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Intraductal papillary mucinous neoplasm of the pancreas with loss of mismatch repair in a patient with Lynch syndrome

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Abstract

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a precancerous lesion with a well-described progression to carcinoma. This case report describes a 61-year-old woman with a history significant for multiple cancers and a confirmed germline mutation of *MSH2*, a mismatch repair gene responsible for Lynch syndrome, who was also found to have an IPMN of the pancreas. Phenotypic manifestations of Lynch syndrome in this patient included multiple adenomas and adenocarcinomas of the colon as well as several other Lynch syndrome-associated cancers. The patient's adenocarcinoma of the colon and IPMN of the pancreas showed identical immunohistochemical staining profiles with loss of expression of MSH2 and MSH6 proteins as well as high levels of microsatellite instability. The immunohistochemical staining and microsatellite instability patterns of the adenocarcinoma of the colon and IPMN gives strong evidence to support the consideration of IPMN as part of the spectrum of lesions found in Lynch syndrome.

Keywords

Intraductal papillary mucinous neoplasm (IPMN); pancreatic cancer; Lynch syndrome; hereditary nonpolyposis colorectal cancer (HNPCC); *MSH2*

Introduction

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant condition caused by germline mutations of mismatch repair genes including *MLH1*, *MSH2*, *MSH6* and *PMS2*.[18] Microsatellite instability (MSI) testing and immunohistochemical analysis (IHC) on pathologic specimens are used to identify patients who have defective mismatch repair mechanisms. Patients with a high level of microsatellite instability and/or a loss of expression of the mismatch repair proteins in their tumor specimens are more likely to have a disease-causing mutation in the mismatch repair genes responsible for their tumor formation. In order to further establish the diagnosis of Lynch syndrome, further testing can be done to identify the specific germline mutation.

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No conflicts of interest exist

Phenotypically, Lynch syndrome is characterized by early onset colonic adenomas and adenocarcinomas. Previously described Lynch syndrome-associated extracolonic tumors include endometrial, ovarian, small intestinal, gastric and transitional cell carcinomas of the ureter and renal pelvis.[11, 19, 20] Pancreatic carcinoma was first described in relation to Lynch syndrome in 1985 by Lynch et al. [12] Since this publication, evidence for the inclusion of pancreatic carcinoma in the Lynch syndrome cancer spectrum has been conflicting.[1, 13, 21] Notably, pancreatic cancer is included as an extracolonic tumor associated with Lynch syndrome in the revised Bethesda guidelines.[17]

There are two primary precursors to pancreatic cancer: pancreatic intraepithelial neoplasms (panIN) and intraductal papillary mucinous neoplasms (IPMN). PanIns are noninvasive microscopic epithelial neoplasms, located in the smaller pancreatic ducts, characterized by cytologic and architectural atypia. Point mutations in the *KRAS2* gene, as well as inactivation of the *p16/CDKN2A*, *tp53* and *SMAD4* genes are involved in the development of these lesions. In contrast IPMNs are grossly visible, noninvasive, mucin-producing epithelial neoplasms that involve the main pancreatic duct and its side branches. Various molecular alterations, including gene mutations in *KRAS2*, *LKB1* and *PIK3CA*, have been reported in the development of IPMNs.[8] In contrast to pancreatic adenocarcinoma, a relationship between IPMN and Lynch syndrome has not been described.

Case Report

The patient is a Caucasian female who first presented to our clinic at the age of 55. Her first diagnosis of cancer was a brain tumor of unknown pathologic type at approximately 12 years of age. Her gynecological malignancies have included a stage 1A endometroid ovarian cancer at 39, and a separate primary stage 1A endometrial cancer that was incidentally found in the pathology specimen of her right salpingooophorectomy and hysterectomy as treatment for her ovarian cancer. At 43 years of age she was diagnosed with an infiltrating ductal carcinoma of the breast. Dermatological cancer diagnoses have included metastatic melanoma of the thigh at 42 years of age, multiple basal cell carcinomas at 54 and 55 and a nasal tip squamous cell carcinoma at 58.

