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Case Report

POLD1 Mutations May be Effective Predictive Biomarker for the Response to Durvalumab plus Gemcitabine and Cisplatin in Metastatic Cholangiocarcinoma: A Case Report

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Abstract

Biliary tract cancers have a poor prognosis with limited treatment options. While immune checkpoint inhibitors have recently shown modest survival benefits as standard first-line therapy, reliable predictive biomarkers for the response to treatment remain lacking. This case report describes a 61-year-old female diagnosed with metastatic intrahepatic cholangiocarcinoma who was treated with durvalumab plus cisplatin and gemcitabine. Next-generation sequencing showed the presence of the *POLD1* R689W mutation, microsatellite stability, and low tumor mutational burden. The best response was complete response, and progression-free survival was 13.8 months. A comprehensive review of bioinformatic databases showed that *POLD1* mutations have rarely been identified in cholangiocarcinoma. Functional studies of this mutation in cholangiocarcinoma are warranted.

Keywords: Biliary tract cancer, case report, immune checkpoint inhibitors, *POLE/POLD1*, predictive biomarker

Introduction

Biliary tract cancers (BTCs) represent a heterogeneous group of malignancies, with cholangiocarcinoma being the most common. Approximately 64%–78% of patients present with unresectable or metastatic disease.[1,2] Immune checkpoint inhibitors (ICIs) have become standard therapy for advanced BTCs, and the TOPAZ-1 trial reported progression-free survival (PFS) and overall survival in patients who did and did not receive durvalumab of 7.2 and 5.7 months ($P = 0.001$) and 12.8 and 11.5 months ($P = 0.021$), respectively.[3] The KEYNOTE-966 trial also showed that adding ICIs improved survival.[4] However, predictive biomarkers remain limited.[5,6] The findings of this case report suggest that mutant *POLD1* may be an effective predictive biomarker for the response to durvalumab plus cisplatin and gemcitabine in patients with

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metastatic intrahepatic cholangiocarcinoma. *In vitro* and *in vivo* functional studies were warranted.

Case Report

A 61-year-old female patient with an Eastern Cooperative Oncology Group performance status of 0 was incidentally found to have a 5-cm hepatic mass during routine employee health screening in May 2023. A physical examination revealed no pale conjunctiva, icteric sclera, spider angiomata, palpable abdominal mass, Murphy's sign, caput medusae, or extremity pitting edema. Her medical history included hypertension, thyroid nodular goiter status post thyroidectomy, uterine leiomyoma, and chronic calculous cholecystitis. In June 2023, she underwent hepatic lobectomy of the S1/2/3/4 lobes, and the pathology report showed cholangiocarcinoma, pT3N1, with focal involvement of hilar soft tissue margin under microscopy (R1 resection). The patient declined adjuvant chemotherapy.

In February 2024, 8 months post-surgery, follow-up imaging revealed disease progression with widespread metastases involving the left second rib, bilateral lungs, mediastinum, hepatic hilar lymph nodes, para-aortic lymph nodes [Figure 1a], T9 vertebral body, and sacrum, with the T9 lesion associated with spinal cord compression.

The patient underwent emergent spinal surgery on February 6, 2024, consisting of T7-T9 laminectomy, tumor debulking, and T8-T10 posterior spinal instrumentation. Comprehensive genomic profiling analysis identified the *POLD1* R689W mutation. Additional biomarker findings included microsatellite stability and low tumor mutational burden (2 mutations/megabase). Detailed molecular profiling data are shown in Table 1.

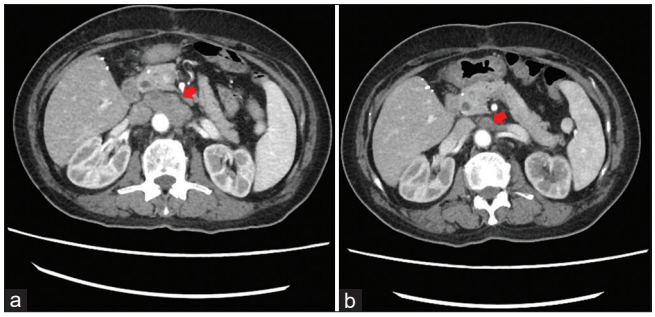

Figure 1: Abdominal computed tomography before and after durvalumab plus cisplatin and gemcitabine. (a) Initial imaging before treatment, para-aortic lymphadenopathy was present. (b) After 3.5 months, the posttreatment response revealed complete remission. Red arrow: para-aortic lymphadenopathy

After clinical stabilization, the patient commenced first-line treatment with durvalumab plus cisplatin and gemcitabine on February 24, 2024, completing nine cycles of combination therapy followed by durvalumab maintenance monotherapy. Due to financial constraints, durvalumab was administered at a reduced dose of 960 mg rather than the standard 1500 mg dose used in the TOPAZ-1 trial. Follow-up abdominal computed tomography (June 2024) showed nearly complete remission of para-aortic lymphadenopathy after 3.5 months of treatment [Figure 1b].

