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Teaching Case

Long-Term Survival Following Chemoradiation in Locoregional Recurrent Germline *ATM* Mutated Pancreatic Ductal Adenocarcinoma

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Introduction

The role of radiation therapy in nonmetastatic pancreatic ductal adenocarcinoma (PDA)[1-4] is uncertain, with no definitive survival advantage over chemotherapy alone but lower odds of locoregional relapse. National Comprehensive Cancer Network guidelines[5] recommend multiagent chemotherapy potentially followed by chemoradiation therapy for patients with locally advanced PDA,[6,7] and these regimens confer progression-free survival and overall survival (OS) rates ranging from 3 to 20 months and 10 to 32 months (median OS, 20 months), respectively.[8,9] Locoregional recurrences in the pancreatic operative bed following resection are managed by enrollment in a clinical trial, systemic therapy with or without chemoradiation, or stereotactic body radiation.[5]

Tumor/somatic molecular profiling is recommended for patients with locally advanced, unresectable, and metastatic PDA to identify rare but potentially actionable molecular alterations. In addition, multigene germline testing is recommended for all patients, given that up to 20% have inherited genetic alterations.[10] This case report describes a patient with locoregional recurrent germline *ATM* mutated PDA with biallelic intratumoral *ATM* inactivation who sustained a complete and durable response with nonablative chemoradiation.

Case Report

A 64-year-old man with chronic hepatitis B infection had a pancreatic cystic lesion incidentally detected on screening abdominal ultrasound. Follow-up pancreatic protocol computed tomography (CT) scan showed 3.7 cm and adjacent 1.1 cm cystic lesions in the tail of the pancreas, abutting the splenic hilum, suspicious of pancreatic mucinous cystadenocarcinoma. Endoscopic ultrasound with fine needle aspiration showed 1 cyst with mildly atypical epithelial cells and the other with atypical glandular epithelium suggestive of a neoplastic mucinous cyst with at least high-grade dysplasia. Baseline CA 19-9 was 20 (0-54 U/mL). Family history was significant for the father and paternal uncle with PDA at ages 72 and 75, respectively. The patient underwent a robot-assisted distal pancreatectomy and splenectomy 2 months later. Pathology demonstrated a 4.5 cm invasive ductal

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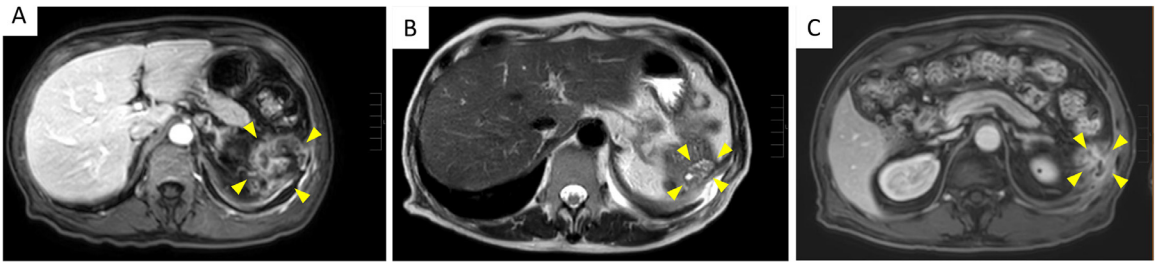

Figure 1 Magnetic resonance imaging at recurrence (A), after FOLFIRINOX (B), and at the completion of radiation (C). The area of locoregional recurrence showed a complete response following radiation treatment but with sequelae of a prior fundal gastric fistula to the abdominal wall and pleura.

adenocarcinoma, moderately differentiated with mucinous features and occasional signet ring cells arising in a cyst (likely intraductal papillary mucinous neoplasm), 0 of 8 lymph nodes involved in carcinoma, and negative margins (pT3pN0cM0 per American Joint Committee on Cance seventh edition, stage IIA). Germline genetic testing with a 13-gene panel (Ambry Genetics) identified a heterozygous pathogenic germline *ATM* mutation c.1339C>T (p.R447*). The patient declined adjuvant chemotherapy.[5]

Follow-up magnetic resonance imaging (MRI) of the abdomen 11 months post resection (Fig. 1A) revealed a new 3.2 × 2.3 cm cystic structure in the left upper quadrant in proximity to the gastric wall, suspicious of locoregional recurrence in the setting of a CA 19-9 rise to 671 U/mL from 4 U/mL. He was asymptomatic and declined biopsy and/or treatment.

