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INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM IN A NEONATE WITH CONGENITAL HYPERINSULINISM AND A *DE NOVO* GERMLINE *SKIL* GENE MUTATION

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Abstract

A 3 day old infant with persistent severe hypoglycemia was found to have a cystic pancreatic tumor. Cessation of glucose infusion led to severe hypoglycemia. Pancreaticoduodenectomy was performed and revealed an intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia. Sequencing of the IPMN revealed a *KRAS* gene mutation not present in surrounding normal tissues. Deep sequencing of the patient's blood for *KRAS* mutations showed no evidence of mosaicism. Whole exome sequencing of the blood of the patient and both parents revealed a *de novo* germline *SKIL* mutation in the child that was not present in either parent. This suggests a possible role for *SKIL* in the pathogenesis of pancreatic tumors.

Keywords

intraductal papillary mucinous neoplasm; neonatal hypoglycemia; *KRAS*; *SKIL*; pancreas

INTRODUCTION

Young age of onset is extremely unusual for intraductal papillary mucinous neoplasms (IPMNs). Neoplasms that occur at an extremely young age suggest a genetic predisposition. Genome-wide sequencing can be used to discover the genetic alteration driving this predisposition.^{[1] [2]} We present the case of a newborn child with an intraductal papillary

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mucinous neoplasm of the pancreas with high-grade dysplasia. Whole exome sequencing of the blood of the patient, the blood of the patient's parents and the patient's tumor revealed a *de novo* germline mutation in the *SKIL* gene, suggesting a possible role for this gene in the genetic predisposition to pancreatic cancer.

METHODS

The patient was a term female infant who presented to the emergency department one day following discharge from the newborn nursery with lethargy, decreased oral intake, and a blood glucose level of 15 mg/dL. She subsequently developed seizures. The patient was reported to have fed vigorously from birth until the morning of presentation. She was immediately started on dextrose-containing intravenous fluids and was admitted to the pediatric intensive care unit. Evaluation for sepsis was unrevealing. Constant administration of 10% dextrose solution administered at a glucose infusion rate (GIR) of 10 mg/kg/min was required to maintain normoglycemia. Reduction in GIR led to severe hypoglycemia. Metabolic evaluation demonstrated elevated insulin levels with corresponding C peptide. Abdominal ultrasound showed a cystic mass adjacent to the right kidney. Abdominal magnetic resonance imaging (MRI) further characterized the mass as a multi-loculated 2.2 × 3.7 × 3.9cm cystic mass arising from the head of the pancreas. Given the coexistence of hyperinsulinism and a focal pancreatic mass, operative excision was indicated. During operative exploration the tumor was found to fully involve the head of the pancreas, precluding simple enucleation. A pancreaticoduodenectomy was required for complete resection. Blood glucose levels normalized immediately after the lesion was removed, while the patient was still in the operating room. MRI at one year post resection demonstrated no evidence of recurrence. The patient has continued to be normoglycemic with appropriate growth and development at 18 months of age.

Pathologic examination of the resected specimen was performed with hematoxylin and eosin staining as well as immunostains for chromogranin, insulin, somatostatin and glucagon. For genetic analyses the resected IPMN was microdissected to enrich for neoplastic cellularity. Whole exome sequencing of white blood cells from the patient and both parents was carried out using Illumina HiSeq2000 and Agilent SureSelect whole exome capture reagents as previously described. [3]

RESULTS

Examination of the resected pancreas revealed a 4.0 cm intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia. The IPMN involved the main and branch ducts, and had a pancreatobiliary phenotype. The islets of Langerhans were enlarged within the tumor as compared to adjacent normal pancreas, confirmed by chromogranin immunostaining. Immunostaining for insulin and somatostatin was positive in the majority of the cells in the clustered islets, as well as in rare cells at the base of the neoplastic epithelial cells in the IPMN. The immunostain for glucagon was positive only in rare cells in the clustered islets of Langerhans, and not in the epithelium of the IPMN itself. (Figure 1)

Whole exome sequencing of the IPMN revealed a G12V *KRAS* gene mutation. Neither *GNAS* nor *RNF43* gene mutations were observed. Sequencing of the nonneoplastic pancreas resected with the tumor and deep sequencing of the patient's blood for *KRAS* revealed only wild-type *KRAS* sequences suggesting that the *KRAS* mutation did not occur early in embryonic development. Blood samples were obtained from the infant and both parents, and the samples submitted for whole exome sequencing. The average read depth was 159.8 (range 137 to 187) with at least 89.7% of the targeted positions covered by at least 10 reads. This analysis revealed a *de novo* mutation in the *SKIL* gene (A512T) in the infant (Figure 2). This mutation changes the hydrophobic amino acid alanine to the polar amino acid threonine, and was one of only three point mutations or insertion/deletions (indels) in the exome in the baby's germline that was not present in either parent. The other two, one in *MUC5B* and the other in *TUBB5*, were felt to be unlikely disease-causing as *MUC5B* codes for a large mucin and *TUBB5* codes for structural protein (a tubulin), although it should be noted that *TUBB5* codes for a protein that has been linked to the Robo-Slit pathway.^[4] Too many heterozygous variants in the parents that were homozygous in the child were identified for evaluation. We therefore cannot rule out a recessive trait as the cause of the child's IPMN.

