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CASE REPORT

Remarkable Response to Pembrolizumab in Metastatic Cancer of Unknown Primary

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ABSTRACT

Background: **Cancer of unknown primary (CUP) is aggressive, with limited options and poor prognosis. Mismatch repair-deficient (dMMR) CUP is rare, and reports of its response to immunotherapy are scarce.**
Case Presentation: **A 52-year-old man presented with extensive liver metastases and severe hepatic dysfunction (bilirubin 14 mg/dL, ECOG 3). The primary site could not be identified; biopsy showed poorly differentiated carcinoma. Immunohistochemistry showed loss of MSH2, MLH1, and PMS2 (dMMR). Pembrolizumab produced rapid improvement, with bilirubin normalizing within three months and complete response by six months, sustained beyond 30 months.**
Conclusions: **Pembrolizumab can achieve durable responses in dMMR CUP despite advanced disease and poor performance.**
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KEYWORDS

cancer of unknown primary, mismatch repair deficiency, dMMR, pembrolizumab, case report

LIST OF ABBREVIATIONS

ALP - alkaline phosphatase
ALT - alanine aminotransferase
AST - aspartate aminotransferase
CEA - carcinoembryonic antigen
CUP - cancer of unknown primary
dMMR - mismatch repair-deficient
ECOG - Eastern Cooperative Oncology Group
FDG PET-CT - fluorodeoxyglucose positron emission tomography-computed tomography
IHC - immunohistochemistry
MMR - mismatch repair
MSI - microsatellite instability
MSI-H - microsatellite instability-high
PD-1 - programmed cell death-1
SUVmax - maximum standardized uptake value

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INTRODUCTION

Cancer of unknown primary (CUP) is a histologically confirmed metastatic malignancy for which the primary site cannot be identified despite comprehensive work-up. CUP accounts for fewer than 5% of all malignancies and is generally characterized by aggressive behavior and poor prognosis, with a median overall survival historically under one year [1,2]. Treatment options are limited; empiric platinum-based chemotherapy yields low response rates, and most patients progress on first-line therapy [1,3]. Molecular profiling and immunohistochemistry have gained an increasingly important role in guiding treatment in this population [4].

Mismatch repair deficiency (dMMR), detected by loss of MMR protein expression on immunohistochemistry, and its molecular correlate microsatellite instability-high (MSI-H) identify tumors that accumulate a high burden of somatic mutations, rendering them immunogenic and highly responsive to immune checkpoint inhibitors [5]. Pembrolizumab, a PD-1 inhibitor, received FDA approval in May 2017 for MSI-H/dMMR solid tumors progressing on prior therapy - the first tissue-agnostic approval of an anticancer agent [6], with efficacy confirmed across tumor types in several trials [7].

The dMMR/MSI-H phenotype and the response to pembrolizumab in CUP specifically remain poorly characterized, as CUP was not a distinct cohort in these trials. Here, we present a case of a dramatic and durable complete response to pembrolizumab in a patient with dMMR CUP who presented with extensive metastatic disease, severe hepatic dysfunction, and poor performance status.

CASE PRESENTATION

A 52-year-old male presented to our hospital with abdominal pain, anorexia, weight loss, and jaundice. Physical examination revealed scleral icterus and hepatomegaly. The ECOG performance status was 2. His medical, family (including family cancer history), and psychosocial history were non-contributory, and no relevant germline genetic information was available.

Laboratory findings:
Initial laboratory testing showed total bilirubin 10 mg/dL, direct bilirubin 7.8 mg/dL, AST 135 U/L, ALT 25 U/L, and ALP 2618 U/L. Among tumor markers, CEA was elevated at 52.4 ng/mL (normal: < 5 ng/mL), while CA 19-9, AFP, and other markers were within normal limits.

Imaging findings:
FDG PET-CT (June 10, 2022) revealed an 11 x 8 cm irregular mass in the left hepatic lobe (SUVmax 15.3) with unclear borders toward the gastric lesser curvature and pancreas, multiple necrotic-appearing liver metastases, and metastatic abdominal and left parasternal lymph nodes (Table 1).