The patient presented to the emergency department 6 months later with left-sided chest pain and dyspnea. CT chest showed a moderate to large loculated left pleural effusion, and ultrasound-guided thoracentesis yielded 1100 mL serosanguinous fluid with negative cytology. MRI of the abdomen (Fig. 1A) revealed a heterogeneously enhancing 4.3 × 4.7 × 4.4 cm soft tissue mass directly invading the gastric wall, left chest wall, and diaphragm. Because of a gastric fistula secondary to tumor invasion with left empyema, he underwent gastro-jejunal tube placement and video-assisted thoracic surgery converted to open decortication. He subsequently started chemotherapy with modified folinic acid, 5-fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) (FFOX) with an initial 20% dose reduction because of comorbidities. Chemotherapy was further dose reduced by another 20% because of toxicities, and 12 cycles were completed. CA 19-9 decreased from 1184 U/mL to 99 U/mL (Fig. 2). Chest CT and MRI of the abdomen postchemotherapy (Fig. 1B) revealed decreased but persistent 3.5 × 2.2 cm soft tissue mass at the posterior aspect of the gastric fundus with supra- and infrahilar diaphragmatic extension. Tumor molecular profiling (Tempus xT) showed *ATM* p.R447*

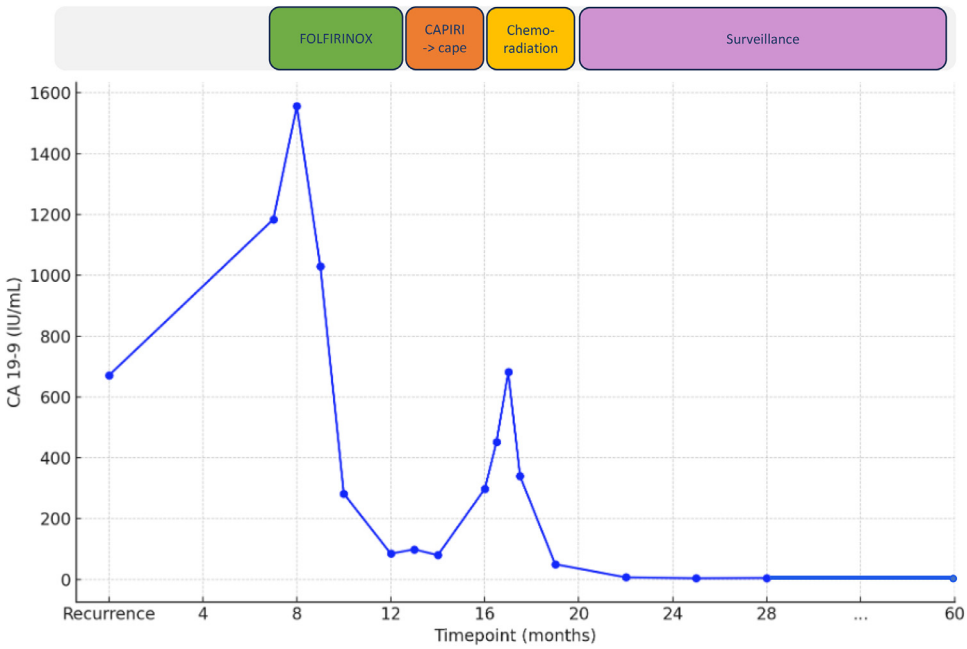

Figure 2 Clinical pattern of response to treatment with CA 19-9 levels corresponding to the timeline showing therapy.

stop-gain loss-of-function (LOF) mutation (variant allele fraction 46.9%), *KRAS* p.G12D gain-of-function mutation, *ATM* p.T1953P missense variant mutation (10.4%), microsatellite stable, and tumor mutational burden 6.3 m/Mb.

The pancreatic cancer multidisciplinary tumor board recommended definitive chemoradiation therapy given the radiosensitizing potential of the pathogenic germline ATM mutation and advised against surgical resection because of high morbidity and risk of recurrence. The patient had concerns about radiation toxicity and instead began deescalated chemotherapy with capecitabine plus irinotecan for a cycle, followed by capecitabine for 2 cycles, but the CA 19-9 increased from 92 to 298 U/mL in a month.

