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Diffuse SALL4 Expression in Hepatocellular Carcinoma of a Postmenopausal Cirrhotic Patient

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Abstract

In rare instances, Hepatocellular Carcinoma (HCC) and Yolk Sac Tumor (YST) have overlapping histologic features. Although α-Fetoprotein (AFP) is frequently used as serum marker for HCC, elevated AFP has been reported in most YST patients. Sal-Like protein 4 (SALL4), a nuclear zinc finger transcription factor, has been reported as a highly sensitive and specific marker for primary and metastatic gonadal and extragonadal YST. Here, we present a case of HCC expressing SALL4 by immunohistochemistry. The patient is a 73 year-old Caucasian female with a history of liver cirrhosis secondary to non-alcoholic steatohepatitis, presented for evaluation of an enlarging 4.8 cm ill-defined heterogenous mass within segment 8, demonstrating arterial enhancement and washout. Laboratory studies showed elevated AFP level of 21,303 ng/mL. By histology, the background liver showed bridging fibrosis with nodular formation. The neoplastic cells consist of columnar cells with dense chromatin, eosinophilic cytoplasm, areas of glandular architecture and focal area of neoplastic cells lining the central vascular core. By immunohistochemistry the neoplastic cells are strongly positive for Cam 5.2, SALL4, Glypican-3, AFP, Arginase-1 (variable) and CK19 (focal). The neoplastic cells are negative for CK7, CK20, ER, GATA-3, CDX-2, Hepar-1, Lung adeno cocktail, synaptophysin, PAX8, Hercep, and WT-1. Although strong immunoreactivity of SALL4 is characteristic of YST, SALL4 expression is reported in up to 46% of HCC cases. Our case highlights the potential pitfall when using SALL4 in distinguishing HCC and YST, especially in limited biopsy material.

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Introduction

Liver cancer is the second leading cause of cancer-related deaths worldwide, and Hepatocellular Carcinoma (HCC) accounts for approximately 75% of all liver cancers [1]. Although the pathogenesis of HCC is not clear, it generally arises in the setting of infections, alcoholic and non-alcoholic fatty liver diseases [1,2]. There are a variety of signaling pathways including Notch, Wnt, Mitogen-Activated Protein Kinase (MAPK) and hedgehog for the occurrence of HCC. Sal-Like protein 4 (SALL4), is a zinc finger transcription factor and is commonly expressed in germ cell tumors [2]. Here we report an aggressive poorly differentiated adenocarcinoma of the liver expressing SALL4 by immunohistochemistry, in a postmenopausal patient with cirrhosis.

Case Presentation

The patient is a 73 year-old female with a history of cirrhosis secondary to NASH, previously decompensated with ascites and portal hypertension requiring paracentesis. She initially developed abdominal pain and underwent Computed Topography (CT) scan of the abdomen which revealed a new hypodense mass-like lesion in the right liver measuring up to 2.2 cm in a background of cirrhosis. A follow-up study after 4 months with CT abdomen and pelvis with contrast showed a heterogeneous enhancement of a 4.8 cm mass in segment 8 with tumoral invasion of right portal vein. The mass did not demonstrate arterial enhancement but did demonstrate mild washout on venous phase with Liver Imaging Reporting and Data System (LI-RADS) category 4, probably HCC. Laboratory studies detected elevated α-Fetoprotein (AFP) of 21,303 ng/mL and CA 19-9 of 65 ng/mL.

