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CASE REPORT

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Comprehensive clinical and genetic characterization of hyperprogressive biliary tract cancer during PD-1 blockade monotherapy: case report and literature review

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Abstract

Background Some genetically characterized patients show the rapid disease progression during immune checkpoint inhibitors (ICIs) monotherapy, a phenomenon known as hyperprogressive disease (HPD).

Case presentation Herein we report a relevant case of biliary tract cancer (BTC) that initially responded to gemcitabine plus oxaliplatin (GEMOX) and PD-1 blockade but subsequently developed HPD in the process of PD-1 blockade maintenance therapy, leading to death within two weeks. Genomic analysis revealed mutations in *CDKN2A*, *PIK3CA*, *KRAS* and *EPHA2* in both baseline and hyperprogressive plasma and tumor samples. Notably, higher KRAS mutation abundance was observed in plasma and ascites after disease progression.

Conclusions These findings suggest a potential association between these negative genes especially *KRAS* mutation and HPD. Therefore, administration of PD-1 blockade monotherapy in this subgroup of patients harboring *KRAS* mutation should be performed with caution. Further studies are warranted to confirm these results and explore the correlation between genomic mutations and HPD.

Keywords Hyperprogressive disease, Biliary tract cancer, *KRAS* mutation, Immunotherapy

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Background

BTC represents a spectrum of highly aggressive and heterogeneous adenocarcinomas, accounting for only 3% of all gastrointestinal malignancies [1]. Although standard chemotherapy based on the cisplatin-gemcitabine (CisGem) combination is the cornerstone of this malignancy, its therapeutic efficacy is often limited. Advances in molecular profiling have identified promising targets such as isocitrate dehydrogenase-1 (*IDH1*), activating serine threonine-protein kinase B-raf kinase (*BRAF*), neurotrophic receptor tyrosine kinase (*NTRK*) mutations, fibroblast growth factor receptor (*FGFR*) translocation, receptor tyrosine-protein kinase erbB-2 (*ERBB2*) amplification, and high-level microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) phenotypes [2]. Recent developments in immunotherapy, particularly ICIs targeting PD-1 and programmed cell death ligand-1 (PD-L1), have shown potential. Results from the KEYNOTE-158 and KEYNOTE-028 studies achieved objective response rates (ORRs) of 6–13% for advanced BTC, regardless of PD-L1 expression, but provided no survival benefits [3]. In contrast, combining ICIs with chemotherapy has yielded more promising outcomes with extended survival and manageable toxicity profiles, which is recognized as an effective and safe first-line strategy for advanced BTC [4].

In our phase II single-arm study (NCT03486678), camrelizumab combined with GEMOX achieved an ORR of 54% and a disease control rate (DCR) of 89%, with median progression-free survival (PFS) and overall survival (OS) of 6.2 months and 12.1 months, respectively [5]. Even so, we still found one special case harboring *KRAS* mutation that responded to combined treatment but failed in PD-1 blockade maintenance therapy rapidly. This phenomenon is known as HPD [6, 7]. HPD is not only referred to as increased tumor growth but also as a rapid poor prognosis [8], which is a deleterious consequence of ICIs monotherapy that accelerates disease progression. We believe that it is necessary to share this case to investigate the potential mechanism of immunotherapy failure. Simultaneously, identifying biomarkers to predict HPD is important. This article aims to provide a clear framework for precision medicine in BTC using our comprehensive analysis based on genomics of advanced BTC combined with treatment response.

