma and allow clinicians to immediately implement potentially lifesaving chemotherapy.

1. Introduction

Hyperacute (<7 days) and acute (7-28 days) liver failure is due to rapid loss in hepatocyte function based on the interval from initial symptom onset to onset of encephalopathy [1,2]. In general, acetaminophen toxicity results in hyperacute failure, where viral hepatitis leads to slower, acute, or subacute onset [1]. Although acetaminophen or drug toxicity and viral hepatitis are the most common etiologies that result in hyperacute and acute liver failure, there are reports secondary to hepatic infiltration by malignancies including Hodgkin lymphoma [3-5], non-Hodgkin lymphoma [6-8], adenocarcinomas [9-14], melanoma [9-12,14], anaplastic tumors [9-12,14], and small cell carcinoma of the prostate [15] or lung [10,12,16].

Small cell carcinoma is one of the most common primary malignancies in the lung and demonstrates extremely aggressive malignant behavior and early metastasis [16]. Small cell carcinoma of the lung has been reported to rarely manifest as acute hepatic failure when it metastasizes to the liver [16]; however, extrapulmonary small cell carcinoma is rare, and there are only a few case reports for liver primary/predominant small cell carcinoma [17-23]. Recently, we have identified a few cases of hyperacute or acute liver failure secondary to diffuse infiltration of the liver primary/predominant small cell carcinoma. We, therefore, reviewed all liver biopsy and autopsy cases of small cell carcinoma over the past 20 years at our institution to evaluate pathologic, clinical, and radiologic findings.

Our data demonstrate that primary/predominant liver small cell carcinoma results in a distinct histologic, clinical, and radiologic presentation in comparison with metastatic small cell carcinoma to the liver. Liver primary/predominant small cell carcinoma exhibited diffuse sinusoidal infiltration of small blue neoplastic cells almost entirely replacing the hepatic parenchyma, whereas metastatic small cell carcinoma demonstrated a nodular pattern histologically. Patients with liver primary/predominant small cell carcinoma also had diffuse hepatomegaly and hyperacute or acute liver failure with no distinct liver nodules identified on radiologic imaging or on autopsy, whereas all patients with metastatic small cell carcinoma had normal liver function and a nodular pattern on imaging. Liver small cell carcinoma patients often presented emergently with rapid progress to death secondary to hyperacute or acute liver failure making a prompt diagnosis difficult. We, therefore, demonstrate the need for liver biopsy in rapid, accurate diagnosis in patients with hyperacute or acute liver failure, diffuse hepatomegaly, and no discrete lesions on imaging.

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2. Materials and methods

2.1. Case selection and review

With approval of the Institutional Review Board from Northwestern University, all autopsy and biopsy cases diagnosed as small cell carcinoma in the liver between 1992 and 2012 were identified from the pathology database at Northwestern Memorial Hospital. Two independent blinded gastrointestinal surgical pathologists reviewed all slides associated with each case previously diagnosed as small cell carcinoma in the liver. Diagnosis of small cell carcinoma on autopsy or biopsy specimens was based on morphologic findings and confirmed by immunohistochemical (IHC) stains in all cases. Retrospective chart review was performed to identify any known primary source of small cell carcinoma or clinical diagnosis of hyperacute, acute, or subacute liver failure. When a history of liver failure was present, confirmation of the timeframe of symptom onset to encephalopathy and subsequent diagnosis of hyperacute, acute, or subacute liver failure was performed. Two independent blinded radiologists reviewed all previous imaging to evaluate liver size and presence or absence of liver lesions and/or metastatic disease in other organs.

2.2. Antibodies and immunohistochemistry

Immunohistochemical staining for synaptophysin, chromogranin, CD56, cytokeratin AE1/AE3 and Cam5.2, CD45, and/or CD99 as well as Hep Par 1 and EBER were performed on formalin-fixed, paraffin-embedded, 5-μm-thick tissue sections. Tissue sections were deparaffinized in xylene for a total of 15 minutes and subsequently rehydrated. Immunostaining was performed using a Ventana XT (Ventana Medical Systems, Inc, Tucson, AZ) automated immunostainer for synaptophysin (clone NA-polyclonal; Cell Marque, Rocklin, CA, USA) and chromogranin (clone LK2H10; Ventana). Cytokeratin AE1/AE3 (clone AE1/3; Dako, Carpinteria, CA) and Cam5.2 (Becton-Dickinson Biosciences, Franklin Lakes, NJ), CD45 (clone 2B11/PD7/26; Dako) and CD99 (a generous gift from the laboratory of Dr William A. Muller, Northwestern University, clone hec 2.2), Hep Par 1 (clone OCH1E5.2.10, 1:80 dilution; Dako), CD56 (clone CD564; Vector, Burlingame, CA), and EBER in situ hybridization (Dako) were analyzed by a Dako autostainer (Dako).