At 50 years of age the patient was diagnosed with an adenocarcinoma contained within an adenoma at the splenic flexure. At age 52, the patient was found to have another polyp suspicious for an intramucosal adenocarcinoma without submucosal invasion. As a result of these adenocarcinomas, the patient underwent a right subtotal colectomy. Following the surgery, the patient had normal surveillance of her rectal remnant without evidence of malignancy. At age 61, the patient was again diagnosed with an invasive adenocarcinoma as well as a villous adenoma in the rectum. She was recommended to undergo an abdominoperineal resection.

A pre-operative abdominal CT scan showed a 0.8 by 0.7 cm low attenuation lesion in the distal body of the pancreas. A MRI done for further evaluation of this lesion noted two cystic lesions within the pancreas at the distal tail measuring 1.2 cm and at the junction of the tail and body of the pancreas measuring 2.3 cm. On MRCP images, these cystic lesions were noted to communicate with the pancreatic ductal system and were suggestive of IPMN. In addition, there were several smaller cystic areas within the body of the pancreas which likely represented small IPMN.

The patient underwent an abdominoperineal resection with completion of her colectomy and end ileostomy as well as a partial pancreatectomy and splenectomy. The post-operative pathologic specimen showed a rectal adenocarcinoma with negative margins and no nodal involvement. The pathologic specimen from the tail of the pancreas showed IPMN of gastric

foveolar-type with moderate dysplasia and no invasive carcinoma. The pancreatic duct appeared mildly dilated (measuring up to 1.2 cm in diameter) and cystic, filled with clear serous contents. No other gross lesions including masses were identified in the pancreatic parenchyma. The specimen showed chronic pancreatitis as well as the presence of multifocal Pancreatic Intraepithelial Neoplasia (PanIN) 1-2. Lymphovascular, venous and perineural invasion were not identified.

Family history for this patient is unavailable as she was adopted and has no knowledge of her biological family's medical history. She does have a 21-year-old son who has no history of cancer and is alive and well. He has declined genetic testing.

Materials and Methods

The patient was hesitant to undergo genetic testing for many years. At age 60, the patient decided to proceed and a peripheral blood sample was drawn for *BRCA1*, *BRCA2*, *MLH1* and *MSH2* germline mutations. DNA from white blood cells was extracted and purified, amplified by polymerase chain reaction, and directly sequenced.

Microsatellite instability testing was performed on the patient's resected colon and pancreas specimens. DNA was separately prepared from microdissected normal and tumor cells and analyzed by a PCR based assay using fluorescent-labeled primers to 10 different microsatellite DNA loci (4 mononucleotide repeats, BAT 25, BAT 26, BAT 40, BAT34c4; 4 dinucleotide repeats, D17S250, D5S346, D18S55, D10S197, ACTC; and a penta-tetra-mononucleotide marker, MYCL1). The normal and tumor allele patterns were compared for each marker.

Immunohistochemical staining for mismatch repair proteins, MLH1, MSH2, MSH6 and PMS2, was performed on sections of the patient's resected colon and pancreas specimens.

Results

The patient was negative for mutations in her *BRCA1*, *BRCA2* and *MLH1* genes. However, she was found to have a germline mutation in the *MSH2* gene, which was a mutation that resulted in deletion of exons 8 to 10 leading to premature truncation of the MSH2 protein and was felt to be deleterious. She was also found to have a second mutation in the *MSH2* gene termed W764C that was of uncertain significance.

Microsatellite instability was detected in 6 of 6 microsatellite markers in the colonic adenocarcinoma and in 4 of 9 microsatellite markers in the IPMN indicating that both specimens had high levels of microsatellite instability. Immunohistochemical studies on the colonic adenocarcinoma indicated a loss of MSH2 and MSH6 expression with intact MLH1 and PMS2 staining. Interestingly, immunohistochemical studies on the IPMN indicated an identical staining pattern. (Figure 1) All specimens had appropriate internal controls.