Because of the CA 19-9 rise, he went on to receive intensity modulated radiation therapy to 50.4 Gy in 28 fractions with concurrent capecitabine 825 mg/m^2 twice daily, Monday through Friday, on radiation days without acute toxicities. Nonablative radiation was chosen because of concerns for enhanced normal tissue radiosensitivity. The CA 19-9 normalized from 682 U/mL at the start of chemoradiation to 50 U/mL on completion of treatment with resolution of the abdominal pain. He did not experience chronic radiation-related toxicities and continues monitoring without evidence of disease 4 years later (Fig. 1C).

Discussion

Radiation therapy for PDA treatment is controversial, but molecular determinants of clinical benefit are poorly characterized. In unselected patients with locally advanced unresectable PDA, the median OS following chemotherapy with and without chemoradiation therapy is approximately 20 months.[9,11] The 2-year local progression-free survival is less than 25% following moderate doses (50-54 Gy) of radiation.[12,13] This case highlights that patient selection may create a more promising future for radiation therapy as a therapeutic option.

PDA is a multifactorial genetic disease and is associated with several inherited syndromes for which predisposing genes have been identified, including Peutz-Jeghers syndrome (*STK11/LKB1*), familial atypical multiple mole and melanoma syndrome (*CDKN2A),* hereditary breast, ovarian, prostate, and pancreatic cancer syndrome (*BRCA1* and *BRCA2*), ataxia-telangiectasia mutated (*ATM)*, Juvenile polyposis syndrome (*SMAD4/BMPR1A*), Lynch syndrome (mismatch repair MLH1, MSH2, MSH6, and PMS2), Li-Fraumeni syndrome (*TP53),* hereditary pancreatitis (*PRSS1/SPINK1*), as well as cancers associated with loss/mutations of *PALB2* and *NBN*.

The *ATM* gene plays a critical role in the DNA damage response system. It was first identified in 1995 during the evaluation of the autosomal recessive ataxia-telangiectasia syndrome, which occurs in 1/40,000 to 1/300,000 live births[14] and is characterized by progressive cerebellar ataxia, oculomotor apraxia, telangiectasias of the conjunctiva and skin, immunodeficiency, radiosensitivity, and increased rate of malignancies, in particular lymphoma and leukemia earlier in life.[15] Germline *ATM* heterozygosity, which is reported in 0.5% to 1% of the population,[16,17] does not cause any of the classic ataxia-telangiectasia syndrome manifestations but has been estimated to confer a 2- to 4-fold increased risk of female breast cancer compared with the general population[18,19] as well as a 4-fold increased risk of prostate cancer[20,21] and PDA (cumulative risk 9.5% by age 80 noncarriers).[22,23]

Roberts et al[22] first reported the association between pathogenic *ATM* variants and PDA in 2012, observing pathogenic variants in 3% of patients with familial PDA. These findings have been replicated in subsequent studies,[24] revealing that as many as 2.3% of patients with PDA unselected for family history will harbor germline pathogenic *ATM* mutations with an absolute risk estimated at 5% to 10% for developing PDA.[25] The total prevalence of *ATM* mutations (germline or somatic) in PDA is approximately 6.4% (range, 1%-34%).[26] Among patients carrying germline *ATM* mutations, as many as 44% may have a second-hit somatic *ATM* mutation, conferring loss of heterozygosity (LOH).[27] The necessity of LOH for therapeutic sensitivity to platinum agents or radiation therapy is unknown.

Several large population studies evaluated the rate of specific *ATM* point mutations and associated cancer predisposition. Our patient had a germline p.R447* mutation, splice site c.1339C>T (p.Arg447Ter), which is located in the coding exon 9 of the *ATM* gene and results from a cytidine to thymidine substitution at nucleotide position 447 predicted to introduce a premature translation termination codon that results in nonsense-mediated messenger RNA decay. LOF variants in ATM are known to be pathogenic. This pathogenic variant has been found more frequently in families with ataxia-telangiectasia syndrome from the Druze population, suggesting a founder effect. To our knowledge, this single nucleotide variant type has not been reported in a patient with PDA.

