Received: 10 May 2019 | Revised: 26 September 2019 | Accepted: 7 October 2019

DOI: 10.1002/pbc.28060

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

BRIEF REPORT

DNAJB1-PRKACA–positive metastatic fibrolamellar carcinoma with unknown primary in a pediatric patient

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Abstract

Fibrolamellar carcinoma (FLC) is a rare variant of hepatocellular carcinoma, occurring in children and young adults without underlying liver disease. The diagnosis is based on morphological characteristics of the tumor, supplemented by immunohistochemistry and/or genetic testing. Recently, the presence of a characteristic DNAJB1-PRKACA fusion gene has been associated with FLC. Herein, we report a case of FLC presenting as peritoneal carcinomatosis in a 14-year-old female. Interestingly, no liver tumor was seen on imaging, and an alternative possibility is that the tumor arose outside the liver as a hepatoid carcinoma with fibrolamellar features.

KEYWORDS

cancer genetics, liver, pediatric hematology/oncology, tumors

1 | INTRODUCTION

Fibrolamellar carcinoma (FLC) is a rare variant of hepatocellular carcinoma (HCC), accounting for about 30% of HCC in children and young adults.[1] The main distinctive clinical features of FLC are a young age at presentation (median age of 25 years) and the absence of underlying liver disease. In contrast, conventional HCC usually occurs in adults between 40 and 70 years of age in the context of preexisting liver disease.[2]

Patients with FLC and HCC frequently present with advanced staged disease.

Complete tumor resection is the only curative option for FLC but is only achievable in 20% to 30% of cases. Orthotopic liver transplantation may be an option when tumor is confined to the liver, but remains otherwise unresectable. In cases of unresectable tumors, chemotherapy is a treatment option, with about 50% of children having a partial response to PLADO chemotherapy and 49% of them whose tumors became resectable.[3]

We describe the case of a 14-year-old female who presented with peritoneal carcinomatosis without a primary liver lesion. The morphology and immunostain findings were that of FLC and FISH analysis confirmed the presence of a highly characteristic DNAJB1-PRKACA transcript.

2 | RESULTS

2.1 | Clinical report

A 14-year-old female was admitted following several days of abdominal pain, bloating, and vomiting. On physical examination, abdominal distension was noted, but the patient had neither a palpable mass nor hepatomegaly.

Laboratory studies showed normal levels of serum aspartate aminotransferase, alanine aminotransferase, bilirubin, and creatinine levels, but elevated CA-125 levels (526.8 kU/L) and borderline elevated alfa-fetoprotein levels (12.3 μg/L). Hepatitis B virus surface antigen and

Abbreviations: cisplatin/doxorubicin, PLADO; computed tomography, CT; fibrolamellar carcinoma, FLC; gemcitabine/oxaliplatin, GEMOX; hepatocellular carcinoma, HCC; magnetic resonance imaging, MRI; Paediatric Hepatic International Tumor Trial Protocol, PHITT.

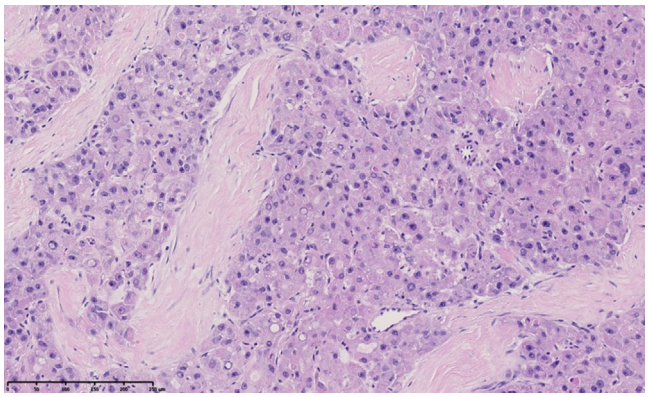

FIGURE 1 Histopathological examination of the tumor showing sheets of polygonal and eosinophilic tumor cells, separated by fibrous bands. Tumor cells have a central nucleus that frequently contains a prominent nucleolus

