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Pancreatic Cancer Early Detection and Interception in an Atypical Case of Peutz-Jeghers Syndrome

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To The Editor:

Pancreatic ductal adenocarcinoma (PDAC) arises from premalignant lesions known as pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasia (IPMN).¹ Even early-stage pancreatic cancer still maintains a poor prognosis; therefore, early detection strategies should be aimed at detecting premalignant lesions rather than cancer itself.² Several institutions have developed programs for high-risk populations, including the University of Texas MD Anderson Cancer Center (MDACC), in which patients with germline mutations at increased susceptibility for PDAC or with a strong family history of PDAC undergo regular surveillance.³

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder with a mutation in the Serine-Threonine Kinase 11/Liver Kinase B1 (*STK11/LKB1*) tumor suppressor gene located on chromosome 19p13.3.^{4–6} Peutz-Jeghers syndrome is associated with a 132-fold increase risk for PDAC as compared to the general population and is clinically characterized by mucocutaneous pigmentation, gastrointestinal hamartomatous polyps, and predisposition to lung, breast, gastrointestinal and gynecological malignancies.⁷

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Case Presentation

A 52-year-old male patient with European descent presented to MDACC for genetic counseling. He had a remote past history of an obstructing hamartomatous polyp in the jejunum. A three-generation pedigree (Supplemental Fig. 1) identified a paternal family history of colon cancer and maternal family history of bladder, breast, and laryngeal cancers. Physical examination did not show any typical pigmentation of PJS such as lip or buccal mucosa pigmentation but upon questioning the patient discussed having one large black spot on his lower lip that had faded with age. Furthermore, the patient did not have a typical childhood presentation of PJS. Based on the patient's previous history of only one hamartoma, absence of typical pigmentation, and family history negative for PJS, he was counseled on the low probability of a PJS diagnosis; however, genetic testing was recommended to rule out or confirm the diagnosis. The *STK11* genetic testing showed a heterozygous partial deletion in *STK11* gene upstream of the initiation codon and in exon 1, which confirmed the diagnosis of PJS, likely de novo.

The patient was advised on PJS screening guidelines based on associated neoplastic risks. Initial surveillance colonoscopy showed multiple polyps in the stomach and colon while capsule study found multiple hamartomatous polyps scattered throughout the small bowel (Fig. 1a). At the initial pancreatic cancer surveillance consult, the patient was asymptomatic. The patient had a normal computed tomography scan (CT) (Fig. 1B) and endoscopic ultrasound (EUS) found a solid 1.28×0.5 cm heterogeneous lesion in the tail of the pancreas (Fig. 1C). Fine needle aspiration (FNA) identified pancreatic adenocarcinoma, which led to a surgical consult. The patient underwent a distal pancreatectomy and margins of proximal transected pancreas were free of tumor. The specimen was resected from the retroperitoneum and lymph node dissection was collected for evaluation. Pathology report revealed chronic pancreatitis, IPMN with focal high grade dysplasia measuring $1.4 \times 1.1 \times 1.0$ cm in the distal pancreas, no invasive carcinoma and no metastatic disease were identified in the lymph nodes.

The most recent surveillance was conducted by magnetic resonance imaging which was negative for suspicious masses (on the remaining pancreas), lymphadenopathy, and metastasis in the abdomen. After 5 years of surveillance the patient will now be evaluated every other year by urology for testicular neoplasia, annually by abdominal magnetic resonance imaging for early detection of pancreatic cancer, and colonoscopy every other year.

DISCUSSION

Here we describe a successful case of pancreatic ductal adenocarcinoma (PDAC) interception in an asymptomatic high risk patient with an atypical presentation of Peutz-Jeghers Syndrome (PJS) who was undergoing his annual surveillance. There are numerous mutations and a significant amount of genetic variability seen in PJS; however, the most common aberrations are deletions, insertions or single base substitutions in the kinase domain encoded between amino acid residues 49 and 309.^{8,9} Even though further genetic analysis is needed to assess the patient's cancer risk, based on mutation type, using his age

of PJS diagnosis he had an approximate 31% risk of developing any type cancer, including an approximate 5% risk for pancreatic cancer.⁹

Most PJS cases have an identifiable *STK11/LKB1* gene mutation, of which 10-20% are presumed to be due to de novo mutations, but there are patients without recognizable mutations, suggesting that there could be another PJS-associated gene.¹⁰ This patient did not exhibit classical symptoms of PJS and family history, but polyp evaluation and genetic status confirmed the PJS diagnosis. His high-risk status made him an ideal candidate for cancer surveillance at MDACC high risk clinics, where the patient had access to a multidisciplinary team of genetic counselors, oncologists, dermatologists, urologists, nutritionists, gastroenterologists, and integrative medicine physicians.

The dramatic difference between the age-matched population risk of pancreatic cancer (<0.1%) compared with the risk in this patient emphasizes the importance of PDAC screening in high risk populations.⁹ This case of an atypical PJS patient with a high-grade premalignant lesion highlights the value of screening asymptomatic high-risk populations for PDAC to attempt diagnosing premalignant lesions while they are still in the window of resection and prior to development of invasive pancreatic cancer.

Lastly, we emphasize the need for standardized cancer screening guidelines in patients with syndromes represented by a spectrum of clinical presentations and various genetic landscapes, especially when patients are at high-risk of aggressive cancers like PDAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Endoscopic and Imaging Results. A, Endoscopic imaging of colonic polyps identified as PJS hamartomatous polyps. B, Baseline CT showed no pancreatic focal masses, dilations, or cysts. C, EUS found a solid nodule described as 1.28×0.5 cm heterogeneous lesion with an anechoic cystic and hypoechoic areas in the tail of the pancreas.