case report

Response to Mammalian Target of Rapamycin–Based Therapy and Incidental Finding of Lynch Syndrome in a Patient With Solid Pseudopapillary Neoplasm of the Pancreas With *AKT1_E17K* Mutation

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INTRODUCTION

Solid pseudopapillary neoplasms (SPNs) of the pancreas are exocrine neoplasms that predominantly affect young females and are considered to have low malignant potential. Surgical resection offers patients an excellent chance of long-term survival, even in cases of local invasion, recurrence, and metastatic disease.[1-3] Recent studies have demonstrated that invasion of these neoplasms into muscular vessels, advanced tumor stage by European Neuroendocrine Tumors Society classification, and distant metastasis correlated with poor prognosis.[4] In such instances—and especially when complete surgical resection is unattainable—use of salvage chemotherapy is needed.[5,6] In this setting, some chemotherapy agents have offered favorable responses,[7-10] yet because of the scarce number of reported cases requiring this treatment modality, no regimen has been demonstrated as definitely superior.[11]

First described by Frank in 1959 and histologically defined as SPNs by the WHO in 2010, SPNs have been demonstrated to harbor somatic point mutations in exon 3 of *CTNNB1*, the gene that encodes for β-catenin, a downstream transcriptional activator in the Wnt signaling pathway that is involved in cell growth regulation.[12,13] SPNs have not previously been associated with genetic mutations linked to DNA mismatch repair (MMR) syndromes, such as Lynch syndrome and hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. Here, we describe the unique case of an adolescent girl with metastatic SPN and the results of somatic and germline clinical genomic analysis.

CASE

A 13-year-old adolescent girl with no family history of cancer presented to an outside institution with severe epigastric pain and emesis after being hit with a soccer ball. On physical exam, there was tenderness on deep palpation but no guarding or rebound. Results of a CBC and complete metabolic panel, including hepatic and cholestatic markers, were unremarkable. Abdominal ultrasonography revealed a complex 12.2- × 11.8- × 12.5-cm mass arising from the pancreas. Additional magnetic resonance imaging confirmed these findings. To clarify the likely oncologic diagnosis, additional workup was performed, including α-fetoprotein, carcinoembryonic antigen, cancer antigen 125, and cancer antigen 19-9 testing, with normal values. The patient underwent a distal laparoscopic pancreatectomy with a gross total resection of the mass, which exhibited a ruptured pancreatic mass and vascular invasion. Postoperatively, she developed acute GI bleeding from a gastric ulcer and remained admitted for more than 30 days.

Pathologic evaluation revealed a uniform grayish-maroon, soft, necrotic, and hemorrhagic lesion macroscopically. Microscopically, it showed solid sheets of uniform tumor cells with numerous hyalinized capillaries, pseudopapillary formation, and areas of hemorrhage and necrosis. Mitoses were inconspicuous. Hyaline globules and foam cells were not prominent. Immunohistochemistry