On April 14, 2025, MRI revealed disease progression with vertebral metastases involving T8-T9, causing spinal cord compression, and worsening sacral metastases extending to S2-S4 segments. The overall survival in our patient to date is 17.6 months ongoing until the last follow-up. The clinical course and treatment response are summarized in Figure 2.

Discussion

The findings of this case report suggest that in patients with metastatic intrahepatic cholangiocarcinoma, *POLD1* mutations may be an effective predictive biomarker for the response to durvalumab plus cisplatin and gemcitabine. The best tumor response in our patient was complete remission, PFS was 13.8 months, and overall survival to date is 17.6 months, ongoing. Although *POLD1* mutations are rare in BTCs, *in vitro* and *in vivo* functional validation studies are needed.[7]

DNA polymerase epsilon (POLE) and delta (POLD1) are essential enzymes involved in DNA replication and repair, with mutations potentially associated with genomic instability and immunotherapy response.[8] *POLD1* encodes the catalytic subunit of DNA polymerase δ, with mutations potentially impairing proofreading function and increasing genomic instability.[9] Recent evidence suggests that *POLE*/*POLD1* mutations may predict favorable responses to ICIs across multiple cancer types, even without high TMB or MSI-H

Table 1: Comprehensive molecular profiling results

Genomic findings	HGVS variant	Variant chromosomal position
POLD1 R689W	NM_002691.2:c. 2065C>T (p.R689W)	chr19:50912834
ARID1A Q1519fs*8	NM_006015.4:c. 4555del (p.Q1519Rfs*8)	chr1:27101267-27101268
KRAS G13E	NM_004985.3:c. 38_39delinsAA (p.G13E)	chr12:25398280-25398281
PIK3C2B R1612*	NM_002646.3:c. 4834C>T (p.R1612*)	chr1:204394051
RB1 Y446*	NM_000321.2:c. 1338C>G (p.Y446*)	chr13:48953735
Biomarker findings		
Microsatellite status	MS-Stable	
Tumor mutational Burden	2 Muts/Mb	

