Pancreatic Ductal Adenocarcinoma with Germline *ATM* Mutation and Somatic *NRG1* Fusion: A Rare Dual Genomic Context

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Case Presentation

A 33-year-old male initially presented with acute pancreatitis and was found to have a cystic lesion in the pancreatic tail. His presentation was complicated by steatorrhea, weight loss, and pancreatic insufficiency. One year after his initial presentation, serial endoscopic ultrasound revealed a 1.9-cm pancreatic head mass with new irregular hepatic lesions. Liver biopsy confirmed moderately differentiated adenocarcinoma of pancreaticobiliary origin, and biopsy of the pancreatic lesion confirmed moderately differentiated pancreatic ductal adenocarcinoma (PDAC).

At diagnosis, serum biomarkers were atypical for PDAC, demonstrating markedly elevated alpha-fetoprotein (AFP 284.6 ng/mL) with normal CA19-9 and CEA levels. Comprehensive tumor profiling revealed a *KRAS* wild-type tumor harboring an *NRG1-ATP1B1* fusion as well as a germline *ATM* alteration (*ATM* c.4019_4029del11). Family history was notable for breast, prostate, and pancreatic cancers.

The patient was initially treated with modified FOLFIRINOX, with 16 cycles ultimately completed. Oxaliplatin was discontinued after cycle 12 due to peripheral neuropathy and fatigue. Imaging after chemotherapy demonstrated decreased size of both the pancreatic mass and hepatic lesions. Following evidence of biochemical progression, treatment was transitioned to Zenocutuzumab, a bispecific HER2/HER3 antibody targeting *NRG1* fusion-driven tumors. The patient completed 12 cycles of Zenocutuzumab with concurrent local therapy, including microwave ablation of liver metastases. Follow-up imaging has since demonstrated no viable liver lesions and no detectable pancreatic mass, and tumor markers have remained within normal limits.

Discussion

Pancreatic ductal adenocarcinoma (PDAC) is associated with poor survival and limited targeted treatment options, making identification of actionable molecular drivers critically important. This case illustrates an exceptionally rare genomic context in PDAC, involving the coexistence of a germline pathogenic *ATM* variant and a somatic *NRG1* fusion in a *KRAS* wild-type tumor. *ATM* alterations disrupt the DNA damage response and may influence sensitivity to DNA-damaging therapies such as platinum-based chemotherapy, whereas *NRG1* fusions function as oncogenic drivers through activation of HER2/HER3 signaling and downstream MAPK and PI3K/AKT pathways.

NRG1 fusions occur in approximately 0.1-0.5% of PDAC cases and represent a clinically actionable subset. Zenocutuzumab, a bispecific HER2/HER3 antibody targeting *NRG1*-driven signaling, has demonstrated promising clinical activity. In this patient, transition from

FOLFIRINOX to Zenocutuzumab resulted in sustained disease control with resolution of radiographically evident disease.

Overall, this case highlights the importance of recognizing rare genomic subsets of PDAC with distinct therapeutic vulnerabilities and underscores the value of comprehensive germline and somatic molecular profiling to identify actionable alterations that may expand precision treatment options in a disease with otherwise limited targeted therapies.