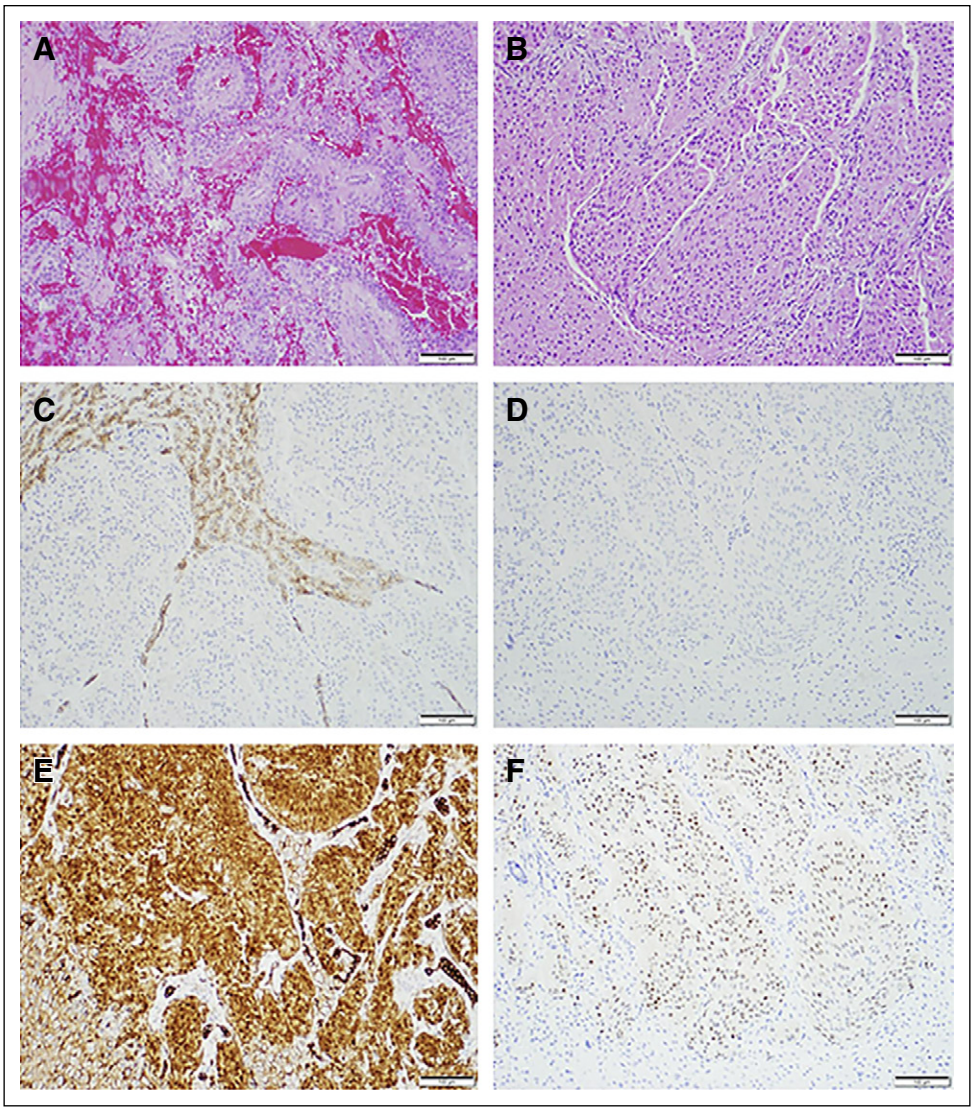

Fig 1. (A) Representative micrograph with hematoxylin and eosin (H&E) staining showing solid pseudopapillary neoplasm (SPN) in the pancreas with extensive intratumoral hemorrhage. (B) Representative micrograph with H&E staining showing metastatic SPN in liver. (C-F) Immunohistochemical staining showing that the liver metastasis is negative for pan-cytokeratin (C) and chromogranin (D), but positive for nuclear expression of β-catenin (E) and progesterone receptor (F). Hepatocytes, which are positive for pan-cytokeratin (C) and negative for nuclear expression of β-catenin (E) and progesterone receptor (F), serve as internal controls. Magnification, ×100 (A-F).

results were positive for vimentin, CD10, β-catenin, progesterone receptor, and synaptophysin, but negative for pan-cytokeratin and chromogranin (Fig 1). These results were consistent with the diagnosis of an SPN involving the pancreatic body and tail.

On the patient's first follow-up after 1 year, abdominal ultrasonography and computed tomography revealed multiple liver masses involving hepatic segments III, VI, VII, and VIII; a tumoral thrombus in the spleno-portal venous confluence; and enlargement of several lymph nodes that raised concern of metastases (Fig 2A). At that time, she underwent a laparoscopic biopsy of the hepatic mass, which confirmed the diagnosis of metastatic SPN in the liver. She was referred to The University of Texas MD Anderson Cancer Center for additional management.

