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## Intracranial Metastasis in Fibrolamellar Hepatocellular Carcinoma

**William J. Hammond, MD<sup>1,2</sup>, Gadi Lalazar, MD<sup>2</sup>, James A. Saltsman, MD<sup>1,2</sup>, Benjamin A. Farber, MD<sup>1,2</sup>, Enrico Danzer, MD<sup>1</sup>, Tshering C. Sherpa, BS<sup>2</sup>, Charles D. Banda, BS<sup>2</sup>, Jeffrey R. Andolina, MD<sup>3</sup>, Sasan Karimi, MD<sup>4</sup>, Cameron W. Brennan, MD<sup>5,6</sup>, Michael S. Torbenson, MD<sup>7</sup>, Michael P. La Quaglia, MD<sup>1</sup>, and Sanford M. Simon, PhD<sup>2</sup>**

<sup>1</sup>Pediatric Surgical Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA

<sup>2</sup>Laboratory of Cellular Biophysics, The Rockefeller University, 1230 York Avenue, New York, NY 10065, USA

<sup>3</sup>Department of Pediatrics, Golisano Children's Hospital, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642, USA

<sup>4</sup>Department of Radiology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

<sup>5</sup>Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA

<sup>6</sup>Department of Neurosurgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

<sup>7</sup>Division of Anatomic Pathology, Department of Pathology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA

### Abstract

Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare liver malignancy in adolescents and young adults. Surgery is the mainstay of therapy for primary and metastatic disease. Most patients relapse, with development of both local and distant metastases. Brain metastases from solid tumors are rare in the pediatric and young adult population. Here we document three patients with brain

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**Corresponding authors:** Michael P. La Quaglia, MD, FACS, FRCS (Eng., Edin. Hon.), FAAP, Department of Surgery, Pediatric Surgical Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Suite H-1315, New York, NY 10065, Phone: 1-212-639-7002 / Fax: 1-212-717-3373, laquaglm@mskcc.org; Sanford M. Simon, PhD, Laboratory of Cellular Biophysics, The Rockefeller University, New York, NY 10065, Phone: 1-212-327-8130, simon@rockefeller.edu.

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Rosalind C. Simmons, Editor, Pediatric and Orthopaedic Services; Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065; 1-212-639-2628; simmonr1@mskcc.org

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metastases from FLHCC, confirmed by histology and molecular characterization of the chimeric fusion *DNAJB1-PRKACA*, each necessitating neurosurgical intervention. These observations highlight the ability of FLHCC to metastasize to the brain and suggest the need for surveillance neuroimaging for patients with advanced-stage disease.

## Introduction

Fibrolamellar hepatocellular carcinoma (FLHCC) is a primary liver malignancy that occurs most commonly in adolescents and young adults, without underlying liver disease. FLHCC is a relatively rare tumor, with an estimated age-adjusted incidence rate of 0.02 per 100,000 in the United States.<sup>1,2</sup> It has a peak age of detection of 21 years, and patients are usually diagnosed between the ages of 10 and 40 years. FLHCC appears to be slightly more common in women, but otherwise is not associated with any known risk factors<sup>4,5</sup>. While initially characterized as a morphologic variant of hepatocellular carcinoma (HCC),<sup>6</sup> FLHCC is uniquely associated with a 400-kb deletion on one copy of chromosome 19 that produces a functional chimeric fusion between the heat shock protein, *DNAJB1*, and the catalytic subunit of protein kinase A, *PRKACA*.<sup>7</sup> The transcriptomic and proteomic changes in FLHCC are consistent from patient-to-patient and distinct from HCC.<sup>8</sup> Molecular assays detecting the *DNAJB1-PRKACA* fusion have improved diagnostic accuracy for FLHCC.<sup>7,9-13</sup>

Current treatment for FLHCC focuses on gross total resection,<sup>14-17</sup> as systemic therapy remains unstandardized.<sup>16,18-20</sup> However, FLHCC is frequently diagnosed at an advanced stage,<sup>12</sup> and the majority relapse within 1 year despite resection.<sup>21</sup> Only aggressive resection of recurrent disease is correlated with improved durable survival.<sup>22</sup> FLHCC exhibits both local invasion into adjacent organs, including the stomach, diaphragm, and pancreas, and lymphovascular spread to celiac, gastric, and para-aortic lymph nodes.<sup>12</sup> Distant lung, peritoneal, bone and adrenal metastases occur in approximately 30% of patients<sup>23,24</sup> Reports of 2 patients with brain metastasis exist in the literature<sup>16,25</sup> but neither provide neuroimaging, pathologic or molecular analysis of the lesions. Here, we report 3 cases of confirmed FLHCC brain metastasis.