Endoscopic evaluation:
Upper gastrointestinal endoscopy and colonoscopy performed to identify the primary site revealed no findings suggestive of malignancy.

Pathological examination:
An ultrasound-guided tru-cut biopsy of a hepatic lesion demonstrated poorly differentiated carcinoma. Immunohistochemical staining was positive for Pan-CK, MOC-31, and GATA3, with focal positivity for CDX2 and PAX8. CK7, CK20, TTF-1, p63, Hepar-1, Melan-A, DOG-1, PSA, calretinin, LCA, and neuroendocrine markers (synaptophysin, chromogranin) were negative. The Ki-67 proliferation index was 25%. The immunohistochemical profile did not permit definitive identification of the primary site but was considered most consistent with a pancreatobiliary or gastrointestinal origin; the pathologist recommended multisystem evaluation.

First-line treatment and response:
In June 2022, given the presumed pancreatobiliary origin, FOLFOX chemotherapy was initiated and six cycles were completed through September 2022. Restaging FDG PET-CT (26 September 2022) demonstrated disease progression, with an increase in the size of the primary mass (to approximately 13 cm) and in its metabolic activity (SUVmax 15.3 to 17.7), an increase in the abdominal metastatic lymph nodes (to SUVmax 11.3, up to 2.4 cm), and new metastatic foci.

Molecular analysis and clinical deterioration:
Following progression, immunohistochemical re-analysis of the biopsy for mismatch repair proteins was performed. Four MMR proteins were evaluated with appropriately reactive internal controls; tumor cells showed loss of MSH2, MLH1, and PMS2 expression with preserved MSH6 expression, consistent with mismatch repair deficiency (dMMR); the reporting laboratory interpreted this as MSI-high. Because of the patient's rapid clinical deterioration and impending liver failure, and limited timely access to molecular MSI testing, treatment was initiated on the basis of the immunohistochemical dMMR result; molecular MSI confirmation (PCR or next-generation sequencing) was not performed. During this period, the patient's condition deteriorated markedly: the ECOG performance status worsened to 3, total bilirubin rose to 14 mg/dL, and signs of hepatic encephalopathy developed. The prognosis was regarded as very poor.

Pembrolizumab treatment and response:
In October 2022, after discussion with the patient and family, pembrolizumab was initiated at 200 mg intravenously every three weeks. A dramatic response was observed within days: total bilirubin fell from 14 to 8 mg/dL by day 4, 2.9 mg/dL at one month (ECOG 1), and normalized by three months, with normalization of

Table 1. Timeline of the clinical course.

Date	Event	Key findings
June 2022	presentation	abdominal pain, jaundice, weight loss; ECOG 2; bilirubin 10 mg/dL, ALP 2618 U/L, CEA 52.4 ng/mL
June 10, 2022	FDG PET-CT (baseline)	left-hepatic mass 11 x 8 cm (SUVmax 15.3); liver metastases; abdominal and parasternal nodes
June 2022	liver biopsy	poorly differentiated carcinoma; primary site not identified
June - September 2022	FOLFOX x6 cycles	first-line chemotherapy (presumed pancreatobiliary
September 26, 2022	FDG PET-CT (restaging)	progression: primary SUVmax 15.3 to 17.7; nodal SUVmax to 11.3; new foci
September - October 2022	MMR IHC re-analysis/ deterioration	loss of MSH2, MLH1, PMS2; MSH6 retained (dMMR). ECOG 3; bilirubin 14 mg/dL; hepatic encephalopathy
October 2022	pembrolizumab started	200 mg IV every 3 weeks
October 2022 - January 2023	early response	bilirubin 14 to 0.9 mg/dL over 3 months; ECOG 3 to 1
January 2023	FDG PET-CT (3 cycles)	marked regression (primary SUVmax 17.7 to 3.4); nodes resolved; CEA 6.2 ng/mL
April 2023	FDG PET-CT (6 cycles)	complete metabolic response; CEA 2.8 ng/mL
October 2024	pembrolizumab completed	35 cycles total; only grade 1 fatigue and pruritus
April 2026	most recent follow-up	ECOG 0; normal laboratory values; no active disease; ongoing complete response