Case presentation

A 64-year-old man was diagnosed with advanced gallbladder cancer (GBC) via liver biopsy on May 31, 2018. Magnetic resonance imaging (MRI) of the upper abdomen revealed a large primary liver mass, multiple metastatic nodules in the right liver lobe, and abdominal lymph node metastases. The patient enrolled in a phase II single-arm study (NCT03486678) and received 5 cycles of GEMOX (gemcitabine 800 mg/m^2 i. v., d1, d15, q2w; oxaliplatin 85mg/m^2 iv, d2, d16, q2w) plus PD-1 blockade (camrelizumab 3 mg/kg iv, d1, d15, q2w). Evaluating indicators, including the detection of tumor markers and imageological diagnosis, were carried out every two cycles according to the Response Evaluation Criteria in Solid Tumors version 1.1. Within the six-month combined treatment period, we observed a persistent decrease in tumor size, which could be recognized as partial response (PR) (Fig. 1A). However, during the first

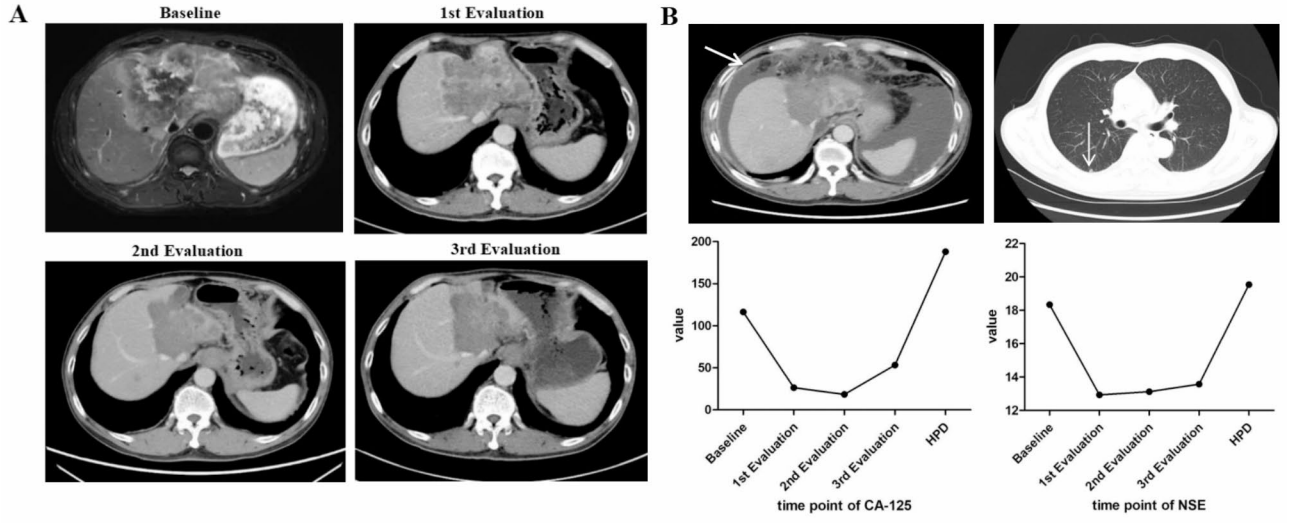

Fig. 1 Changes of radiography and tumor markers at different period of treatment. (**A**) Imaging examinations (CT or MRI scans) performed at baseline and at first, second, third evaluation (every 2 treatment cycles as one round of radiographic evaluation), showed approximately 23%, 31% and 32% decreases in sum of diameters of target lesions compared with baseline imaging. (**B**) CT scans performed at fourth evaluation when deveioping HPD to camrelizumab revealed the changes in ascites and pulmonary metastases, accompanied by rapidly increasing NSE and CA-125 levels. The red arrows indicate tumor lesions

Table 1 Timeline of the patient's clinical course

Date	Event
May 31, 2018	Diagnosis of advanced gallbladder cancer (GBC).
June 1, 2018	Initiation of GEMOX and camrelizumab.
November 30, 2018	Partial response observed after six months of combination therapy.
December 15, 2018	Transition to PD-1 blockade maintenance therapy.
January 14, 2019	Development of HPD with malignant ascites and pulmonary metastases.
January 28, 2019	Patient's death.

cycle of PD-1 blockade maintenance therapy, the patient developed abdominal swelling and tenderness. Imaging revealed new malignant ascites and pulmonary metastases, along with elevated levels of neuron-specific enolase (NSE) and carbohydrate antigen 125 (CA125), indicating progressive disease (PD) (Fig. 1B). The patient deteriorated rapidly and succumbed to HPD within two weeks. To facilitate understanding, a timeline summarizing the patient's clinical course is presented in Table 1. This visual representation outlines key treatment milestones, evaluations, and the development of HPD.