At our institution, the pathologic findings of her primary and metastatic lesions were found to be identical to those obtained at the outside institution. She completed four cycles of chemotherapy with oxaliplatin, irinotecan, and fluorouracil, with subsequent computed tomography images that demonstrated mild progression of metastatic disease (Fig 2B). The patient was enrolled

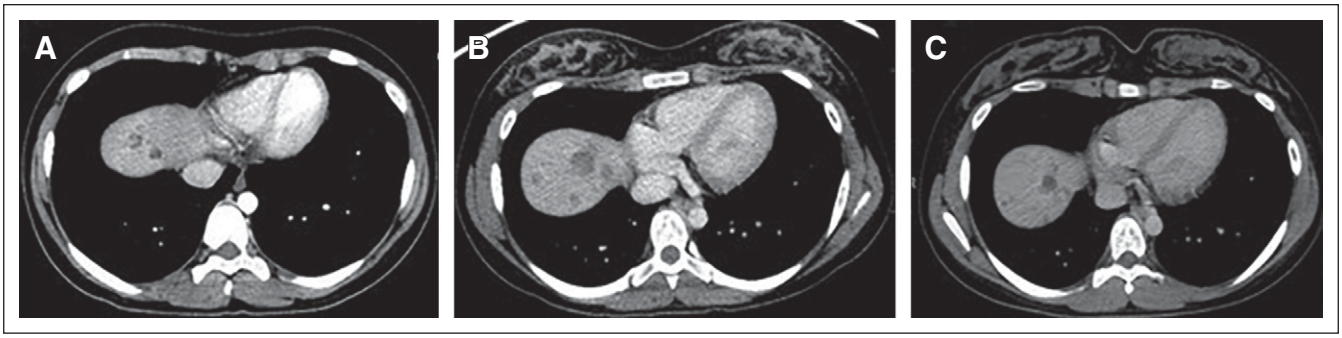

Fig 2. (A) Computed tomography (CT) scan of the liver dome showing metastatic solid pseudopapillary neoplasm in a 13-year-old girl before arrival at our institution. (B) CT scan showing progression of disease after conventional chemotherapy with oxaliplatin, irinotecan, and fluorouracil. (C) CT scan 3 years after the initiation of everolimus. The patient continues to show stable disease.

in a molecular testing protocol (ClinicalTrials.gov identifier: NCT01772771), which identified mutations in *AKT1_E17K*, *CTNNB* and *MET*. On the basis of the *AKT1* mutation, the patient was enrolled in a clinical trial (ClinicalTrials.gov identifier: NCT01582191), with each cycle consisting of 28 days of oral vandetanib (300 mg); a multikinase inhibitor of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and RET; and oral everolimus (10 mg), a mammalian target of rapamycin (mTOR) inhibitor. She completed a total of eight cycles with mixed response and an overall trend toward enlargement of the liver metastases. Adverse events included grade 2 hypertension, grade 1 acneiform rash, and grade 1 fatigue, all of which were attributed to vandetanib. These adverse effects led to treatment discontinuation during the last month of therapy when tumors were within stable disease, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. She was taken off the protocol and continued on single-agent everolimus at the same dosing schedule.

The patient has remained on mTOR-based therapy for more than 3 years with excellent performance status and stable disease (15% reduction) from baseline tumor size (Fig 2C). She has had several episodes of mucositis that have been managed with topical corticosteroids and sucralfate or a brief interruption of therapy.

Fourteen months after the start of single-agent everolimus, additional genetic testing using targeted exome sequencing of 202 genes with tumor and matched normal DNA resulted in the identification of a pathogenic germline *MSH6* mutation (c.2147_2148delCA), which is consistent with Lynch syndrome/HNPCC syndrome and later confirmed in a Clinical Laboratory Improvement Amendments–certified laboratory (Table 1) and via immunohistochemistry testing. The patient received genetic counseling and is currently managed with increased surveillance. Her mother underwent genetic testing and was found to be negative for the mutation.

Table 1. Genomic Annotation Table of the Patient

Gene	Alteration	Origin	Functional Significance	Literature
AKT1	E17K	Somatic	Activating	Mahadevan et al[14]
CTNNB1	D32Y	Somatic	Activating	Al-Fageeh et al[15]
MET	T1010I	Somatic/ germline	Activating	Liu et al[16]

DISCUSSION

To our knowledge, this is the first case reporting the use of genomic testing to guide the treatment of metastatic SPN of the pancreas. The clinical genomic assessment that included somatic and germline evaluations resulted in the identification of actionable genes in the patient and the diagnosis of Lynch syndrome. On the basis of these results, she was administered an mTOR-based therapy and received genetic counseling for Lynch syndrome. The patient continues to demonstrate a sustained clinical benefit 3 years after the initiation of this therapy and after experiencing disease progression on conventional cytotoxic chemotherapy.