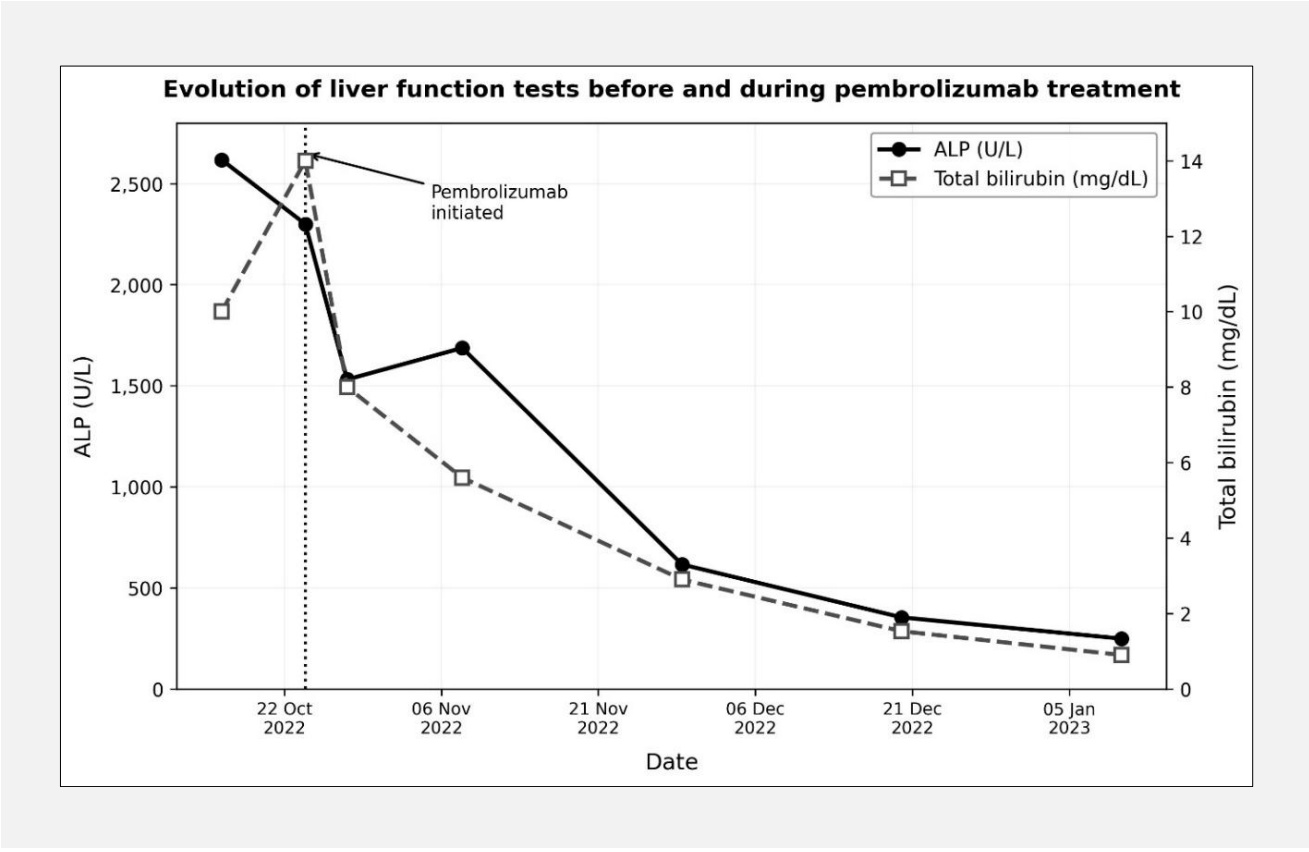

Figure 1. Evolution of total bilirubin and alkaline phosphatase (ALP) before and during pembrolizumab treatment.

The dotted vertical line indicates the initiation of pembrolizumab. Both markers declined rapidly after treatment and returned toward normal.