HGVS: Human Genome Variation Society

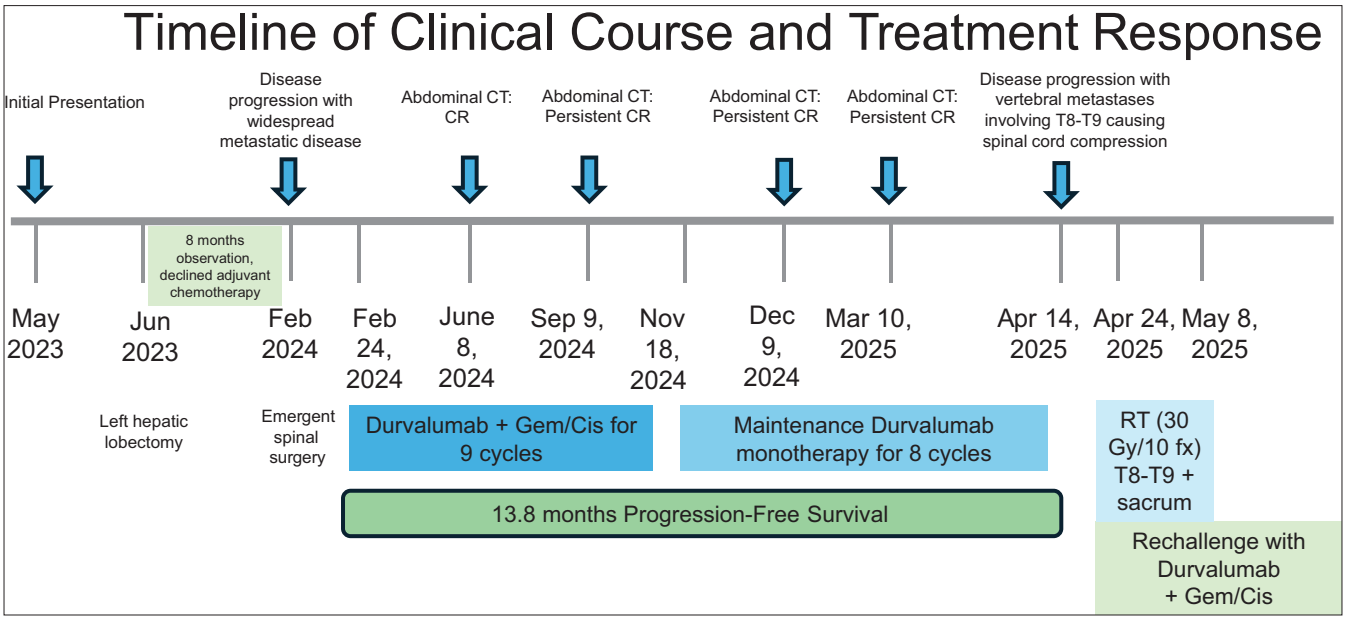

Figure 2: Timeline of clinical course and treatment response. First-line therapy with durvalumab plus cisplatin and gemcitabine for a total of nine cycles was administered, followed by maintenance with durvalumab alone per month for a total of eight doses. Progression-free survival was 13.8 months

status.[10] Ma *et al*. reported that *POLE*/*POLD1* mutations may be potential molecular markers for predicting immunotherapy efficacy in various cancers.[11]

The *POLD1* R689W mutation has been identified in colorectal cancer and hepatocellular carcinoma;[12,13] however, it has rarely been identified in BTC. We comprehensively reviewed the annotations of *POLD1* mutations in BTC in the COSMIC (cancer.sanger.ac.uk/cosmic), OncoKB (www.oncokb.org/), and cBioPortal (www.cbioportal.org/) informatic databases. According to OncoKB, the *POLD1* R689W mutation is a likely oncogenic mutation with loss-of-function and that it is located in the polymerase domain of the protein. The database reports that *POLD1* R689W has been identified in colorectal cancer and that *POLD1* mutations have been associated with a positive effect on the response to immune checkpoint therapy in colorectal cancer. In cBioPortal, a total of 23 *POLD1* mutations were detected from 2683 pan-cancer analyses in the TCGA database. Among these 23 mutations, only the *POLD1* T473W mutation has been identified in cholangiocarcinoma, and its function is unknown. As above, the *POLD1* R689W mutation was not reported in cholangiocarcinoma. Mertz *et al*. reported that most *POLD1* mutations are found in MMR-deficient tumors and do not show a noticeable concentration in the exonuclease domain and that most of these mutations affect conserved amino acid residues in the DNA polymerase motifs.[14] Daee *et al*. reported that the *POLD1* R689W mutation encodes an error-prone DNA polymerase and causes a catastrophic increase in spontaneous mutagenesis.[15] *In vitro* and *in vivo* functional studies of this mutation in cholangiocarcinoma are needed.

Wang *et al*. demonstrated that across multiple tumor types, patients harboring *POLE*/*POLD1* mutations had significantly prolonged overall survival when treated with ICIs compared to their wild-type counterparts (median overall survival: 34 vs. 18 months), an effect observed even in microsatellite-stable tumors. Although their cohort included 213 cholangiocarcinoma patients, of whom 11 (5.2%) carried *POLE*/*POLD1* mutations, their survival analyses included patients with all types of cancer without specific subgroup analysis focusing on cholangiocarcinoma.[10] Our patient had the *POLD1* R689W mutation and was associated with a good response and prolonged survival. Functional studies of this point mutation in cholangiocarcinoma are limited, and future studies are warranted.

The dosage of treatment is another important point. Our patient received a reduced dose of durvalumab (960 mg) instead of the standard 1500 mg dose as used in the TOPAZ-1 trial. Huang *et al*. reported that a durvalumab dose < 1000 mg was associated with potentially inferior outcomes compared to a higher dose (1000–1500 mg).[16] Despite this suboptimal dosing, our patient achieved an exceptional therapeutic response, suggesting that *POLD1* mutations may serve as positive predictive biomarkers for the response to ICIs plus chemotherapy.

One possible explanation for the enhanced immunotherapy response observed in *POLD1*-mutated tumors, despite low TMB and MSS status, is that DNA repair deficiencies may lead to increased tumor-infiltrating lymphocytes and upregulation of immune checkpoint molecules, thereby creating a microenvironment conducive to ICI efficacy.[11]

In summary, we report a patient with metastatic intrahepatic cholangiocarcinoma and *POLD1* R689W mutation who was treated with durvalumab plus cisplatin and gemcitabine as the first-line therapy. The best tumor response was complete

remission, and PFS was 13.8 months. A comprehensive review of bioinformatic databases showed that the *POLD1* R689W mutation has rarely been identified in intrahepatic cholangiocarcinoma. *POLD1* mutations have been associated with a favorable prognosis across several cancer types in previous studies. Future researches to validate the function of these mutations are needed, especially for BTC.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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