To investigate the potential mechanism of immunotherapy failure, findings based on genomics (Table 2) showed that *CDKN2A*, *PIK3CA*, *KRAS* and *EPHA2* mutated genes were detected in both the baseline and hyperprogressive plasma and tumors, *KRAS* mutations were high (7.97%) in plasma after disease progression compared to the *EPHA2*, *CDKN2A*, *PIK3CA* mutated genes, which declined to 5.89%, 5.16%, and 4.98%, respectively. Consistent with the results of peripheral blood tests, the highest abundance (35.39%) of *KRAS* mutations was detected in ascites, suggesting its role in HPD. In addition, we also made a peripheral blood gene detection that only presented with the *CDKN2A* (0.71%), *PIK3CA* (1.55%) and *EPHA2* mutation (0.74%) when first assessed effective. It can be assumed that there is a possible relationship between HPD and higher circulating levels of *KRAS* mutations.

Genomic analysis methods

We performed next-generation sequencing (NGS) using a panel of 437 cancer-related genes (Geneseeq Prime™, Nanjing Geneseeq Technologies Inc.) in a Clinical Laboratory Improvement Amendments-certified and College of American Pathologists-accredited clinical testing laboratory (Nanjing Geneseeq Technology Inc., Nanjing, China). Sample processing and sequencing analysis procedure were performed according to previously described methods [9, 10]. Briefly, genomic DNA was extracted from FFPE tumor biopsy samples using the QIAamp DNA FFPE Tissue Kit (QIAGEN, Dusseldorf, Germany) following the manufacturer's instructions. Genomic DNA was extracted from leukocyte using the DNeasy Blood and Tissue Kit (QIAGEN, Dusseldorf, Germany) as normal control. Libraries preparations were performed using the KAPA Hyper Prep Kit (KAPA Biosystems, Wilmington, MA, USA) with optimized protocols. Libraries with different indices were pooled for targeted enrichment with Geneseeq Prime™ targeted NGS panel and xGen Lock-down Hybridization and Wash Reagents Kit (Integrated DNA Technologies), and then were sequenced on a Novaseq6000 platform (Illumina).

Sequencing data processing

Trimmomatic was used for FASTQ file quality control [11]. Qualified data (QC above 15 and without extra N bases) was then mapped to human genome Hg19 using Burrows-Wheeler Aligner(BWA-mem, v0.7.12; https://github.com/lh3/bwa/tree/master/bwakit).Local realig nment around indels and base quality score recalibration were performed using the Genome Analysis Toolkit (GATK 3.4.0; https://software.broadinstitute.org/gatk/) and duplicates were removed using Picard. VarScan2 was applied to detect single-nucleotide variations (SNVs) and INDELs. SNVs were filtered out if the mutant allele frequency (MAF) was less than 1% for tumor tissue. Copy number variations (CNVs) were called by FACETS (Fraction and Allele-Specific Copy Number Estimates from Tumor Sequencing) [12] to obtain tumor purity-, ploidy-, and clonal heterogeneity-adjusted copy number data. Gene fusions were identified by FACTERA [13]. All fusions were manually confirmed using the Integrative Genomics Viewer (IGV). Microsatellite Instability (MSI) was estimated based on 158 indel sites in the Geneseeq Prime panel. Tumor mutational burden (TMB) was calculated as the total number of nonsynonymous mutations divided by the length of the genomic target region.

