

Case Report

Metastasis-Specific APC Alteration and Nuclear β -Catenin Accumulation in IPMN-Associated Pancreatic Ductal Adenocarcinoma: Genomic Analysis of Matched Precursor, Carcinoma, and Liver Metastasis—A Case Report

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Abstract

Background: The molecular changes associated with the progression of intraductal papillary mucinous neoplasm (IPMN) to pancreatic ductal adenocarcinoma (PDAC) and distant metastasis remain incompletely understood. **Case Presentation:** A man in his late 70s underwent pancreaticoduodenectomy and partial hepatectomy for a pancreatic head tumor with synchronous liver metastasis. Histology showed a 4.5 cm moderately differentiated PDAC arising in an IPMN with high-grade dysplasia (pT3N1M1). Genomic analysis of the IPMN, PDAC, and liver metastasis identified *KRAS* p.G12D, *CDKN2A* deletion, and *GNAS* p.R201H in the IPMN; additional *SMAD4* p.R361C in the PDAC; and *KRAS* p.G12D, *CDKN2A* deletion, *SMAD4* p.R361C, and *APC* p.R1450Ter in the liver metastasis. The *APC* alteration was confirmed by targeted sequencing and was accompanied by loss of heterozygosity at the *APC* locus. β -Catenin showed membranous expression in the IPMN and PDAC, but nuclear accumulation in the liver metastasis. **Discussion:** The shared *KRAS*, *CDKN2A*, and *SMAD4* alterations support a common clonal origin of the PDAC and metastatic tumors. The absence of a detectable *GNAS* alteration in the liver metastasis and the presence of a metastasis-specific *APC* alteration are compatible with, but do not prove, branching evolution and selection of a metastatic subclone. **Conclusions:** This case shows a metastasis-specific heterozygous *APC* truncating alteration with loss of heterozygosity, accompanied by nuclear β -catenin accumulation, in an IPMN-associated PDAC.

Keywords: pancreatic ductal adenocarcinoma; intraductal papillary mucinous neoplasm; liver metastasis; APC; β -catenin; clonal evolution; case report

Academic Editor: Chunsheng Kang

Received: 25 June 2026

Revised: 16 July 2026

Accepted: 22 July 2026

Published: 23 July 2026

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with a poor prognosis [1–3]. Because early disease is often clinically silent, many patients present with lo-

cally advanced or metastatic tumors. The presence of metastatic disease at diagnosis and genomic studies of pancreatic cancer evolution suggest that metastatic competence may be acquired during tumor progression before clinical detection [4]. The liver is one of the most frequent sites of distant spread and is a major determinant of mortality in patients with PDAC [5].

Metastasis is a multistep and heterogeneous process involving dissemination from the primary tumor, survival in the circulation, adaptation to a foreign microenvironment, and colonization of the distant organ [6,7]. Genomic analyses have shown that metastatic PDAC generally retains major driver alterations from the primary tumor, while additional alterations and microenvironmental adaptations may emerge during progression [8,9]. Previous genomic studies comparing primary PDACs and matched metastases have shown that metastatic lesions usually retain major driver alterations from the primary tumor, with additional patient-specific or site-specific changes. However, most studies have focused on invasive PDAC and its metastases. Fewer reports have examined the matched precursor lesion, associated invasive carcinoma, and synchronous distant metastasis from the same patient. Such cases may help clarify whether metastatic clones arise through simple linear accumulation of alterations or through branching evolution and subclonal selection.

Here, we report a case of intraductal papillary mucinous neoplasm (IPMN)-associated PDAC with synchronous liver metastasis in which matched IPMN, invasive PDAC, and liver metastasis were analyzed separately. This case addresses the clonal relationship among the three lesions and describes a metastasis-specific heterozygous APC truncating alteration accompanied by nuclear β -catenin accumulation in the liver metastasis.

2. Case Presentation

2.1. Clinical and Pathological Findings

A man in his late 70s presented with abdominal discomfort. Physical examination was unremarkable, and his medical history included hypertension and diabetes mellitus. Laboratory findings were as follows: aspartate aminotransferase/alanine aminotransferase, 85/71 IU/L (reference range, 0–40 IU/L); alkaline phosphatase, 585 U/L (35–105 U/L); total bilirubin, 5.19 mg/dL (0.2–1.1 mg/dL); and gamma-glutamyl transferase, 896 IU/L (8–73 IU/L). Abdominal computed tomography revealed an irregular enhancing lesion involving the pancreatic head, distal common bile duct, and second portion of the duodenum, with diffuse biliary dilatation. An ill-defined enhancing mass was also identified in the left hepatic lobe. Imaging findings suggested a pancreatic solid and cystic malignancy with synchronous liver metastasis.

