Mismatch Repair-Deficient Pancreatic Ductal Adenocarcinoma in a 30-Year-Old Male

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**Background**
Pancreatic cancer is uncommon before 45 years of age. Although pancreatic cysts are commonly identified incidentally following trauma, malignant tumors are rare. Disconnected-duct syndrome is a rare outcome of trauma.

**Summary**
A 30-year-old male smoker suffered mild abdominal trauma resulting in disconnected-duct syndrome. After multiple minimally invasive attempts to manage his pancreatitis over the course of one year with endoscopic-retrograde cholangiopancreatography (ERCP) and stents, the patient underwent a distal pancreatectomy and splenectomy. Pathology showed stage IIB pancreatic ductal adenocarcinoma (PDAC), which was found to be mismatch repair protein deficient (MMR-d), lacking nuclear expression of MSH2 and MSH6. No germline MMR gene mutation or double somatic mutations were identified; instead, only a single somatic MLH1 mutation did not explain the MSH2 and MSH6 deficiency. As the patient had no family history of Lynch syndrome-associated cancers, this was consistent with an uncommon sporadic (non-Lynch syndrome) MMR-d/MSI-H PDAC, and his only risk factor was smoking. Following a complicated recovery, he received adjuvant chemotherapy and then chemoradiation. After 26 months, he developed liver metastases and was started on pembrolizumab. Finally, after two six-week cycles, his CA19-9 had decreased from 442 to 167 U/mL.

**Conclusion**
Disconnected-duct syndrome is a rare sequela of trauma, usually severe in nature. While chronic pancreatitis is a risk factor for pancreatic cancer, this case illustrates the importance of considering malignancy as a possible underlying etiology for acute or subacute pancreatitis cases, regardless of the patient’s age. Although PDAC recurs in most patients, given the MMR-d/MSI-H phenotype of our patient’s tumor, checkpoint inhibition/immunotherapy is a viable treatment option with the potential for a durable response.

**Key Words**
pancreatic cancer; trauma; disconnected-duct syndrome; mismatch repair deficiency; microsatellite insufficiency
Case Description

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death in men and women and is almost always fatal. The peak incidence of pancreas cancer occurs between ages 65-69 in males and 75-79 in females. Pancreas cancer is rare before the age of 49, with a lifetime risk in this group of 0.1%. PDAC is usually detected due to symptoms. However, up to 16% of pancreatic tumors are incidentally discovered, usually due to urologic symptoms or staging for other cancers, and only rarely are they found due to trauma. We present the case of a 30-year-old male incidentally who developed disconnected-duct syndrome after mild abdominal trauma, which required surgical resection with pathology surprisingly revealing PDAC.

The patient is a 30-year-old male 1.5-pack-per-day smoker who suffered mild epigastric trauma while wrestling with coworkers, after which he developed progressive abdominal pain and clinical pancreatitis. A CT scan of the abdomen showed inflammation surrounding the body of the pancreas and a 1.6 cm low-attenuation area with associated upstream pancreatic duct (PD) dilation (Figure 1A and Figure 1B). Given the history of trauma in a young patient, this abnormality was suspected to represent a site of PD disruption. The patient underwent endoscopic-retrograde cholangiopancreatography (ERCP) that indicated PD disruption with contrast extravasation at this site, which was crossed with a wire and stented (Figures 1C–1E) with a resolution of his pain.

Figure 1. Imaging Findings Demonstrating Peripancreatic Inflammation and PD Disruption. Published with Permission

Contrast-enhanced axial CT images showing A) inflammatory changes at pancreatic body; and B) 1.6 cm area of hypoattenuation with associated upstream PD dilation. ERCP fluoroscopy images show extravasation at C) disrupted PD, which was D) crossed with wire and E) stented. Arrows indicate key findings for each image.
A repeat ERCP showed a persistent but smaller leak two months later, so the stent was replaced. After an additional three months, no further leak was seen on ERCP. The stent was placed for post-ERCP pancreatitis prophylaxis with plans for short interval removal; however, the patient developed pancreatitis requiring hospital admission. Imaging studies (CT, MRCP) suggested ongoing pancreatitis with a fluid collection at the suspected site of PD disruption. An endoscopic ultrasound (EUS) showed changes in the pancreas consistent with pancreatitis without focal mass. A repeat ERCP two months later again showed continued extravasation, so the stent was replaced. At this point, the patient was referred for distal pancreatectomy for management of disconnected-duct syndrome.