## Case Reports

### Patient 1

An 18-year-old female presented with a symptomatic abdominal mass and underwent resection of her primary liver tumor. One year after surgery, she underwent a liver transplant for disease recurrence. Post-transplant, she developed metastases in the lungs, left ovary, and apex of the vagina, which necessitated multiple resections. Five years post-diagnosis, her disease progressed to include the transplanted liver and she underwent radiofrequency ablation and treatment with Oxaliplatin, Gemcitabine, and Bevacizumab. Seven years after diagnosis she had further disease progression with metastasis to the lungs. She underwent resection of the left upper lobe of the lung, stereotactic radiation of her pulmonary metastases, partial pericardiectomy, and sorafenib. Eight years post-diagnosis CT scan of the chest showed increased thoracic, pleural and pulmonary metastasis, and left vocal cord

paralysis. She was treated with palliative radiation (3Gy X 10, 5 F/W) to the mediastinum, and received ENMD-2076 (NCT02234986), a small molecule multi-kinase inhibitor with activity against Aurora kinase A, VEGFRs, FGFRs, c-Kit, CSFR1 and Flt3. She then developed headache, altered mental status, and a generalized tonic-clonic seizure. Brain imaging revealed a hemorrhagic left frontal lobe mass with midline shift (Figure 1 A,B). She underwent a left frontotemporal craniotomy and removal of the mass. Histology was consistent with FLHCC (Figure 2 A,B). PCR for the *DNAJB1-PRKACA* mRNA fusion was positive (Figure 2G). MSK-IMPACT™ testing on the brain metastasis demonstrated BCOR, HGF and ROS1 somatic alterations. She died 3 months after surgery due to progressive extracranial disease.

### Patient 2

An 18-year-old female presented with a 1-year history of vague abdominal pain. Imaging revealed a large left hepatic mass with scattered lesions in the remaining liver and an enlarged peri-pancreatic lymph node. She underwent a left hepatectomy, resection of satellite hepatic lesions and peri-pancreatic lymph node. One month after surgery, disease at the hepatic resection margin was treated with arterial embolization. Post-operatively her disease progressed despite treatment with Fluorouracil and Interferon-alpha<sup>26</sup>, and 1 year later she underwent surgical debulking of her abdominal disease. Postoperative surveillance imaging again revealed a para-esophageal mass and new pulmonary metastasis in the lingula. She then developed acute mental status change and CT scan revealed a mass with acute intracranial hemorrhage (Figure 1 C,D). The patient underwent craniotomy and resection of the lesion. Histology was consistent with FLHCC (Figure 2 C,D). PCR on the primary tumor and metastasis confirmed the presence of the *DNAJB1-PRKACA* fusion transcript (Figure 2G). MSK-IMPACT™ testing on the brain metastasis additionally demonstrated loss of Chromosome 8q, and *CTNNB1*, *ATR*, *SOX17*, *ZFH3* somatic alterations. One year after resection of her brain metastasis, she received palliative radiation to metastases in her pelvis and lower abdomen and Erlotinib. She is currently alive, without recurrence of her brain metastases and continuing therapy with Erlotinib for her extracranial disease.

### Patient 3

An 18-year-old female presented with recurrent emesis and lethargy. Initial workup revealed hyperammonemia, a right hepatic mass, and a pulmonary nodule; and an extensive left leg deep vein thrombosis (DVT) requiring fasciotomy and anticoagulation. After management of her DVT, the patient underwent resection of the liver tumor and lung metastasis. Over the next 3 years she received multiple chemotherapeutic regimens including: imetelstat; tivantinib; cisplatin, gemcitabine and necitumumab; sorafenib, denosumab, everolimus, letrozole and leuprolide; all with inadequate response. Due to progressive pulmonary disease she received ENMD-2076 (NCT02234986). She then developed severe headache, left-sided blurry vision, nausea and vomiting. Neuroimaging demonstrated brain metastases (Figure 1 E,F). The patient underwent resection of the dominant lesion, and histology was compatible with FLHCC (Figure 2 E,F). PCR confirmed the presence of the *DNAJB1-PRKACA* fusion transcript (Figure 2G). MSK-IMPACT™ on the brain metastasis identified somatic alterations in WT1, SYK, SF3B1, NOTCH3, GRIN2A, BRD4, and AGO2. Postoperatively,