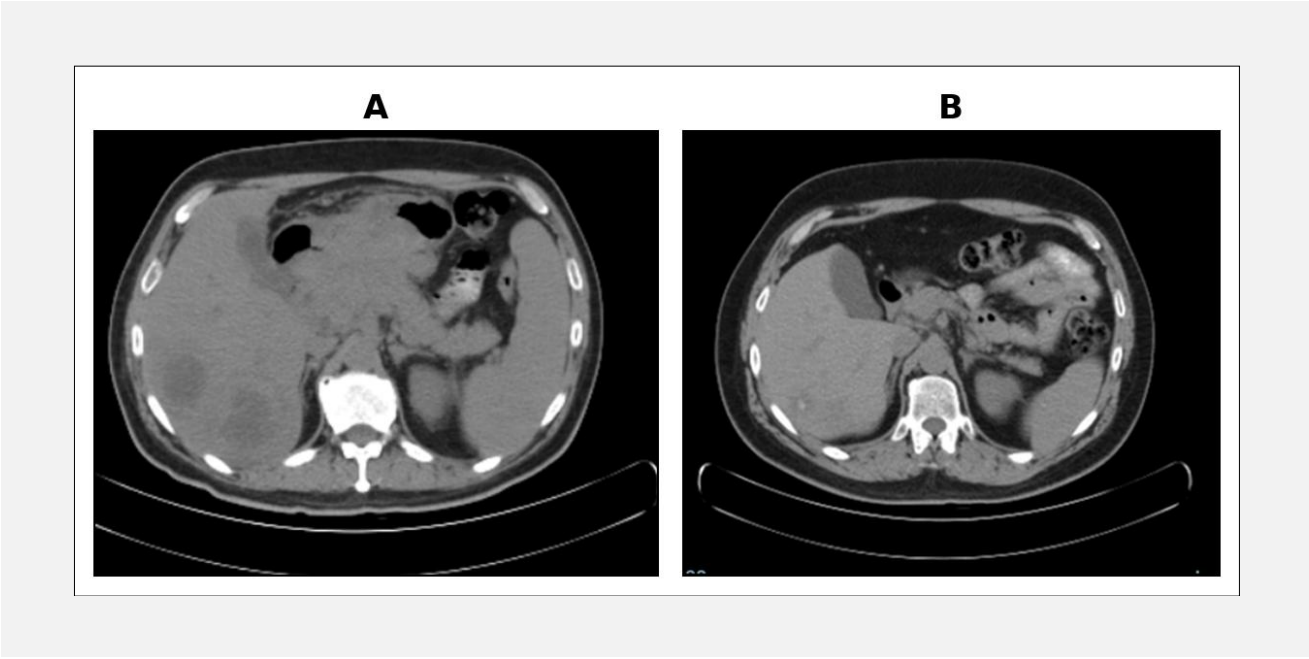

Figure 2. Axial computed tomography images of the liver.

A: Before pembrolizumab (September 2022), showing extensive hepatic involvement, B: During the first year of pembrolizumab (October 2023), showing marked regression of the hepatic disease.

liver enzymes (Figure 1).

Radiological response and response assessment:
Treatment response was assessed by serial FDG PET-CT using a PERCIST-based metabolic approach with supportive biochemical markers, interpreted by the reporting nuclear-medicine physicians. PET-CT in January 2023 (after three cycles) showed marked regression of the primary mass (SUVmax 17.7 to 3.4), complete regression of most liver metastases with reduced size and metabolic activity in the remainder, and complete regression of the intra-abdominal and parasternal lymph nodes; CEA decreased to 6.2 ng/mL. PET-CT in April 2023 (after six cycles) demonstrated a complete metabolic response in all lesions with no evidence of active disease apart from residual scar tissue; CEA was 2.8 ng/mL (normal). The radiological regression of hepatic disease is shown in Figure 2.

Follow-up and current status:
The patient completed a total of 35 cycles of pembrolizumab in October 2024. The only treatment-related adverse events were grade 1 fatigue and grade 1 pruritus. He then remained under surveillance off treatment. The most recent evaluation in April 2026 showed normal laboratory values, an excellent clinical condition (ECOG 0), and no evidence of active disease on imaging. The complete response is ongoing beyond 30 months, and more than 18 months after treatment completion.