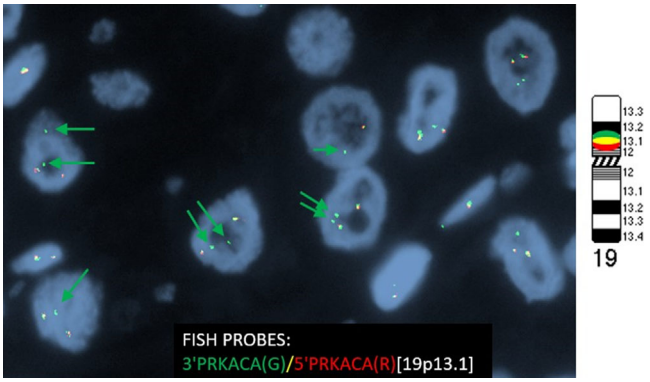

FIGURE 3 Break-apart FISH for PRKACA. Arrows indicate loss of the 5′PRKACA probe and retention of the 3′PRKACA probe

hepatitis C virus antibody were negative. Analysis of the peritoneal ascites showed exudate without neoplastic cells.

Abdominal ultrasound and an 18-FDG-PET CT scan revealed multiple peritoneal nodules, peritoneal carcinomatosis, and bilateral ovarian tumors. Complete imaging showed no other lesion.

Abdominal laparoscopic exploration demonstrated multiple peritoneal nodules and large bilateral adnexal masses. A biopsy was performed on one of the peritoneal nodules.

Histopathological examination of the tumor revealed large polygonal cells with ample eosinophilic cytoplasm and central nuclei with prominent nucleoli (Figure 1). The tumor cells formed sheets that were separated from each other by bands of lamellar fibrosis. The tumor cells were positive for makers of hepatocellular differentiation (BSEP, ABCB11), cytokeratin (CK) 7, and glypican 3, whereas negative for inhibin and cytokeratin 19 (Figure 2). The overall findings strongly suggested a diagnosis of FLC. Because of this atypical presentation, however, genetic testing was performed to confirm the diagnosis of FLC. PRKACA FISH demonstrated the presence of a rearrangement involving the PRKACA gene region (19p13.2) with loss of the 5′ PRKACA probe and retention of the 3′PRKACA probe (Figure 3). This positive test, in conjunction with histomorphology, meets the clinical diagnostic standards for a diagnosis of FLC, and it was initially hypothesized that a primary liver lesion was present, one that was protruding into the abdomen and mimicking peritoneal nodules. A liver MRI with gadolinium injection, however, showed normal liver parenchyma, confirming the absence of a primary liver tumor, suggesting the tumor arose outside the liver, perhaps in the ovary.

The patient was treated according to the Paediatric Hepatic International Tumor Trial protocol (PHITT). Treatment consisted of six cycles of cisplatin, doxorubicin (PLADO), and sorafenib and led to a rapid decrease in ascites. Posttreatment abdominal MRI showed a significant but transient decrease in the size and amount of abdominal and peritoneal lesions. Chemotherapy also led to significant decrease in CA-125 levels (74 kU/L) and stability of alfa-fetoprotein level (14.3 μg/L). Unfortunately, the tumor was not resectable even after chemotherapy and progressive disease led to the patient's death 15 months later. No liver tumors were found during follow-up imaging studies.

3 | DISCUSSION

FLC differs from HCC in terms of clinical and morphological characteristics, occurring in young adults without underlying liver disease. The tumor consists of large cells with prominent nucleoli and eosinophilic cytoplasm, with a lamellar pattern of intratumoral fibrosis.[1,2] Several immunohistochemical markers have been employed to help diagnosis of FLC, such as CK7 and CD68. Glypican 3 is positive in 50% of cases.[4,5] Recently, it has been shown that > 99% of all FLC have a highly characteristic DNAJB1-PRKACA rearrangement, one that can be detected by FISH, whereas HCC lack this gene rearrangement.[6,9] Thus, the current pathology diagnostic guidelines for FLC are based on (1) compatible morphology and (2) confirmation by either molecular