stereotactic radiation was administered to the remaining intracranial metastases. Twelve months from resection, she had >10 foci of intracranial metastases, and developed a metastasis to the acetabulum. She is currently not receiving therapy.

### 3. Methods

Tissue specimens were either fresh frozen in optimal cutting temperature (OCT) compound or fixed in 10% formalin and embedded in paraffin (FFPE). The histology for each case was reviewed by a liver pathologist (M.S.T.). RNA extraction from FFPE or OCT embedded tissue was completed using the miRNeasy FFPE Kit or miRNeasy Kit (Qiagen; Venlo, The Netherlands), respectively. The presence of the *DNAJB1-PRKACA* chimera was confirmed by PCR for the fusion mRNA transcript *DNAJB1-PRKACA* as previously described.<sup>7</sup> Samples underwent Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™) testing.

### 4. Discussion

We describe the first 3 patients with confirmed FLHCC metastasis to the brain. On molecular analysis, each patient's brain tumor demonstrated the *DNAJB1-PRKACA* fusion. All three developed multiple relapses at extrahepatic sites after undergoing initial resection of their primary disease, including pulmonary metastases. None underwent neuroimaging prior to developing neurological symptoms.

Solid tumor metastasis to the brain is rare in the pediatric population, with sarcomas comprising the majority of reported cases.<sup>27</sup> Cursory reference to brain parenchymal metastasis in a patient with FLHCC exists twice in the literature.<sup>16,25</sup> Clinical history is only available for one patient who was diagnosed at the age of 46, uncommon for FLHCC, and the diagnosis was not molecularly confirmed. A potential third case in the literature describes a hemorrhagic cerebellar stroke in a young patient with unresectable FLHCC and pulmonary metastasis receiving Sorafenib.<sup>28</sup> It is unclear how the diagnosis of FLHCC was made and the authors conclude the hemorrhagic stroke was a rare adverse drug event, rather than a metastasis.

Assessment of the time course from disease onset to development of brain metastasis proves challenging. Intracranial metastasis was detected 9, 2, and 5 years post-diagnosis (Patients 1, 2, and 3, respectively). All patients had large asymptomatic intraparenchymal lesions prior to their acute presentation, suggesting a lengthy period of indolent intracranial disease. All underwent image-guided surgical resection of their intracranial lesions without operative complication.

Currently, no prescribed recommendations exist for surveillance neuroimaging in patients with FLHCC. Given the frequency of advanced stage at diagnosis, the lack of effective systemic therapies, and low progression-free survival among resected patients, we believe the at-risk cohort of patients for brain metastases is nontrivial. Additionally, with an absence of serum tumor markers, current surveillance relies on physical examination and imaging. The presence of lung metastasis, which occurs in approximately 30% of FLHCC patients, may be associated with the risk for developing brain metastasis. We recommend that patients

with advanced stage FLHCC, particularly those with lung metastases, undergo neuroimaging at time of diagnosis, even in the absence of symptoms. For those without intracranial metastasis at time of diagnosis, there is currently no data to support the interval for surveillance neuroimaging, but it is our recommendation that it be incorporated into the assessment of extra-cranial disease.