At the initial surgical consultation, a CT scan showed relative non-enhancement of the pancreas distal to the suspected disruption with the stent crossing a focal area of hypoattenuation (Figure 2A). Thirteen months after his initial presentation, the patient underwent an open distal pancreatectomy/splenectomy, which was difficult due to severe peripancreatic inflammation. Unexpectedly, his pathology revealed invasive adenocarcinoma with extensive signet-ring and mucinous features, 2 of 15 lymph nodes were involved by direct extension, and margins were negative (AJCC 8th edition pT2N1M0; Figure 2B).

Immunohistochemistry (IHC) revealed mismatch repair (MMR) protein deficiency in MSH2 and MSH6 (Figure 2C), suspicious for Lynch syndrome. Of note, the patient had no family history of cancer other than non-melanoma skin cancers and breast cancer in his maternal grandmother in her 70s. The patient was referred for a colonoscopy, which was normal. He was referred to a genetic counselor and had germline testing via the Ambry Genetics CancerNext panel, which was normal. His tumor tissue samples were sent for somatic testing via the Ambry Genetics TumorNext-Lynch™ panel (molecular findings summarized in Table 1). Overall, this testing confirmed microsatellite instability (MSI-H) and showed a somatic mutation in MLH1 but did not show germline MMR gene mutations or double somatic mutations. As is seen in most pancreatic cancers, a KRAS G12V mutation was seen. In addition, the patient enrolled in a multi-institutional oncology genomics protocol (the Oncology Research Information Exchange Network). Whole exome next-generation sequencing was performed of his germline DNA, which similarly did not show a pathogenic germline mutation predisposing him to cancer. Overall, the molecular findings showed that he did not have Lynch syndrome but rather a sporadic MMR-d PDAC.

Figure 2. Presurgical Imaging and Pathology. Published with Permission

Contrast-enhanced axial CT images showing A) PD stent crossing hypoattenuating lesion at site of PD disruption (arrow)—note resolution of peripancreatic inflammation; B) hematoxylin and eosin stain (20x) showing invasive pancreatic ductal adenocarcinoma (PDAC) (left side of image) and extensive mucinous and signet-ring differentiation (right side of image); C) immunohistochemical stains (40x) showing loss of nuclear MSH2 and MSH6 expression within malignant epithelial cells and preserved expression in infiltrating lymphocytes (top row), and retained MLH1 and PMS2 expression (bottom row).
The patient went on to receive six cycles of adjuvant gemcitabine and capecitabine. Given his node-positive disease and the high risk for recurrence, he underwent 5400 cGy of daily image-guided intensity-modulated radiation therapy in 27 fractions. Seven months later, he developed gastric outlet obstruction and was found to have a benign radiation-induced stricture of the duodenal bulb, which required surgical gastrojejunostomy. Twenty-six months after his initial operation, he developed multiple liver metastases and was started on pembrolizumab 400 mg IV every six weeks. After only two cycles, his serum CA19-9 had decreased from 442 to 167 U/mL.

**Discussion**

We present the intersection of multiple rare phenomena, with a sporadic MMR-d PDAC found in a 30-year-old who presented with trauma-induced pancreatitis. Risk factors for PDAC include advanced age, smoking, chronic alcoholism, chronic pancreatitis, obesity, diabetes, family history, and H pylori infection. Although he was a heavy smoker, he did not exhibit any other risk factors. It is well documented that chronic pancreatitis can increase the risk of pancreatic cancers and it may be difficult to discern adenocarcinomas from chronic pancreatitis radiographically. Trauma can predispose patients to chronic pancreatitis, however, the incidence of trauma-induced pancreatitis leading to PDAC is unknown. Before our patient’s mild abdominal trauma from wrestling, he had no symptoms or complaints. Disconnected-duct syndrome would more typically be seen after severe trauma, not mild trauma. We suspect that the tumor may have predisposed him to a fracture of his pancreas at that site, which was the inciting factor for pancreatitis, not the converse.

