Case Reports in Oncology

Case Rep Oncol 2023;16:797–804
DOI: 10.1159/000533377
Received: May 3, 2023
Accepted: July 26, 2023
Published online: September 4, 2023

Case Report

A Chromosome 9p24.1 Amplification in Colorectal Cancer with Metastases to the Kidney and Adrenal Gland: A Case Report

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Keywords

Colorectal cancer · Renal metastasis · Adrenal metastasis · Molecular profiling · Immune checkpoint inhibitors · Programmed cell death ligand 1 · Programmed cell death ligand 2

Abstract

Colorectal cancer (CRC) is the third leading cause of mortality worldwide. The Food and Drug Administration recently designated pembrolizumab, an immune checkpoint inhibitor (ICI) against a programmed death-1 receptor, as a breakthrough drug for the treatment of patients with mCRC whose tumors have deficient mismatch-repair gene expression (as evidenced by microsatellite instability-high) and patients with solid tumors with a high tumor mutational burden with ≥10 mutations/megabase. We present a patient with metastatic CRC having renal and adrenal gland metastases. Comprehensive molecular profiling performed on a site of metastatic CRC in the kidney revealed multiple genomic alterations characteristic of CRC and rare chromosome 9p24.1 amplification, resulting in a co-amplification of the *PDL1*, *PDL2*, and *JAK2* genes. Although this genomic alteration may predict the response to ICI, the lack of pembrolizumab prevented the patient from receiving targeted treatment and succumbing to the disease.

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DOI: 10.1159/000533377

Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer. Its mortality has decreased over the decades in high-income countries, while developing countries still face high mortality due to the lack of screening programs and delayed cancer treatments [1, 2]. The liver is the most common site of CRC metastases [3]. Metastases in kidneys are rare, comprising less than 3% of secondary renal neoplasms [4, 5]. Adrenal metastases from CRC occur at a rate ranging from 3.1 to 14.4%. Metastatic adrenal deposits can be discovered in multiple synchronous metastases in other organs, but solitary adrenal metastasis is uncommon [6].

Most studies on renal metastases are case reports and retrospective analyses of patients where the most common primary tumor site was the lung, CRC, head and neck, breast, soft tissue tumors, thyroid, gastric, melanoma, and unknown primary cancers [7, 8]. Recent advances in diagnostics and the treatment of CRC have substantially affected the outcome of CRC patients, including those with advanced/metastatic disease. These include emerging surgical approaches, novel-targeted treatment options with (multi)tyrosine kinase inhibitors, and immunotherapy with immune checkpoint inhibitors (ICIs) [9–12]. We report a unique case of a 58-year-old man with renal and adrenal gland metastases of CRC whose metastatic cancer harbored an amplification of chromosome *9p24.1*, causing a co-amplification of *PDL1, PDL2*, and *JAK2* genes.

Case Presentation

The timeline of diagnostic tests and treatment modalities is summarized in Table 1. In May 2018, a 58-old-year man presented with abdominal pain, constipation, and weight loss (18 kg) for 6 months. On physical examination, he was in good clinical condition. A computed tomography (CT) scan of the abdomen and pelvis and rectosigmoidoscopy revealed an 11-cm solid mass in the sigmoid colon without distant metastases (only liver cysts were found). The mass filled ~90% of the bowel circumference. The patient underwent sigmoid resection of 17 cm in size. The surgical procedure passed uneventfully. Histopathologic examination revealed a high-grade intestinal adenocarcinoma, AJCC stage 3B (T3N1aM0), with clean surgical margins. Based on the intraoperative surgical report of a palpable solitary lesion in the liver, a positron emission tomography (PET) with a diagnostic CT scan revealed abnormal metabolic accumulation in the left kidney, suggestive of synchronous renal neoplasm (Fig. 1). Preoperatively observed liver cysts on CT scan were further confirmed by PET/CT. Based on that finding, the patient underwent a left nephrectomy because of highly suspected primary kidney cancer 2 months after a diagnostic PET/CT. The histopathologic findings of the left kidney revealed a high-grade metastatic adenocarcinoma (Fig. 2a), whose cells were strongly positive for CDX-2 (Fig. 2b) and negative for CD10 (Fig. 2c), suggesting intestinal origins of the kidney mass. At that point, the patient's laboratory test results showed ferritin of 1,260 μg/L, iron of 37 μmol/L, and hemoglobin of 155 g/L, and he was referred to a hematologist. Laboratory tests, especially iron and hemoglobin, remained high during systemic oncological treatment. Serum levels of carcinoembryonic antigen (CEA) and CA-19-9 were within normal limits.