The *ATM* gene, located on chromosome 11q22-23, encodes an apical phosphatidylinositol 3'-kinase—related serine/threonine kinase that plays a key role in the maintenance of genome integrity by responding to and repairing DNA double-strand breaks. In the presence of DNA damage, such as that induced by ionizing radiation or chemotherapy, the ATM kinase acts at the transition between the G1 and S phase by exerting itself as the main transducer in the DNA double-strand break repair process. ATM also functions at the G2 to M transition. In the absence of ATM, cells can accumulate somatic mutations. In some cases, heterozygous germline ATM mutations result in an abnormal protein rather than producing no detectable ATM kinase, causing a dominant negative effect

by interfering with the function of the product of the normal allele.[28] However, we are not aware that this dominant negative effect has been described for this variant.

Radiosensitivity is a hallmark of ataxia-telangiectasia syndrome caused by biallelic germline *ATM* inactivation.[29,30] Ionizing radiation potently induces double-strand breaks, and ataxia-telangiectasia cells fail to arrest the cell cycle after DNA damage, thus reducing the opportunity for the repair of the genome before DNA replication or mitosis.[31] Preclinical data demonstrated that the knockdown of *ATM* results in radiosensitization.[32,33] In contrast, exposure of nonmutated cells to ionizing radiation results in cell cycle arrest, and ATM appears to be critical for the induction of DNA repair.

Yet, the clinical implications of heterozygous *ATM* inactivation have remained poorly understood. In a retrospective analysis of 1085 patients at Memorial Sloan Kettering Cancer Center with a variety of advanced cancers, including PDA, harboring somatic or germline *ATM* mutations, of whom 357 received radiation therapy during their disease course, genetic inactivation of *ATM* was associated with improved radiotherapeutic efficacy.[34] The 2-year cumulative incidence of irradiated tumor progression was 13.2% versus 27.5% for tumors harboring an *ATM* LOF mutation versus a variant of unknown significance allele, respectively (hazard ratio, 0.51; $P = .001$). Tumors with biallelic LOF were more likely to be controlled with radiation than those with monoallelic LOF, with a 2-year cumulative incidence of irradiated tumor progression of 3.4% and 16.9% for biallelic and monoallelic *ATM* LOF mutated tumors, respectively. There was no statistically significant interaction between *ATM* genotype and cancer subtype in multivariable regression analysis. Additionally, there was no statistically significant difference in tumor control observed for germline versus somatic LOF mutations ($P = .74$). A notable finding, however, was the observation that *ATM* inactivation was predictive of improved irradiated tumor control in *TP53* wild-type but not in *TP53* mutant tumors. The mechanism by which *TP53* mutation attenuates radiosensitivity in ATM-deficient tumors remains unclear. Our patient's cancer was *TP53* wild-type and had a likely pathogenic second-hit mutation in *ATM* denoted p.T1953P. Although this specific variant is not characterized, another missense variant at this amino acid position (T1953I) is classified as likely pathogenic by 2 reputable laboratories.[35] *ATM* p.T1953I is kinase-impaired, and genetic and pharmacologic evidence suggests that ATM kinase inactivation confers a distinct phenotype from complete *ATM* loss in preclinical models.[35,36] It is reasonable to speculate that kinase impairment, rather than LOH, may impact sensitivity to radiation.

Our case is unique because it provides an example of an enhanced radiosensitive tumor phenotype among PDA patients with germline *ATM* mutations with biallelic loss in the tumor, without the potential for late normal tissue complications, and offers potential applications to the personalization of radiation treatment. Despite its relatively common use in PDA treatment, radiation therapy has not yet entered the era of precision medicine. The data presented here provide novel evidence that biallelic *ATM* inactivation can potentially serve as a biomarker to better select patients who may benefit from radiation therapy.

Conclusions

PDA remains one of the most lethal solid malignancies with few therapeutic options. Comprehensive germline and somatic genetic analysis in patients with PDA identify therapeutically relevant alterations. Mutational defects in genes that regulate the DNA damage response system, such as *ATM*, are opportunities to explore targeted treatments and radiation therapy. This remarkable response obtained from chemoradiation in a patient with a germline *ATM* mutation with biallelic inactivation in the tumor, if supported by further studies, could offer an alternative therapeutic option to a subset of PDA patients who are not operative candidates to induce lasting remissions.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

AI and/or AI-Assisted Technologies were not used in the writing process.

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