Discussion

We report the first case of an IPMN of the pancreas occurring in a patient with Lynch syndrome, in whom a mismatch repair gene germline mutation has been identified. Despite her unknown family history due to adoption, the patient's clinical history, which includes a wide range of cancers diagnosed at young ages, suggested a hereditary cancer syndrome. In this patient, positive testing for an *MSH2* germline mutation confirmed the clinical suspicion of Lynch syndrome. In addition to her germline mutation, the patient's resected colon specimen showed loss of expression of the MSH2 protein and a high level of microsatellite instability. This loss of expression as well as a high level of microsatellite instability in the tumor tissue provides further evidence of the mutation in her *MSH2* gene and the diagnosis of Lynch syndrome.

A pathologic association between IPMN and Lynch syndrome has been a source of controversy in the past. Mucinous noncystic (colloid) carcinoma of the pancreas, a variant of ductal adenocarcinoma that has been shown to arise from IPMN, was demonstrated in one of eight cases to show a high level of microsatellite instability.[9, 10] Additionally, multiple case reports have demonstrated microsatellite instability as well as *MLH1* and *MSH2* gene mutations in medullary carcinoma of the pancreas, a newly described variant of adenocarcinoma with an unknown relationship to IPMN.[2, 5, 22] Another study looking at pancreatic adenocarcinoma showed that 13% of sporadic pancreatic cancer cases were MSI high and that these samples were associated with poor differentiation. This study also looked at a subset of 3 patients with confirmed *MLH1* germline mutations and found that the pancreatic cancers in these patients had a high level of microsatellite instability and were poorly differentiated. This study concluded that pancreatic adenocarcinomas with MSI-H represent a distinct oncogenic pathway, but this study did not comment on a relationship between IPMNs and pancreatic carcinoma.[23]

A study looking at MMR protein staining of IPMNs directly showed presence of staining of MLH1 and MSH2 in 100% of samples. The conclusion from this study was that MMR does not play a significant role in the pathogenesis of IPMNs. However, this study analyzed random pathology samples and not specifically samples from patients with Lynch syndrome. [7] The pancreatic resection specimen of the patient described here showed a loss of expression of the MSH2 protein, as well as a high level of MSI, which strongly suggest the presence of an underlying *MSH2* gene mutation as the cause of her pancreatic cells undergoing malignant change. Because mutations in the *MSH2* gene are known to cause Lynch syndrome, evidence of an *MSH2* gene mutation in this patient's pancreatic specimen suggests that IPMN be considered part of the spectrum of cancers found in Lynch syndrome families.

A population-based study estimated the incidence of extrapancreatic neoplasms in patients with IPMN to be 10%.[14] Retrospective studies have shown that IPMN is associated with extrapancreatic neoplasms, specifically colorectal adenomas and adenocarcinomas as well as gastric carcinomas.[4, 16] This finding suggests that patients with IPMN may have an increased genetic susceptibility for tumor formation. Some have proposed that IPMN be considered a manifestation of attenuated familial adenomatous polyposis, whereas others have suggested it be considered part of the Peutz-Jeghers syndrome cancer spectrum.[3, 15] This case report suggests that IPMN may also be part of the extracolonic tumors found in Lynch syndrome. Evidence of a mutation known to cause Lynch syndrome-associated tumors found in both this patient's germline and pancreatic lesion supports this claim. Furthermore, this is supported by the fact that colorectal adenomas and adenocarcinomas as well as gastric carcinomas, the two most common extrapancreatic neoplasms in individuals with IPMN, are both found with increased frequency in Lynch syndrome families.

This case report is complicated by the patient's extensive cancer history because some of her cancers, in addition to her IPMN, cannot be explained by her Lynch syndrome mutation. Specifically, infiltrating ductal carcinoma of the breast, as was seen in this patient, is not part of the classic tumor spectrum in Lynch syndrome. Additionally, not enough information could be collected on the patient's childhood brain tumor. However, brain tumors have been described as part of Lynch syndrome in the subset of Turcot's syndrome, which involves a primary tumor of the central nervous system and multiple concurrent colorectal adenomas.[6]

We report evidence supporting the inclusion of IPMN in the growing list of extracolonic Lynch syndrome-associated tumors. It is important to identify patients with familial cancer syndromes in order to recommend appropriate screening intervals and modalities. IPMN is a precancerous condition that can be diagnosed with noninvasive radiology or ERCP and treated with

pancreatic resection to prevent progression into carcinoma. Further studies are necessary to determine the prevalence of IPMN in Lynch syndrome families.