The increase in genetic sequencing capability combined with the decrease in the cost of testing has allowed for the identification of frequent germline mutations that underlie advanced cancers.[17] Following American College of Medical Genetics and Genomics guidelines,[18] our patient obtained comprehensive genetic counseling on the clinically relevant incidental finding of the pathogenic germline *MSH6* mutation.[17,18]

Lynch syndrome/HNPCC syndrome is an inherited disorder caused by mutations in DNA MMR genes—for example, *MLH1*, *MSH2*, *MSH6*,

and *PMS2*—that result in microsatellite instability. Identification of this syndrome initially arose from its causal association with colorectal cancer. Pembrolizumab, a programmed death-1 checkpoint inhibitor, recently demonstrated immune-related clinical benefit, which resulted in US Food and Drug Administration approval for its use in MMR-deficient colorectal neoplasms.[19] Of importance, this genetic entity has also been reported in pancreatic neoplasms.[20] Geary et al[21] investigated 130 families with MMR mutations that were comparable to that of our patient and reported 22 cases of early-onset pancreatic cancers. Well-differentiated pancreatic neuroendocrine tumors, medullary carcinomas, and intraductal papillary mucinous neoplasms of the pancreas, among others, have been associated with microsatellite instability syndromes,[22,23] but SPNs have not been previously described in association with Lynch syndrome.

Although a few case reports have demonstrated that chemotherapy agents offer variable degrees of activity toward this rare neoplasm,[7-11] we elected treatment with the well-known regimen for GI tumors, oxaliplatin, irinotecan, and fluorouracil; however, the tumor progressed. Identification of an *AKT1_E17K* aberration via next-generation sequencing analysis established a phase I therapeutic possibility, which was pursued and resulted in some tumor response. Although SPNs are known to almost universally express *CTNNB1*, these neoplasms have also been found to have several other genetic mutations. Recently, Guo et al[24] conducted whole-genome sequencing analysis on nine patients' SPNs and identified numerous genetic mutations, including *USP9X*, *EP400*, *PDK1*, *MED12*, *HTT* and *AR*. *MET* germline mutations have been associated with renal cell and hepatocellular carcinomas, breast, colorectal, gastric, and lung cancer. *MET* germline mutations have never been reported in association with SPNs, yet its presence in this case is of interest and could have also contributed, in part, to the development of this disease. Molecular testing in this disease affords the opportunity of identifying a targetable mutation, as demonstrated in our case.

Targeting the phosphatidylinositol 3-kinase/AKT/mTOR pathway, which is known for its participation in cell proliferation, apoptosis, and angiogenesis,[25] was effective in our patient with SPN. Analogous to the response achieved in cases of pancreatic neuroendocrine tumors,[26] treatment with everolimus, an oral signal transduction inhibitor that blocks mTOR, resulted in stable disease. The patient continues to tolerate the treatment well, with most adverse events being managed successfully with medical treatment.

Although germline *MSH6* mutation–associated Lynch syndrome/HNPCC syndrome and SPN may have been separate entities arising coincidentally in our patient, suspicion of the genetic inherited disorder as an impending trigger for this neoplasm is warranted. Additional studies are required to understand the potential association of both conditions. Obtaining longitudinal analysis of the mTOR pathway activation posteverolimus as well as the *AKT_E17K* mutation frequency in the tumor would have allowed us to obtain additional data; however, we elected to keep research interventions in this pediatric patient at a minimum.

SPNs should be considered in the differential diagnosis of pancreatic masses in patients with Lynch syndrome/HNPCC syndrome. Seeking targetable mutations should continue to play a leading role in the management of this rare neoplasm, especially in those patients who lack defined treatment alternatives.

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