After the second surgery recovery, the patient was presented and discussed on the multidisciplinary tumor board (MTB), recommending adjuvant chemotherapy with FOLFOX 4 protocol. Because of the second surgery, the patient had a 4 months delay in initiating the oxaliplatin-based adjuvant chemotherapy after sigmoid resection. The treatment did not produce any side effects, and the patient was in good clinical condition. Because of quite unusual initial metastatic presentation, CEA and CA-19-9 serum levels were routinely checked after 4 months of adjuvant chemotherapy with FOLFOX 4 protocol. They revealed CEA 11.4

Table 1. The timeline of diagnostic tests and interventions in our patient

Date	The diagnostic test and interventions
May 22, 2018	Multi-slice CT of abdomen and pelvis
June 6, 2018	Rectosigmoidoscopy
July 27, 2018	Sigmoid colon resection
August 21, 2018	Pathology report
August 30, 2018	First examination by an oncologist
September 14, 2018	PET diagnostic CT
November 11, 2018	Left nephrectomy
November 27, 2018	Pathology report
December 6, 2018	MTB presentation
December 14, 2018	First cycle of oxalipatin-based chemotherapy
March 25, 2019	MRI of abdomen and pelvis
May 2, 2019	PET diagnostic CT
May 31, 2019	Right adrenal gland extirpation and tumor resection
June 7, 2019	Pathology report
October 2, 2019	Multi-slice CT of abdomen and pelvis
November 6, 2019	First cycle of irinotecan based chemotherapy with VEGF inhibitor
February 14, 2020	MRI of abdomen and pelvis
March 10, 2020	NGS using kidney specimen
June 15, 2020	Patient died

MRI, magnetic resonance imaging.

μg/L and CA-19-9 58 U/ml. Following testing of CEA and CA-19-9, magnetic resonance imaging of the abdomen and pelvis showed progression in the right adrenal gland with a mass measuring ×4.3 3.8 cm and 4.8 cm. The mass, probably metastatic, was also confirmed with the subsequent PET/CT scan (Fig. 3). The initially observed liver cysts did not show any progression on PET/CT scan, and metastatic liver deposits were not detected. Based on these new findings, expert opinion from another hospital suggested the surgery in a high-volume operation center. The patient underwent extirpation of the right adrenal gland and tumor resection. The histopathologic report was consistent with the previous one, revealing metastatic high-grade intestinal adenocarcinoma to the right adrenal gland.

Five months later, a CT scan of the abdomen and pelvis revealed local recurrence in the region of the previously extirpated right adrenal gland, peritoneal deposits, and recurrent tumor in the region of the previously operated left kidney. CA-19-9 levels were 188 U/ml. After the presentation on MTB, the patient received the seven cycles of combined treatment with FOLFIRI and VEGF inhibitor bevacizumab. Diagnostic imaging 3 months later revealed the progression of the disease. MTB recommended molecular profiling using a metastatic sample obtained from the left kidney. The specimen was profiled at Foundation Medicine Laboratory using the next-generation sequencing (NGS) test (Foundation Medicine, Cambridge, MA, USA). Molecular genomic profiling revealed a microsatellite stable CRC with *JAK2/PD-L1/PD-L2* gene amplification *(9p24.1).* Additional molecular findings included *KRAS, CCND2, CDK8, FGF23, FGF6, FLT3*, and *KDM5A* gene amplifications. Mutations of *APC (V1320fs1 R283), TP53 (S241fs19),* and *CDH1* loss exons 1–2 were also observed (Table 2). Tumor mutational burden (TMB) was four mutations/Mb (Table 2). Despite chemo-resistant

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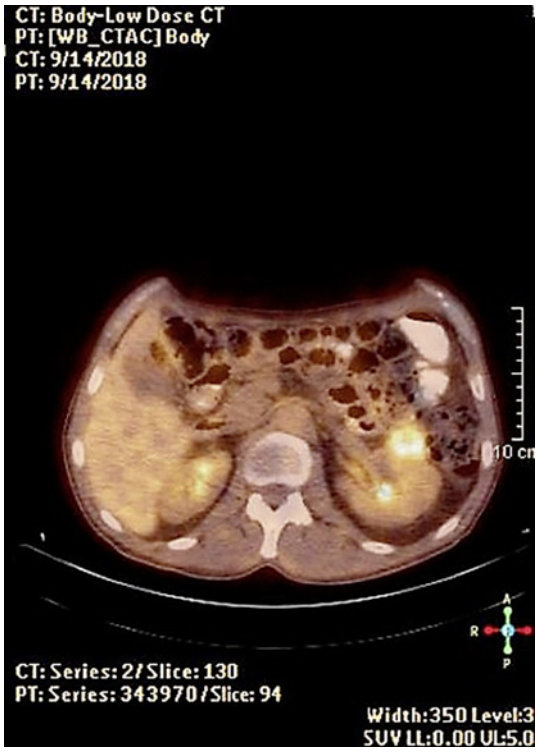

Fig. 1. PET/CT scans revealed abnormal metabolic accumulation in the left kidney.