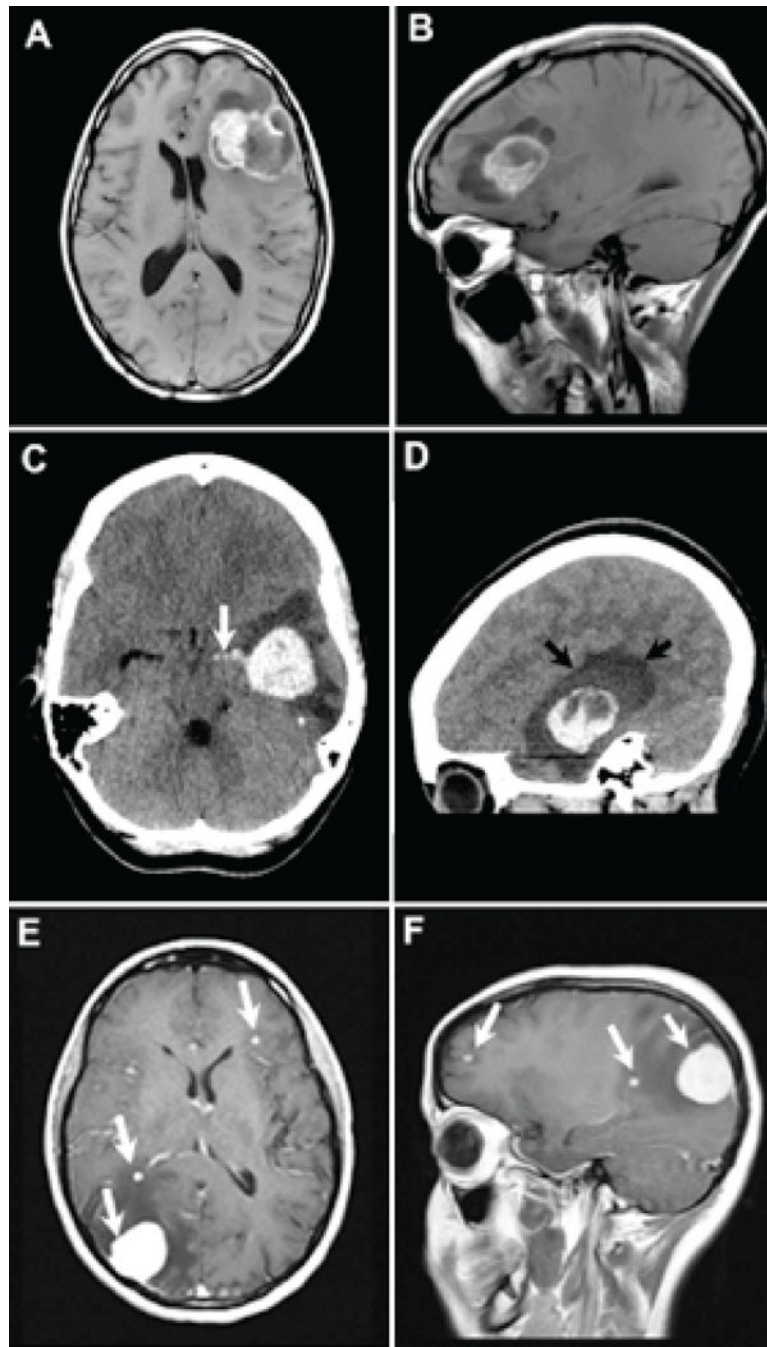
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**Figure 1.**

*Patient 1:* Axial (A) T1-weighted contrast-enhanced and sagittal (B) T1-weighted pre-contrast, demonstrate a cystic and solid metastasis within the left frontal lobe resulting in mid line shift. The metastasis contains T1 iso to hyperintense material that are iso to hyperintense on the T2-weighted images consistent with blood products (arrows). Sagittal contrast enhanced T1-weighted images depict the solid enhancing components surrounded by cystic parts of the metastasis. *Patient 2:* Axial (C) and sagittal (D) reformatted CT images demonstrate a hyperdense hemorrhagic metastasis within the left temporal lobe. Rupture

into ventricular system with blood extending into temporal horn of the lateral ventricle [white arrow image (C)]. Edema surrounding the metastasis dark shade of gray designated by black arrows on image (D). *Patient 3*: Axial (E) and sagittal (F) T1-weighted contrast enhanced images reveal several enhancing metastases (white arrows).