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Abbreviations

IPMN

Intraductal papillary mucinous neoplasm

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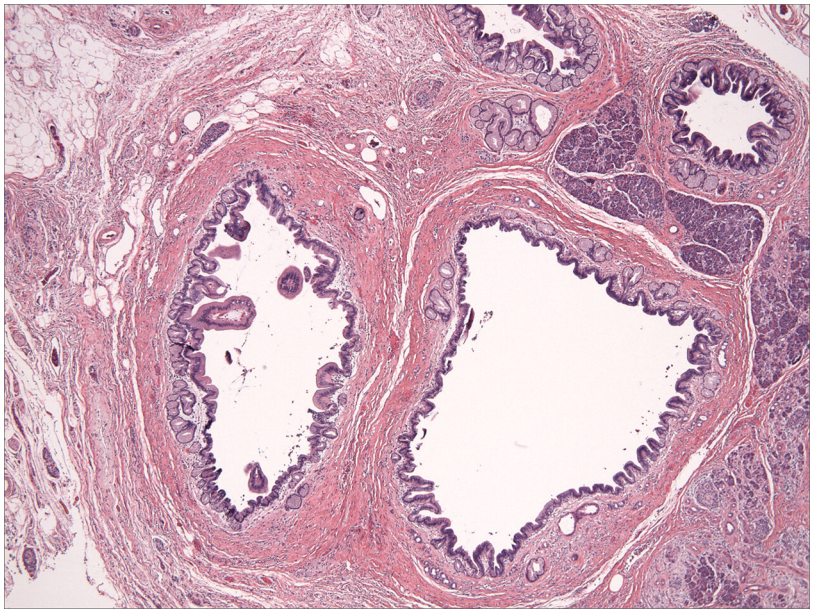