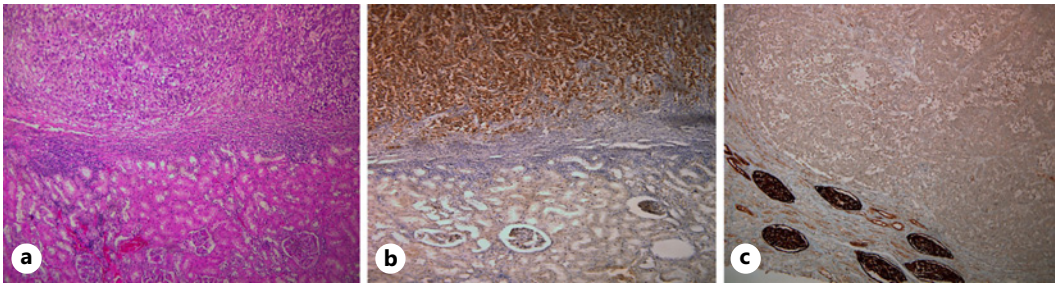

Fig. 2. a Hematoxylin and eosin slide of the kidney specimen with metastatic adenocarcinoma (×10). **b** The tumor cells were strongly positive for CDX-2; please note the absence of staining in the adjacent normal kidney (lower part of the image). **c** The absence of CD10 expression in tumor cells were highly suggestive of metastatic cancer (note diffuse CD10 expression in adjacent normal renal tubules) (×10).

metastatic CRC and targetable genomic alterations, ICIs could not be provided, and the patient succumbed to the disease in June 2020.

The authors completed the CARE Checklist for this case report, which is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533377).

Discussion

CRC is one of the most common cancers worldwide, contributing significantly to cancer morbidity and mortality [1]. Some 20% of CRC patients have metastatic disease at presentation, while another 20–50% later develop metastases [13, 14]. The liver is the most common site of metastatic CRC. Metastases to other organs, such as the kidney, have been

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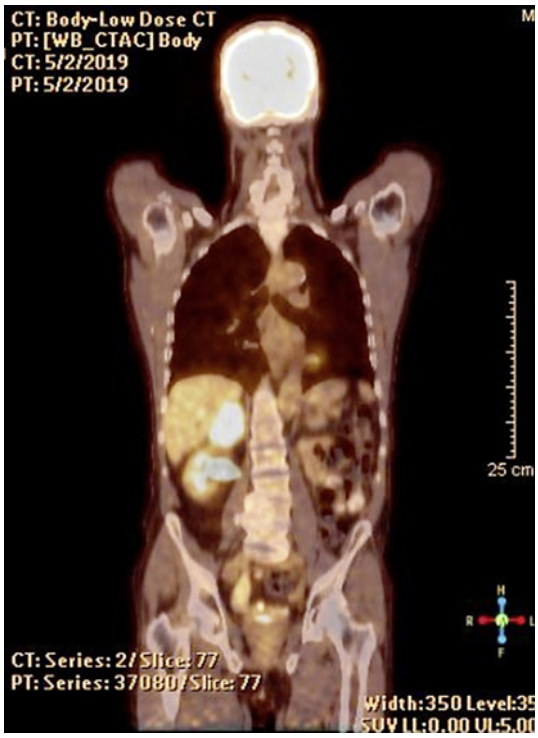

Fig. 3. A positron emission tomography (PET) scan reveals abnormal metabolic accumulation in the right adrenal gland.

reported in 2.7% of postmortem analyses, far rarer than that in clinical practice [15, 16]. Because the kidneys are highly vascular organs, metastatic infiltration is often the result of arterial embolization or direct invasion [5, 8, 17]. Although cytoreduction surgery has been shown to benefit patients with CRC and soft tissue sarcomas, nephrectomy with curative intent in oligometastatic CRC to kidney remains controversial, mainly due to the absence of established guidelines for such specific groups of patients [7, 8, 18, 19].