The patient underwent pylorus-preserving pancreaticoduodenectomy and partial hepatectomy. Histopathologic examination revealed an IPMN with high-grade dysplasia (grade 3) and an associated 4.5 cm moderately differentiated tubular-type PDAC (Figure 1A,B). Lymphatic and perineural invasion were present. Metastatic carcinoma was identified in two of nine regional lymph nodes, and the hepatic lesion was confirmed as metastatic PDAC (Figure 1C). The pathologic stage was pT3N1M1.

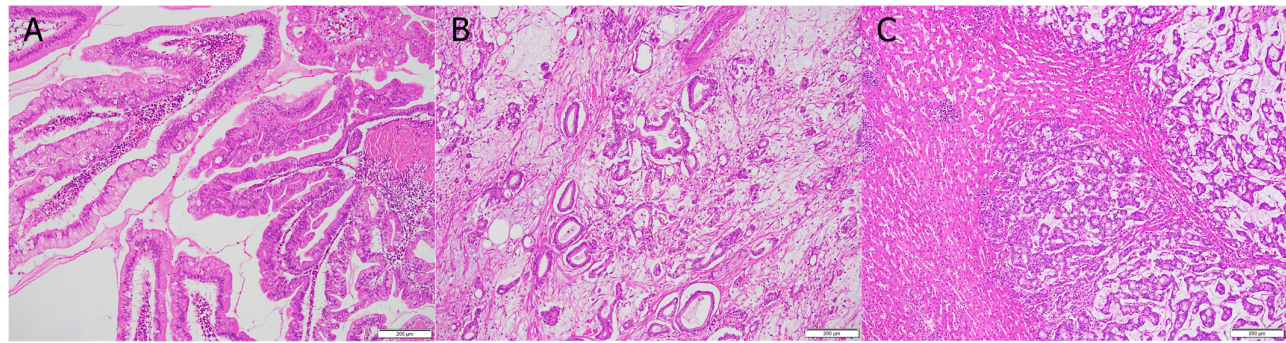


Figure 1. Histopathologic features of the matched lesions. (A) Intraductal papillary mucinous neoplasm with high-grade dysplasia (grade 3). The lesion showed irregular papillary projections lined by mucin-producing epithelial cells, with irregular branching and cribriform architecture, accompanied by loss of nuclear polarity and nuclear pleomorphism. (B) Moderately differentiated tubular-type pancreatic ductal adenocarcinoma. The tumor consisted of haphazardly distributed infiltrative glands within desmoplastic stroma. (C) Metastatic pancreatic ductal adenocarcinoma in the liver. The hepatic lesion showed infiltrating atypical ductal structures within normal hepatic parenchyma. Hematoxylin and eosin-stained section; original magnification, $\times 200$; scale bars, 200 μm .

2.2. Genomic Analysis and Immunohistochemical Findings

To characterize molecular changes associated with invasion and metastasis, whole-exome sequencing was performed separately on the IPMN, PDAC, and liver metastasis, with matched blood and normal pancreatic duct tissue used as controls (Supplementary Method S1). The IPMN harbored *GNAS* p.R201H, *KRAS* p.G12D, and *CDKN2A* deletion. The PDAC retained *GNAS* p.R201H, *KRAS* p.G12D, and *CDKN2A* deletion and additionally harbored *SMAD4* p.R361C. The liver metastasis retained *KRAS* p.G12D, *CDKN2A* deletion, and *SMAD4* p.R361C, showed no detectable *GNAS* alteration, and harbored a truncating *APC* p.R1450Ter alteration (Table 1 and Supplementary Tables). This *APC* alteration found by whole-exome sequencing (46/76 reads; VAF, 60.5%) was independently confirmed by targeted sequencing using the Ion Torrent Oncomine Comprehensive Assay v3 (478/721 reads; VAF, 66.3%). Copy-number and loss of heterozygosity (LOH) analysis demonstrated LOH at the *APC* locus, supporting loss of the wild-type *APC* allele and bi-allelic *APC* inactivation in the liver metastasis. Immunohistochemistry for β -catenin (a mouse monoclonal antibody, clone 14) was interpreted according to cellular localization, as described in Supplementary Method S1. Nuclear accumulation was observed only in the liver metastasis, whereas the IPMN and PDAC showed predominantly membranous expression (Figure 2). For clarity, Table 1 summarizes Tier I/II alterations based on the AMP/ASCO/CAP variant interpretation framework. An expanded list of additional filtered somatic variants is provided in the Supplementary Tables.