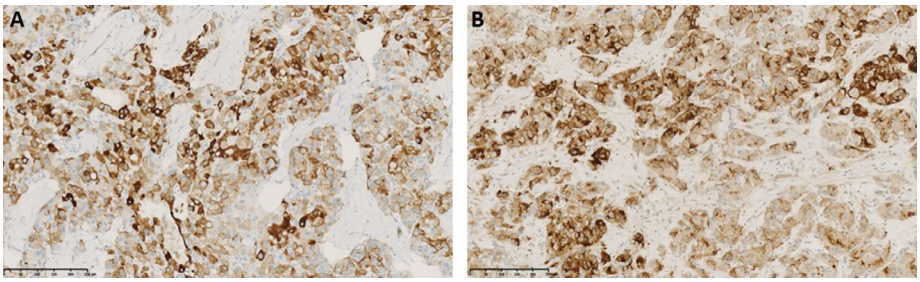

FIGURE 2 On immunohistochemistry, tumor cells showed diffuse positivity for CK7 (A) and glypican-3 (B)

testing (preferred) or immunostains for CD68 and CK7 if molecular testing is not available.

In the current patient, the initial presentation of peritoneal carcinomatosis without any liver lesion on abdominal ultrasound and MRI made the diagnosis challenging. The differential diagnosis of peritoneal malignancy in children is broad, including rhabdomyosarcoma, Burkitt lymphoma, germ cell tumor, desmoplastic small round cell tumor, digestive and ovarian tumors, and rarely various carcinomas. In the case reported here, the morphology of the tumor and subsequent molecular testing pointed to a diagnosis of FLC.

In 2014, Honeyman et al described the presence of a DNAJB1-PRKACA fusion gene in FLC, resulting from a 400-kB deletion on chromosome 19.8. The specificity of this fusion gene transcript for FLC in the setting of primary liver tumors was subsequently confirmed in several cohorts, which showed that the DNAJB1-PRKACA fusion gene was not observed in other primary liver tumors.[7,9] In our patient, FISH analysis was performed on the tumor sample, revealing the presence of this characteristic deletion.

This is the first reported case of a tumor compatible with FLC without a primary liver tumor. Classical HCC can sometimes present as a pedunculated tumor that extends from the liver into the abdomen, mimicking a metastatic tumor.[10,14] In 2002, Yeh et al reported a cohort of 432 patients with HCC, including 18 patients with a pedunculated growth pattern; this group had a mean age at diagnosis of 47.8 years.[13] In 2014, Jung et al described the case of a 74-year-old woman, without underlying liver disease, presenting with a large pelvic mass initially that was initially considered to be a myoma, but surgical exploration revealed a pedunculated HCC.[10]

Hepatoid carcinomas that closely mimic conventional HCC can arise from multiple different organs, including the ovaries, and it is possible the same holds true for FLC.[16] In the current case, no tumor was seen within the liver on imaging, suggesting the tumor arose outside the liver as a hepatoid carcinoma with fibrolamellar features. This case would be the first reported example. Tumor morphology and protein expression pattern seen by immunohistochemistry are inconsistent with both conventional ovarian carcinoma and primary carcinomas of the peritoneal cavity.

The management of HCC and FLC remains difficult in children. Because of the prevalence of metastatic disease, complete resection of all sites of disease is achievable only in approximately 20% to 30% of patients and, because outcomes for children with unresectable tumor are extremely poor, with a five-year event-free survival of 0%.[4,16]

There has been progress, however, as pediatric HCC demonstrate a nearly 50% response rate to chemotherapy.[17] The PHITT current preoperative approach for patients with unresected/metastatic tumor consists of randomization to either PLADO and sorafenib or PLADO/GEMOX (gemcitabine/oxaliplatin) and sorafenib. Surgery is then discussed as an option if the tumor becomes resectable.

In conclusion, this is the first case of a carcinoma compatible with FLC presenting as peritoneal carcinomatosis, but without a liver tumor. The absence of a liver tumor made the diagnosis challenging and suggests this represents the first reported case of a hepatoid carcinoma with FLC features. The presence of a DNAJB1-PRKACA fusion gene on the tumor cells was a very useful tool to confirm the diagnosis.

ACKNOWLEDGMENTS

We thank Patricia T Greipp and her team from the Cytogenetics Research Core of the Mayo Clinic in Rochester for the excellent technical work in developing the FISH assay.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Balbeur S, Dumortier A, Mergen J, et al. DNAJB1-PRKACA–positive metastatic fibrolamellar carcinoma with unknown primary in a pediatric patient. *Pediatr Blood Cancer*. 2019;e28060. https://doi.org/10.1002/pbc.28060