DISCUSSION

Congenital hyperinsulinism (CHI) may occur in focal or diffuse forms, and the identification of focal hyperinsulinism generally relies on (18)F DOPA PET-CT scanning to identify a causative lesion as they are generally not evident on standard cross-sectional imaging.^[5] Unusually, this patient had a large cystic neoplasm obviating the need for additional imaging studies. Although IPMN occurring concomitantly with neuroendocrine tumors have been reported,^[6;7] IPMN in association with CHI is a novel finding.

This patient presented with an IPMN of the pancreas at an extremely young age of onset. It has been estimated that approximately 10% of pancreatic cancers have a familial basis.^[8] Clues to a genetic predisposition include young age of onset, multiple cancers and a family history of cancer.^[9] Sequencing of DNA isolated from the IPMN identified a *KRAS* mutation, while sequencing of the patient and the patient's parents germline DNA revealed a *de novo* germline *SKIL* mutation in the infant's germline. The *SKIL* gene codes for a protein that functions in the transforming growth factor β pathway (TGF β).^[10] In the absence of TGF- β signaling, *SKIL* binds to the promoter regions of TGF β -responsive genes and recruits a nuclear repressor complex, turning off the expression of TGF- β responsive genes. When TGF- β signaling is activated, smad3 is translocated to the nucleus where it degrades *SKIL*, allowing TGF- β responsive genes to be expressed. Inactivating *SKIL* gene mutations would therefore be predicted to increase the expression of TGF- β responsive genes, and activating *SKIL* mutations would suppress TGF- β signaling.^[11] Of interest, the *SMAD4* gene, which also codes for a member of the TGF- β signaling pathway, is one of the most commonly somatically mutated genes in sporadic pancreatic cancer.^[12] While we would favor the hypothesis that the germline *SKIL* gene mutation caused this patient's IPMN, we cannot exclude the possibility that the *KRAS* mutation occurred in a normal cell in the pancreas early during embryogenesis and initiated the IPMN, with the *SKIL* mutation playing no role.

The coexistence of an IPMN and congenital hyperinsulinism (CHI) is a unique feature of this case. Persistent CHI in the neonate is associated with mutations in a wide variety of genes leading to dysregulation of insulin production.^[13] Sequencing of the baby's germline did not identify any mutations in *KCNJ11*, however, a missense V560M variant was identified in *ABCC8*. The minor allele frequency for this variant in the population is 0.005. The variant was inherited from the father who was phenotypically normal and did not have any reported blood glucose abnormalities. We were not able to identify a relationship between the mutation identified and beta cell function. The exact cause of the hyperinsulinism in this patient is therefore unclear, but the process resolved immediately after the IPMN was resected.

In summary, this infant presented with an unusual congenital pancreatic mass causing hyperinsulinism. Pancreaticoduodenectomy proved curative, and revealed an IPMN with high-grade dysplasia. Sequencing revealed a somatic *KRAS* gene mutation in the IPMN and a de novo germline *SKIL* gene mutation in the infant, suggesting but not establishing a possible role for *SKIL* mutations in the genesis of IPMN.