Patient perspective:
The patient recalled that, at the start of treatment, he had felt severely unwell and had not expected to recover. He reported feeling noticeably better as early as the day after the first dose of pembrolizumab, and he described the improvement in his jaundice and appetite during the following weeks as unexpected and encouraging. He tolerated the long course of treatment well. At the most recent follow-up he reported feeling healthy, having returned to his usual daily activities, and expressed satisfaction with the outcome of his care.
A dated summary of the clinical course is provided in Table 1.

DISCUSSION

In this patient with dMMR CUP and severe hepatic dysfunction, pembrolizumab produced a dramatic and durable complete response.
CUP is usually advanced at diagnosis, with low response rates to empiric chemotherapy and median overall survival historically under one year [2,8]. Molecular profiling and immunohistochemistry are increasingly central to identifying actionable subgroups, the majority of CUP tumors harboring at least one actionable alteration [4].
The dMMR/MSI-H phenotype is uncommon, reaching roughly 15% in colorectal cancer but being rarer in most other advanced solid tumors. Its precise frequency

in CUP is not well established, with only limited reports available [9]. In our patient, dMMR was identified only after first-line failure, on re-analysis of the original biopsy, highlighting the importance of testing MMR/MSI status in CUP, ideally at diagnosis.

The efficacy of pembrolizumab in dMMR tumors is well established. In the tissue-agnostic study by Le et al., objective responses were seen in 53% and complete responses in 21%, durable across 12 tumor types [5,7]. In the first-line KEYNOTE-177 trial, pembrolizumab prolonged progression-free survival versus chemotherapy in dMMR colorectal cancer [10].

The most striking aspect is the rapidity of the response. Total bilirubin, which had risen to 14 mg/dL with hepatic encephalopathy, fell to 8 mg/dL within four days and normalized within three months. Such rapid improvement in impending liver failure is rarely described and suggests a swiftly activated antitumor immune response. Not all dMMR tumors respond equally to PD-1 blockade - roughly half are refractory - and Mandal et al. showed that the degree of microsatellite instability and mutational load, particularly insertion-deletion burden, influence both response and survival [11]. The response seen here is consistent with the more favorable end of this spectrum, although MSI intensity and mutational load were not quantified.

The recovery from ECOG 3 with hepatic encephalopathy to ECOG 0, together with a complete response durable beyond 30 months, further distinguishes this case. Although durable responses to pembrolizumab are documented in dMMR tumors, including advanced pancreatic cancer [12], such a rapid and durable complete response in CUP specifically remains rarely reported.

This case has limitations. First, MMR deficiency was established by immunohistochemistry alone, without molecular MSI confirmation, and the atypical loss pattern (MSH2, MLH1, and PMS2 loss with retained MSH6) was not further characterized; antibody clones and the staining platform could not be retrieved retrospectively. Second, response was assessed retrospectively rather than by prespecified criteria. Third, the primary site could not be definitively identified. Finally, as a single case report, the findings cannot be generalized, and the outcome cannot be attributed to pembrolizumab with certainty. Nevertheless, the case reinforces the importance of routine MSI/MMR evaluation in CUP, since identifying this subgroup can offer a highly effective option even in patients with otherwise dismal prognostic features.

CONCLUSION

This case demonstrates the efficacy of pembrolizumab in dMMR metastatic CUP. Even with advanced disease, severe hepatic dysfunction, and poor performance status, a dramatic and durable response can be achieved. Routine molecular profiling - in particular MSI/MMR status - is critical in CUP, as it can identify patients who may derive substantial and lasting benefit from immunotherapy.

Consent for Publication:
Written informed consent was obtained from the patient for publication.

Ethical Considerations:
This study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was not required for this single case report at our institution. Written informed consent for publication of the clinical details and accompanying images was obtained from the patient.

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During the preparation of this work, the authors used a generative AI tool solely to improve the language and assist with figure preparation. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Interest:
The authors declare no conflicts of interest relevant to the contents of this article.

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