The patient underwent CT-guided needle core biopsy of the liver that showed background liver with bridging fibrosis (Figure 1A) and sheets of neoplastic consisting columnar cells with dense chromatin, increased mitosis and pale cytoplasm. There are areas of gland formation and focal area where the neoplastic cells lines around a central vascular core (Figure 1A). By

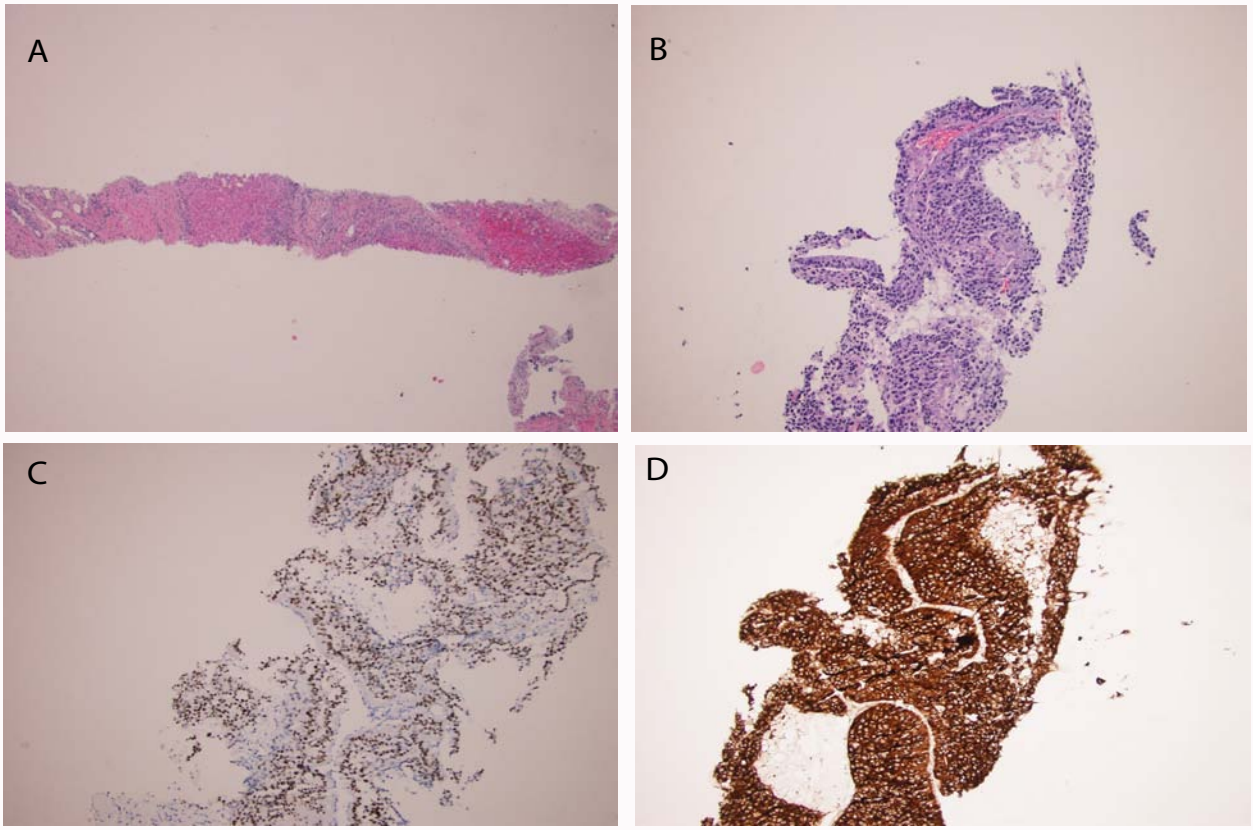

Figure 1: A: The background liver with increased portal/periportal and focal bridging fibrosis (hematoxylin-eosin, original magnifications at 40x); B: Poorly differentiated adenocarcinoma with neoplastic cells lining around a vessel; (hematoxylin-eosin, original magnifications at 100x); C and D: Immunohistochemistry showing strong and uniform expression of SALL4 and Glypican-3, respectively (immunohistochemistry, original magnifications at 100x).