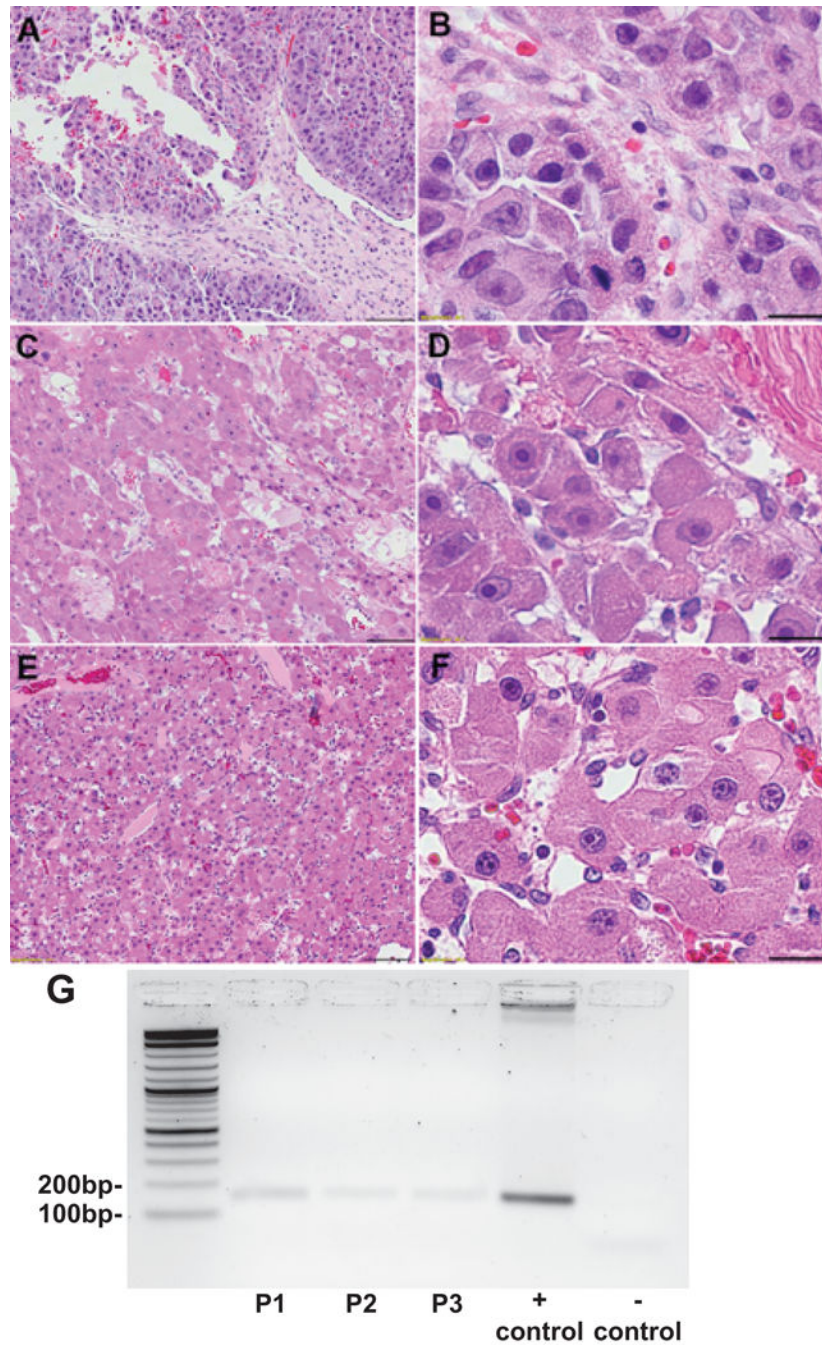
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**Figure 2.** H&E of resected brain metastasis at 10x (A,C,E) and 60x (B,D,F) magnification from Patient 1 (A,B) and Patient 2 (C,D) and Patient 3 (E,F), demonstrating well-differentiated tumor cells with abundant eosinophilic cytoplasm and prominent nucleoli. Fibrous bands, classic for FLHCC are demonstrated in Patient 2 (D, top right corner) and were absent in Patients 1 and 3. Scale bars 100 microns (A,C,E) and 20 microns (B,D,F). RT-PCR agarose gel electrophoresis for the *DNAJB1-PRKACA* fusion mRNA, is positive for a 148bp amplicon in brain metastases from Patient 1 (lane 2), Patient 2 (lane 3), Patient 3 (lane 4),

positive control for *DNAJB1-PRKACA* (lane 5) and a negative control (lane 6). Lanes are shown from left to right with a 10Kb ladder (lane 1) (G).

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