Table 1. Genetic alterations of IPMN ¹, PDAC ², and liver metastasis.

Genes	IPMN	PDAC	Liver Metastasis	Variant Type
<i>GNAS</i> p.R201H	+	+	–	Activating hotspot
<i>KRAS</i> p.G12D	+	+	+	Activating hotspot
<i>CDKN2A</i> deletion	+	+	+	Likely oncogenic/functional alteration
<i>SMAD4</i> p.R361C	–	+	+	Likely oncogenic/functional alteration
<i>APC</i> p.R1450Ter	–	–	+	Truncating

¹ IPMN, intraductal papillary mucinous neoplasm; ² PDAC, pancreatic ductal adenocarcinoma; +, indicates detected; –, not detected.

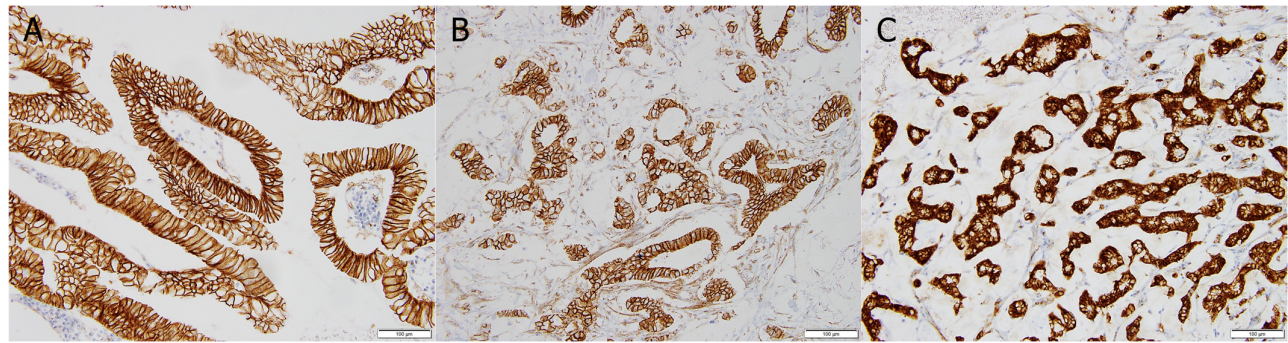


Figure 2. Immunohistochemical staining for β -catenin (a mouse monoclonal antibody, clone 14) in the matched lesions. Staining was interpreted according to cellular localization. IPMN (A) and primary PDAC (B) show predominantly membranous expression, whereas the liver metastasis (C) shows nuclear β -catenin accumulation in approximately 80% of tumor cells. Scale bars, 100 μ m.

2.3. Clinical Follow-Up

The patient received three cycles of palliative gemcitabine. He was subsequently admitted because of peritoneal dissemination, and chemotherapy was discontinued because of intolerance. He was transferred to a hospice care facility for supportive management. The report was prepared in accordance with the CARE guidelines.

3. Discussion

Matched analysis of the three lesions provides a molecular snapshot of progression from a noninvasive precursor to invasive and metastatic disease. The IPMN with high-grade dysplasia harbored *GNAS* p.R201H, *KRAS* p.G12D, and *CDKN2A* deletion, which were retained in the PDAC, together with an additional *SMAD4* p.R361C alteration. *KRAS*, *GNAS*, and *CDKN2A* are well-established early driver alterations in IPMN, whereas abnormalities involving *SMAD4* and other tumor suppressor genes are enriched in invasive lesions [10–13]. A multi-region genomic study of neoplastic pancreatic cysts and associated carcinomas found that *SMAD4* and *TGFBR2* alterations were frequently restricted to the invasive component and documented complex clonal dynamics during malignant transformation [14]. In our case, the liver metastasis retained *KRAS* p.G12D, *CDKN2A* deletion, and *SMAD4* p.R361C, showed no detectable *GNAS* alteration, and harbored a metastasis-specific *APC* p.R1450Ter alteration accompanied by LOH at the *APC* locus, supporting loss of the wild-type *APC* allele. The observed pattern is compatible with a common clonal origin of the PDAC and liver metastasis, followed by possible branching evolution and subclonal selection. However, this interpretation remains provisional [15]. The absence of a detectable *GNAS* alteration in the liver metastasis may reflect selection of a subclone without *GNAS* alteration, but technical factors, including tumor cellularity, sequencing coverage, sampling bias, or assay sensitivity, cannot be excluded. In addition, an alternative linear-evolution model with failure to detect *GNAS* in the metastatic sample remains possible.