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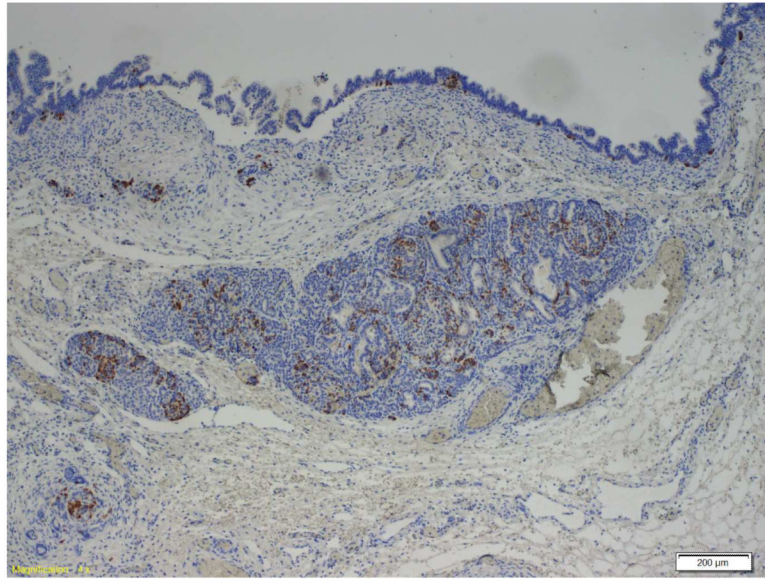
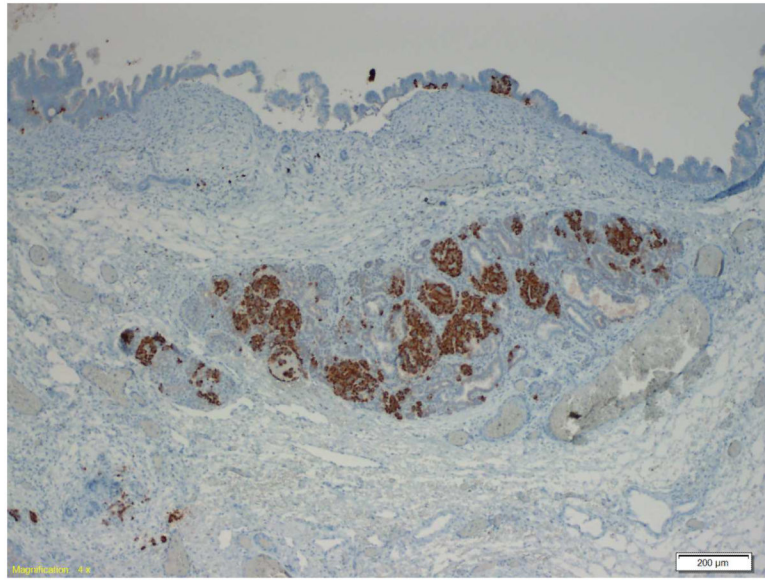
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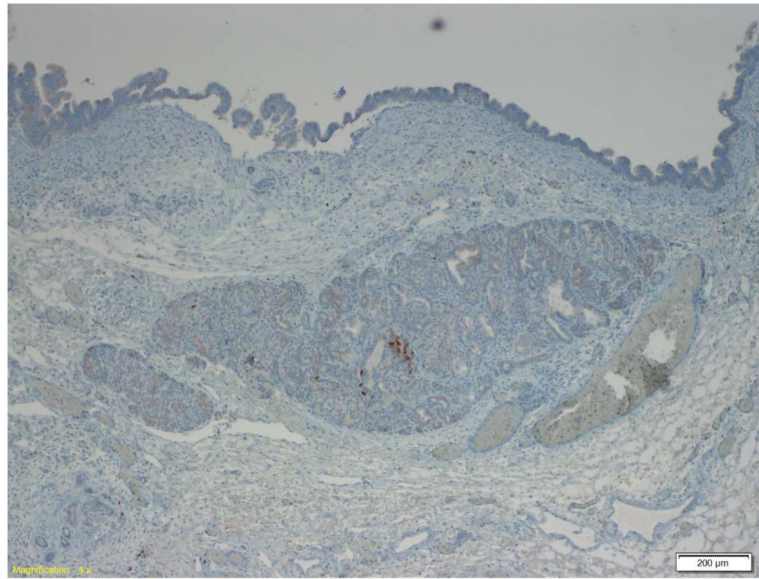


Figure 1. Immunostain demonstrating islet cells (below) and IPMN epithelium (top). Insulin and somatostatin are expressed in the islet cells and rare IPMN cells. Glucagon is expressed only in rare islet cells. 1a: insulin, 1b: somatostatin, 1c: glucagon.

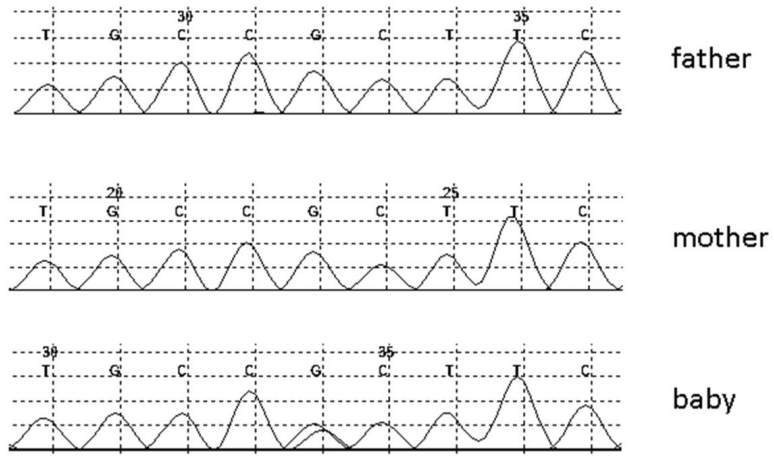


Figure 2. Traces from the index patient and both parents for the coding region of *SKIL* demonstrating *de novo* mutation in the baby that is not present in either parent.

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