PDAC in the young (≤65 years old) is rare. In a single-institution cohort study of 3202 biopsy-proven PDAC cases from Memorial Sloan Kettering Cancer Center, 136 (4.4%) were ≤45 years old, with only 4 (0.1%) of these between 20 and 29 and 38 (1.1%) between 30 and 39 years old. Like our patient, the majority (90%) of this young cohort did not have a family history of pancreatic cancer. Similar to the elderly population, the minority (25.7%) of young PDAC patients presented with early-stage disease and underwent resection. However, compared to two recent national clinical trials showing a median of 18 to 22 months overall survival (OS) after resection of early-stage
PDAC, these patients fared better after resection (median OS 41.8 months), possibly due to fewer comorbidities.24 Unfortunately, early diagnosis is achieved the minority of the time since most are asymptomatic or display nonspecific, vague symptoms until late stages.14,17 Incidental findings requiring urgent follow-up are seen in up to one-third of patients undergoing CT scans for trauma, although pancreatic masses and cysts are seen only 0.3% and 0.2% of the time, respectively.25 There are multiple reports identifying pancreatic cysts,26–27 pseudocysts,28 and in particular solid pseudopapillary neoplasm (Franz’s tumor)29–32 following trauma; however, there is scant literature linking PDAC and trauma.

Interestingly, our patient’s tumor showed MMR-d with loss of nuclear MSH2 and MSH6 expression by IHC as well as microsatellite instability (MSI-H), which are typical of Lynch syndrome (LS).33,34 By age 70, 3.7% of LS patients will develop PDAC, compared to 1.5% for the general population.34 In our patient, however, germline analysis did not identify any hereditary cancer syndrome, and further molecular analysis of the tumor did not find double somatic mutations to explain the loss of MSH2 and MSH6 in the tumor. We did find a somatic MLH1 mutation, although this is not associated with loss of MSH2 and MSH6 by IHC. The literature varies on the exact proportion of MMR-d/MSI-H PDAC, but in several recent large series with modern detection techniques, 1 to 2% of all PDAC were found to have this phenotype.35 This is more often seen in medullary and acinar cell carcinomas of the pancreas,35 while our patient showed signet-ring cell and mucinous features with areas of ductal differentiation. There is debate35 on the proportion of MMR-d PDAC arising from germline mutations (i.e., LS), ranging from all (7 of 7 MMR-d)36 to none (0 of 4)37 and varies depending on the patient population tested and detection methods. Overall, while multiple mechanisms to achieve an MMR-d/MSI-H PDAC exist, the common phenotype result is a high mutational burden, postulated to lead to increased neoantigen presentation to infiltrating cytotoxic T cells.35 Checkpoint inhibition (immune therapy) is increasingly being utilized in MSI-H cancers, including PDAC,38–45 with proof of principle seen in a recent study in which the cohort of eight PDACs receiving pembrolizumab had two complete responses, three partial responses, and one with stable disease.

Conclusion

PDAC is rare in the young. Incidental radiographic findings at trauma or during workup for other conditions are common and should be critically evaluated for malignant potential. Pancreatitis may be caused by trauma, and chronic pancreatitis is a risk factor for PDAC. Here we report a case in which disconnected-duct syndrome and chronic pancreatitis following mild abdominal trauma uncovered the diagnosis of PDAC in a 30-year-old male. Since the patient’s tumor demonstrated an MMR-d/MSI-H phenotype, he was able to receive immunotherapy at the time of his recurrence.

Lessons Learned

It is important to closely follow patients with incidentally discovered pancreatic abnormalities, particularly those that develop pancreatitis, as this can be an early sign of malignancy, regardless of age.

References