The preservation of major driver alterations between the PDAC and liver metastasis is consistent with prior genomic studies. Makohon-Moore et al. demonstrated marked concordance of known driver mutations among multiple untreated metastases from individual patients with pancreatic cancer [16]. In a paired analysis of synchronous primary PDACs and hepatic metastases, Yang et al. reported that synchronous primary PDACs and liver metastases were genomically similar, but the metastases showed additional changes in copy number, gene expression, metabolism, and the tumor microenvironment [17]. Recently, Loveček et al. compared whole-exome profiles of 20 matched primary PDACs and site-specific metastases, and observed broadly similar frequencies of *KRAS*,

TP53, *CDKN2A*, and *SMAD4* alterations, together with site- and patient-specific genomic differences [18]. The *APC* alteration in our case should not be interpreted as a recurrent or universal driver of PDAC liver metastasis. Rather, it may represent a private alteration enriched or selected in the hepatic metastatic clone.

APC is a core component of the β -catenin destruction complex and negatively regulates canonical Wnt signaling [19]. Loss or impairment of APC function can stabilize β -catenin, promote its nuclear translocation, and activate transcriptional programs related to proliferation, survival, and cellular plasticity. APC alterations have been reported in a subset of PDACs, and epigenetic silencing of APC has also been described during pancreatic carcinogenesis [20,21]. However, experimental APC knockdown in PDAC cell-line models does not necessarily induce β -catenin nuclear localization or canonical Wnt pathway activation, indicating that the relationship between APC loss and β -catenin signaling in PDAC may be context-dependent [21].

In the present case, the truncating *APC* p.R1450Ter alteration was identified only in the liver metastasis. The alteration was detected by whole-exome sequencing with 46 alternate reads among 76 total reads (VAF, 60.5%) and by targeted sequencing with 478 alternate reads among 721 total reads (VAF, 66.3%). Copy-number and LOH analysis demonstrated LOH at the *APC* locus, supporting loss of the wild-type *APC* allele in the metastatic lesion. Thus, the *APC* p.R1450Ter alteration with LOH provides genomic evidence compatible with *APC* inactivation in the hepatic metastatic clone. Nuclear β -catenin accumulation was observed in the same metastatic lesion, whereas the IPMN and primary PDAC showed predominantly membranous β -catenin expression. This finding raises the possibility that β -catenin pathway-related changes emerged in the metastatic clone (Figure 3). Experimental PDAC studies have likewise shown that enhanced β -catenin signaling can promote epithelial–mesenchymal transition, migration, invasion, tumor growth, and metastatic behavior through regulators such as IQGAP1, WDR1, and FAM83A [22–24]. These observations provide biological context for the nuclear β -catenin accumulation observed in the metastatic lesion. Nevertheless, although the *APC* p.R1450Ter alteration with LOH supports loss of the wild-type *APC* allele in the metastatic lesion, nuclear β -catenin accumulation is not specific for APC-mediated pathway activation. In this case, downstream canonical Wnt/ β -catenin target genes, including *MYC*, *CCND1*, *AXIN2*, *BIRC5*, *BCL2*, and *MMP* family members, were not assessed by qPCR, Western blotting, RNA sequencing, or other functional assays. Therefore, these findings should be interpreted as hypothesis-generating and do not establish a causal role of *APC* alteration in liver metastasis or functionally proven Wnt/ β -catenin pathway activation [25].