immunohistochemistry the neoplastic cells are strongly positive for Cam 5.2, SALL4 (Figure 1C), Glypican-3 (Figure 1D), α-fetoprotein, Arginase-1 (variable) and CK19 (focal) while negative for CK7, CK20, ER, GATA-3, CDX-2, Hepar-1, Lung adeno cocktail, synaptophysin, PAX8, Hercep, and WT-1. Although the immunoprofile is suggestive of yolk sac tumor with diffuse SALL4 expression, this entity is very rare in postmenopausal women. In correlation with radiology, the overall findings support a yolk sac component of a high-grade epithelial neoplasm, consistent with hepatocellular carcinoma in a postmenopausal patient with cirrhosis. The term "somatic derived yolk sac tumors" has been described in this age population, where there is a yolk sac component associated with a high-grade epithelial neoplasm [3]. The patient was not a candidate for surgical or locoregional intervention and the decision was made to transition the patient to palliative care. The patient died approximately three months after the tissue diagnosis.

Discussion

There are rare variants of hepatoid yolk sac tumor which can be difficult to distinguish from HCC by morphology alone [4]. In clinical practice, immunohistochemistry is utilized to differentiate metastatic carcinomas that are morphologically similar and further workup of tumor of unknown origin [5]. SALL4 is a highly sensitive and specific marker for metastatic germ cell tumors and is particularly useful in the detection of metastatic Yolk Sac Tumors (YST) with diffusely finely granular SALL4 nuclear expression pattern [6,7]. But, it is also frequently expressed in serous carcinoma of the ovary, urothelial high-grade carcinoma, gastric adenocarcinoma (intestinal type),acute myeloid leukemia, Wilms tumor, rhabdoid tumors of kidney and extrarenal sites [6,8]. In addition SALL4 expression is also seen in forty-six percent of hepatocellular carcinoma, in punctate/clumped nuclear pattern [7]. The expression of SALL4 in both germ cell and non-germ cell tumors could lead to a potential diagnostic pitfall in the differential diagnosis of HCC versus YST.

There is a recent trend in using immunohistochemistry as prognostic and mutation-specific markers to guide clinical management [5]. HCCs with immunoreactivity to SALL4 are poorly differentiated with frequent vascular invasion and intrahepatic metastasis [9]. In our patient, subsequent CT scan one month after the biopsy showed increasing size of the primary lesion from 4.8 cm to 5.3 cm and an adjacent satellite lesion measuring 1.4 cm with arterial enhancement and washout (LI-RADS category 4). In large meta-analysis studies, SALL4 expression in cancers increases both cancer recurrence and patient mortality, suggesting that SALL4 is a promising prognostic biomarker and a potential target for personalized medicine [10,11]. Yong et al. [12] demonstrated by gene-expression microarray the HCCs with high levels of SALL4 are associated with progenitor-like gene signatures and poor prognosis. In addition, the absence of SALL4 expression in the background normal liver would serve as a potential for targeted therapy and provide less toxicity in patients with underlying cirrhosis [12,13].

The universal application of SALL4 as a biomarker for HCC should be approached with caution due to the geographic variation

in the dominant etiology of HCCs. Western patients develop HCC after hepatitis C viral infection, alcohol and nonalcoholic fatty liver diseases, while Asian HCC patients are commonly carriers of Hepatitis B Virus (HBV) [14]. SALL4-immunoreactive HCCs rose more frequently in HBV- positive background [9]. Additional markers such as Histone Deacetylase 1 (HDAC1) and Histone Deacetlyase 2 (HDAC2) has been shown to coexpress with SALL4, that correlated with underexpression of PTEN and unfavorable prognosis with worse overall and disease-free survival rates after surgery [15]. In addition, SALL4 expression has been implicated in Wnt/β-catenin pathway in both gastric and hepatocellular carcinomas [16,17].

In summary, SALL4 is a highly specific marker for metastatic yolk sac tumors but can be expressed in other cancers such as HCCs. SALL4 expression in HCCs is associated with frequent vascular invasion and intrahepatic metastasis. In addition, to avoid potential diagnostic pitfall in the differential diagnosis of morphologically similar neoplasms, it is important to correlate immunohistochemistry profile with the background liver, clinical and radiologic findings.

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