In brief, antigen retrieval was carried out at 97°C for 20 minutes in citrate buffer. After blocking the endogenous peroxidase activity with 3% hydrogen peroxidase for 10 minutes, the primary antibody incubation was carried out for 60 minutes at room temperature. Bound primary Abs were detected with an EnVision Horse Radish Peroxidase System (Dako) according to the manufacturer's instructions. Staining was considered positive when tumor cells showed cytoplasmic/nuclear reactivity (chromogranin, synaptophysin, cytokeratin AE1/AE3, CD45, CD56, and CD99). Negative controls (substituting Tris-buffered saline for primary antibody) were run simultaneously. Two blinded pathologists assessed the slides.

3. Results

3.1. Unique autopsy findings of liver predominant/primary small cell carcinoma

Two autopsy cases were performed on patients who presented to outpatient clinic with symptoms of vague abdominal pain, jaundice, or icterus. One patient also had recent mental status changes reported by a family member. For both patients, elevated aspartate aminotransferase (741 and 12574 U/L), alanine aminotransferase (291 and 5768 U/L), total bilirubin (25.6 and 10.8 mg/dL), and direct bilirubin (10.0 mg/dL, performed on 1 patient only) were identified on initial laboratory workup. Both patients were admitted and rapidly decompensated with aspartate aminotransferase progressing from 741 to 22867 U/L and alanine aminotransferase progressing from 291 to 3882 U/L in 1 patient within 2 days of presentation. Ultrasound (US) imaging obtained the day before death in 1 case revealed marked hepatomegaly and a heterogenous nodular contour to the liver with hypoechoic areas and no evidence of a definitive mass lesion. No imaging was performed in the other case. Despite aggressive efforts, the patients died 7 and 2 days from the time of presentation in hyperacute liver failure.

Autopsies revealed livers with marked hepatomegaly, weighing 4380 and 5360 g, respectively, which contained multiple scattered small nodules ranging from 0.1 to 0.6 cm in size (Fig. 1A). Histologically, liver sections in both cases demonstrated all of the salient morphologic features of small cell carcinoma including small blue cells with scant cytoplasm, nuclear molding, and a finely granular “salt and pepper” chromatin pattern as well as absent or inconspicuous nucleoli. The small neoplastic cells diffusely infiltrated the sinusoidal spaces and almost completely replaced the liver parenchyma (Fig. 1B). Abundant necrosis and only rare viable hepatocytes were also identified. Despite extensive examination and sampling of the lung and peribronchial parenchyma, a primary source of the small cell carcinoma or evidence of further metastasis was not detected in either case. Further review of the clinical history revealed no prior diagnosis of liver dysfunction, small cell carcinoma, or other malignancies. Immunohistochemical stains were obtained in both cases and revealed that the residual hepatocytes were highlighted by cytokeratin Cam 5.2 (Fig. 1C), and neoplastic small cells were strong positive for CD56 (Fig. 1D) and AE1/AE3, at least focally positive for chromogranin (Fig. 1E) and synaptophysin, and negative for thyroid transcription factor 1 (TTF-1), CD99, Hep Par 1, and Epstein-Barr encoding region (EBER).

3.2. Morphologic features of liver predominant/primary small cell carcinoma compared to metastatic small cell carcinoma in liver needle core biopsies

A total of 13 patients with diagnosis of liver small cell carcinomas in liver core biopsies were retrieved over the past 20 years at our institution. Histologically, 2 distinct histologic patterns were identified in these biopsies. One group ($n = 6$) demonstrated a diffuse pattern of small blue neoplastic cells infiltrating into the hepatic parenchyma (mainly in the sinusoidal spaces) and almost completely replacing the liver parenchyma (Fig. 2A and B), identical to our initial autopsy cases. The other group ($n = 7$) demonstrated a nodular growth pattern of small blue neoplastic cells with abundant necrosis adjacent to the well-delineated background hepatic parenchyma consistent with metastatic disease (Fig. 3A and B).

Immunohistochemistry was performed in all cases. Both the diffuse infiltrating and nodular growth patterns of small blue neoplastic cells showed that neoplastic cells were positive for cytokeratin AE1/AE3 (Fig. 4A), and the residual hepatocytes were highlighted by cytokeratin Cam 5.2 (Fig. 4B) and variably positive for TTF-1 as well as neuroendocrine markers including at least focally positive for chromogranin (Fig. 4C), synaptophysin (Fig. 4D), and CD56. CD45 and CD99 were negative in all cases to rule out other possible small blue cell malignancies including peripheral neuroectodermal tumor/Ewing tumor and lymphoma. The overall IHC patterns of expression confirmed a diagnosis of small cell carcinoma in all cases.

3.3. Clinical presentation and imaging features of liver predominant/primary small cell carcinoma compared with metastatic small cell carcinoma

Chart review revealed that the 2 distinct histologic patterns of liver small cell carcinoma correlated to different clinical presentations and imaging patterns, as summarized in the Table. In patients with the liver primary/predominant, diffuse infiltrating pattern of liver small cell carcinoma ($n = 6$), all reported prodromal symptoms included