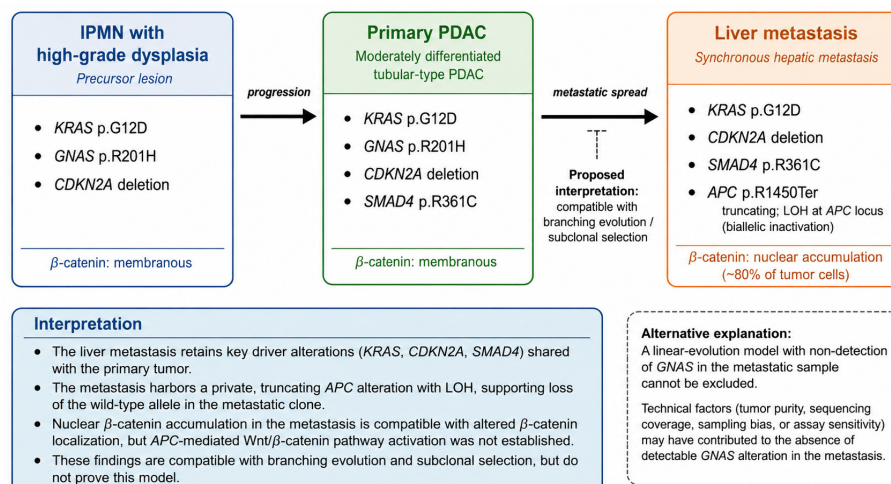


Figure 3. Schematic summary of matched lesions and proposed clonal evolution.

This report has several limitations. First, it describes a single patient and therefore cannot establish the prevalence or clinical significance of metastasis-specific APC alterations in PDAC. Second, spatial intratumoral heterogeneity and differences in tumor purity among the IPMN, PDAC, and liver metastasis may have influenced mutation detection. Third, although APC p.R1450Ter was independently confirmed by targeted next-generation sequencing and LOH at the APC locus supported loss of the wild-type APC allele, functional APC-mediated Wnt/ β -catenin pathway activation was not directly demonstrated. Fourth, nuclear β -catenin accumulation is supportive of altered β -catenin localization but is not specific for APC-mediated Wnt/ β -catenin pathway activation. In addition, downstream Wnt/ β -catenin target genes were not evaluated by RNA- or protein-based functional assays; therefore, functional activation of the canonical Wnt pathway was not directly demonstrated. Fifth, the absence of a detectable GNAS mutation in the metastasis may have either a biological or technical explanation. Finally, the three synchronously resected specimens provide a cross-sectional view of tumor evolution rather than longitudinal sampling.

4. Conclusions

In conclusion, this matched three-stage case demonstrates shared driver alterations among an IPMN, associated PDAC, and synchronous liver metastasis, together with a metastasis-specific APC p.R1450Ter alteration with LOH at the APC locus and nuclear β -catenin accumulation in the liver metastasis. These findings are compatible with, but do not prove, branching evolution and subclonal selection. Although the APC alteration with LOH raises the possibility of altered β -catenin signaling in the metastatic lesion, nuclear β -catenin accumulation is not specific for APC-mediated pathway activation, and functional Wnt/ β -catenin pathway activation was not established. Additional studies with complete multi-region sequencing, formal phylogenetic analysis, and functional pathway assessment are required.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jcm15155782/s1>, Method S1: Whole exome sequencing and immunohistochemistry; Table S1: Whole exome sequencing data of IPMN; Table S2: Whole exome sequencing data of PDAC; Table S3: Whole exome sequencing data of liver metastasis. References [26–36] are cited in the Supplementary Materials.

Author Contributions: Conceptualization, C.G.W., K.J., J.K., E.-G.K. and O.-J.L.; methodology, C.G.W., K.J. and J.K.; formal analysis, K.J. and J.K.; investigation, C.G.W.; data curation, C.G.W.; writing—original draft preparation, C.G.W. and O.-J.L.; writing—review and editing, C.G.W., K.J., J.K., E.-G.K. and O.-J.L.; supervision, E.-G.K. and O.-J.L. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (RS-2020-NR049557).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Chungbuk National University Hospital (protocol code 2024-05-021; date of approval: 1 July 2024).

Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper and the accompanying images.

Data Availability Statement: The genomic and histopathological data presented in this study are available from the corresponding author upon reasonable request. The data are not publicly available because they contain potentially identifiable patient-specific genomic information.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

IPMN Intraductal Papillary Mucinous Neoplasm
PDAC Pancreatic Ductal Adenocarcinoma
LOH Loss of Heterozygosity

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