Table 2 The gene detection analysis during treatment

Time		2018.06.01 (baseline)		2019.01.14 (HPD)	
Gene		Plasma	Tumor Tissue	Plasma	Tumor Tissue
CDKN2A	missense mutation	7.96%	2.36%	5.16%	-
PIK3CA	missense mutation	7.87%	3.90%	4.98%	21.93%
EPHA2	frameshift mutation	6.57%	3.73	5.89%	18.24%
KRAS	missense mutation	4.90%	-	7.97	35.39%

Discussion

ICIs, including PD-1/PD-L1 and cytotoxic T lymphocyte antigen 4 (CTLA-4) antibodies, have revolutionized cancer therapy by offering durable efficacy and mild toxicity across various malignancies [14]. However, low response rates and HPD remain significant challenges, especially in BTC. HPD, characterized by accelerated tumor growth and poor survival, has been associated with ICI monotherapy [15]. Criteria for HPD include [16]: [1] time to treatment failure (TTF) from the beginning of ICI therapy to an interruption with no reason within 2 months (TTF ≤ 2 months) [2], tumor growth rate (TGR) twice greater post-treatment than before (TGR ≥ 2), and [3] tumor growth kinetics (TGK) that objective lesions change in unit interval determined by evaluation of the largest diameters according to RECIST (TGK ≥ 2). Herein we report a relevant case of BTC that initially responded to gemcitabine plus oxaliplatin (GEMOX) and PD-1 blockade but subsequently developed HPD in the process of PD-1 blockade maintenance therapy, leading to death within two weeks (TTF ≤ 2 months).

As HPD has been recognized to cause adverse outcomes, it is critical to identify relevant biomarkers that can predict the possibility of HPD occurring after immunotherapy. Here, we reviewed and summarized the known biomarkers [15], including tumor cell biomarkers [*MDM2/4* amplification, *EGFR/BRCA2* mutation, MMR deficiency, and tumor mutational burden (TMB)], tumor microenvironment biomarkers [activated Treg cells, exhausted T cells, inactive dendritic cells, myeloid-derived suppressor cells (MDSCs), M2 macrophages, cancer-associated fibroblasts (CAFs), insensitivity to IFN-γ and other compensatory immune checkpoints in T cells], laboratory biomarkers [increased absolute neutrophil count (ANC) and C-reactive protein (CRP)], and clinical indicators (regional recurrence in an irradiated field, more than two metastatic sites, and age ≥ 65 years), which provide different approaches for predicting HPD patients and ICI efficacy. In summary, HPD occurrence depends on the cancer type and immune microenvironment.

In this case, *KRAS* mutation was associated with rapid disease progression during PD-1 blockade maintenance therapy. In order to interpret the treatment outcome, genomic analyses were performed before, during and after treatment respectively. The results showed first decreasing and then increasing trend in abundance of *CDKN2A*, *PIK3CA*, *KRAS* and *EPHA2* mutations. Among of them, a higher abundance of *KRAS* mutation in the plasma and ascites was detected after the disease progression. From this, it can be assumed that these genes predicted poor prognosis and *KRAS* mutation was likely to be an important molecular mechanism underlying HPD. Genomic alterations such as *CDKN2A* and *PIK3CA* mutations may exacerbate immunotherapy failure by activating oncogenic pathways [17, 18]. Simultaneously, the correlation between *ARID1A* and *PI3K/AKT* pathway alterations may lead to activation of *PIK3CA* mutation [19]. Novel findings regarding *EPHA2*, a member of the tyrosine kinase family that is frequently mutated in intrahepatic cholangiocarcinoma (ICC) and is closely associated with lymph node metastasis [20]. Notably, *KRAS* mutation was reported to be refractory to ICI therapy. Kang et al. [7] found two genomic characteristics (*KRAS* mutation and chromosomal instability [CIN] tumors) are associated with resistance to immunotherapy. *KRAS*-altered tumors exhibit low tumor-infiltrating lymphocyte (TIL) density and immunogenicity, contributing to ICI resistance. Chen et al. [6] also reported that genomic alterations in advanced BTC could be an effective method to predict specific prognosis and immunotherapy outcomes, and a single *KRAS* mutation seemed to have a less favorable response to immunotherapy compared to *KRAS-TP53* co-mutations in advanced cholangiocarcinoma (CHOL). In view of the opinions mentioned above, alterations in *CDKN2A*, *PIK3CA* and *EPHA2* seemed to suggest a poor prognosis, whereas *KRAS* mutation correlated with ICI-related HPD more directly. Another point that needs to be explained is why this *KRAS*-mutated BTC patient responded to immunochemotherapy but failed the PD-1 blockade maintenance therapy. The nature of the immune microenvironment prior to therapy may play an important role in the occurrence of HPD. Following immunochemotherapy treatments, resistant clones were unleashed because of their ability to escape immunological surveillance when ICIs were administered solely [21]. Therefore, PD-1 blockade monotherapy in this subgroup of patients harboring *KRAS* mutation should be performed with caution, although these results need to be confirmed in more clinical trials.