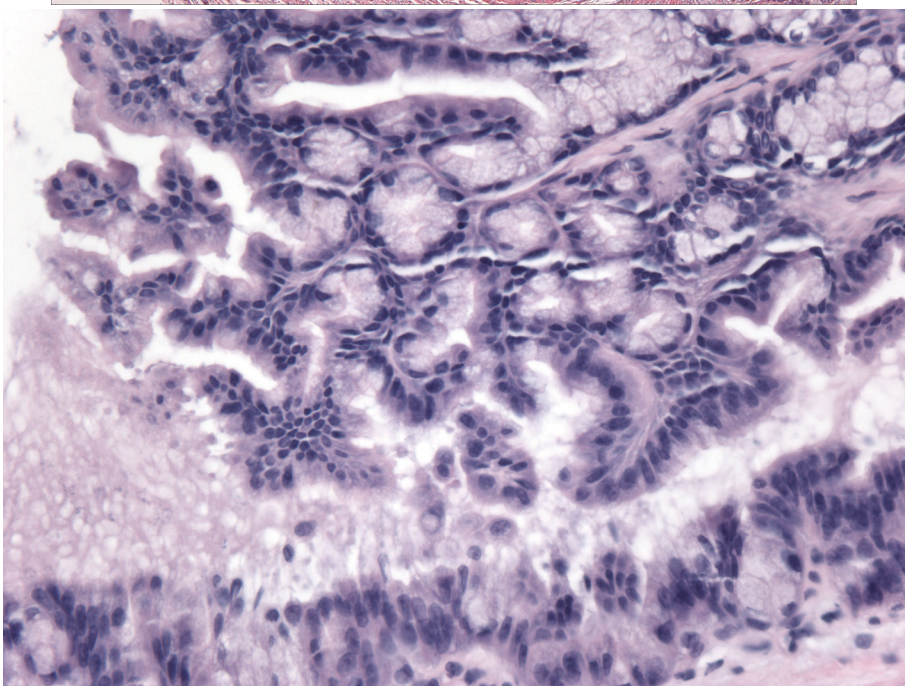

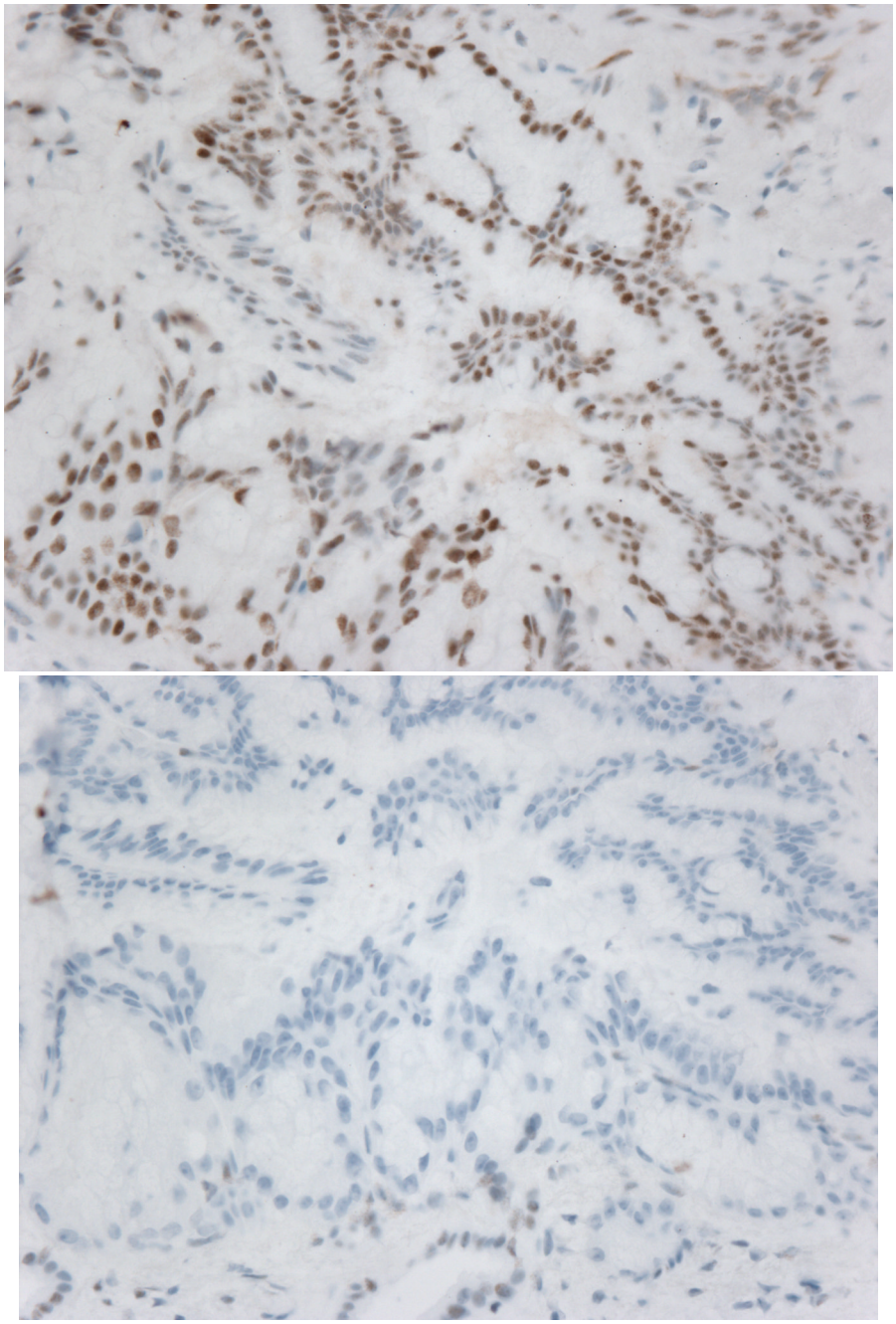

Figure 1.
Microphotographs of the IPMN A) Low-Power H&E staining B) High-power H&E staining C) Intact MLH1 immunohistochemical staining, D) Absence of MSH2 immunohistochemical staining