Conclusions

This case highlights a rare instance of HPD in a *KRAS*-mutated BTC patient undergoing PD-1 blockade maintenance therapy. Comprehensive genomic analysis revealed higher circulating levels of *KRAS* mutation in plasma and ascites, implicating this mutation in HPD development. Future clinical trials should investigate these findings further to establish predictive biomarkers and optimize treatment strategies. Recent studies have expanded the therapeutic landscape for BTC. For example, targeted therapies against IDH1, FGFR, and HER2 have shown promise in clinical trials [22, 23]. Immunotherapy combinations, such as ICIs with chemotherapy or tyrosine kinase inhibitors (TKIs), are also under investigation for their synergistic effects [24, 25]. Given the elevated risk of HPD with ICI monotherapy, combination therapies

remain preferable for patients with high-risk genomic profiles, but to take notice of safety and tolerance [26, 27].

Abbreviations

ICIs	Immune checkpoint inhibitors
BTC	Biliary tract cancer
GEMOX	Gemcitabine plus oxaliplatin
HPD	Hyperprogressive disease
CisGem	Cisplatin-gemcitabine
IDH1	Isocitrate dehydrogenase-1
BRAF	Activating serine threonine-protein kinase B-raf kinase
NTRK	Neurotrophic receptor tyrosine kinase
FGFR	Fibroblast growth factor receptor
ERBB2	Receptor tyrosine-protein kinase erbB-2
MSI-H	High-level microsatellite instability
dMMR	Deficient mismatch repair
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
ORR	Objective response rate
DCR	Disease control rate
PFS	Progression-free survival
OS	Overall survival
GBC	Gallbladder cancer
MRI	Magnetic resonance imaging
PR	Partial response
PD	Progressive disease
NSE	Neuron specific enolase
CA125	Carbohydrate antigen 125
CTLA-4	Cytotoxic T lymphocyte antigen 4
TTF	Time to treatment failure
TGR	Tumor growth rate
TGK	Tumor growth kinetics
TMB	Tumor mutational burden
MDSCs	Myeloid-derived suppressor cells
CAFs	Cancer-associated fibroblasts
ANC	Absolute neutrophil count
CRP	C-reactive protein
GP	Gemcitabine and platinum–based therapy
ICC	Intrahepatic cholangiocarcinoma
CIN	Chromosomal instability
TIL	Tumor infiltrating lymphocyte
CHOL	Cholangiocarcinoma
NGS	Next-generation sequencing
SNVs	Single-nucleotide variations
MAF	Mutant allele frequency
CNVs	Copy number variations
IGV	Integrative genomics viewer

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Author contributions
All authors contributed to the conception and design, selection and acquisition of data, drafting or revision of the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Data availability
Sequence data that support the findings of this study have been deposited in the declarations section with the reference number of ethics approval 2017-SR-291.

Declarations

Ethics approval and consent to participate
The study was approved by relevant regulatory and independent ethics committee of the First Affiliated Hospital with Nanjing Medical University and done in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The written informed consent for the publication of clinical details and images was obtained from the patient and his family members. Patient identification and other personal information that could be used to reveal the identity of the patient were protected. The case details and images were approved for publication by the First Affiliated Hospital of Nanjing Medical University.

Consent for publication
Yes.

Competing interests
The authors declare no competing interests.

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