Our study appears to be the first case of a patient in whom NGS was performed at a site of metastatic CRC to the kidney. Most previous NGS reports were based on primary tumor samples or other more common metastatic sites (e.g., liver, lungs) [20, 21]. As reported in the Cancer Genome Atlas project and extensive research, multiple essential genes and pathways are implicated in the development and progression of CRC, including WNT, RAS-MAPK, PI3K, TGF, TP53, and DNA mismatch-repair pathways [22]. *PDL1/PDL2/CD274* amplification is a rare genomic event reported in 0.7% of 118,187 tumor samples from >100 tumor types, including 0.18% CRC. However, changes in programmed cell death ligand 1 (*PDL1/CD274*) and programmed cell death ligand 2 (*PDCD1LG2* or *PDL2*) expression can enhance response to ICI. *PDL1* CNAs have been strongly linked to response to ICI, with a 66.7% response rate among 9/13 patients with *PDL1* amplification treated with ICI [23–25]. Additionally, some NSCLC patients with *PDL1* amplification had an 80% 1-year PFS rate and a 100% 1-year OS rate [26]. The importance of *PDL1* CNAs in ICI therapy was first noted in a prior study that showed a high rate (87%) of response to nivolumab, including a 17% complete response in extensively pretreated Hodgkin lymphoma with a very low TMB [27]. *PDL2* is always co-amplified with *PDL1*, whereas *JAK2* (Janus kinase 2) is co-amplified in ~96% of tumors with *PDL1* gains, suggesting a potential mechanism of long-term response to ICI [27, 28]. Although the FDA approved the ICI pembrolizumab for patients with solid tumors with a TMB ≥10 mutations/mb and high microsatellite instability/deficiencies in DNA mismatch-repair, more research is needed to determine the mechanistic basis for *PDL1* amplification-associated response to ICI

Table 2. Results of the comprehensive genomic profiling of the metastatic CRC to the left kidney

Gene	Genomic alteration
PDL1	
PDL2	Amplification (9p24.1 amplicon)
JAK2	
KRAS	Amplification
CCND2	Amplification
APC	Mutation (V1320 fs*11, R283*)
CDK8	Amplification (equivocal)
FGF23	Amplification
FGF6	Amplification
FLT3	Amplification (equivocal)
KDM5A	Amplification
TP53	Mutation (S241 fs*19)
CDH1	Loss in exons 1–2
Additional findings	
MSI status	MS-stable
TMB	Four mutations/mb

[29, 30]. As demonstrated in our patient and the first-documented case report of a patient who exhibited a remarkable radiographic response to ICI, most *PDL1* amplified tumors had low to intermediate TMB [19, 20].

Although routine molecular testing (e.g., MMR status, *KRAS, NRAS, BRAF*) has been recommended by the ESMO guideline for all newly diagnosed CRC patients, in our case, it was first done in the metastatic setting [14]. While molecular profiling is increasingly used to match targeted medications to biologically relevant targets, many obstacles remain, particularly in developing and low to middle income countries [1, 31]. Logistical issues such as insurance coverage may exist for drugs approved for other disease types (off-label use). In Bosnia and Herzegovina, for example, the cause may be a lack of government financing and a lack of coherent health policy due to the complex political structure [1]. Even when approved, the availability may be limited, and waiting lists, like in our case, adversely affect the patient's treatment and outcome [1].

In conclusion, we presented a rare case of CRC with renal and adrenal gland metastases, harboring *JAK2/PDL1/PDL2* amplification (*9p24.1*). This is probably the first study in which NGS was performed on a site of metastatic CRC in the kidney. It further confirmed the clinical utility of comprehensive molecular profiling with targetable alterations in advanced CRC. Despite recent advancements in Bosnia and Herzegovina, particularly in treating malignant melanoma, lung, and breast cancer, ICIs are currently unavailable in other cancer types (for example, CRC and kidney cancer). There is an urgent need to implement a personalized approach in all cancer types, expand existing indications, and introduce additional targeted oncological therapies.

Acknowledgment

The Qatar National Library (QNL) covered the article-processing fee for this article.

Statement of Ethics

The patient provided informed consent for comprehensive genomic profiling. Written informed consent was obtained from the patient's next of kin for publication of the details of his medical case and accompanying images. The study was approved by a Local Institutional Review Board (Ethical Committee of the University Hospital Mostar, number 1306/23).

Conflict of Interest Statement

The authors report no conflict of interest.

Funding Sources

No specific funding was received for this study.

Author Contributions

Conceptualization and data curation: Ana Paric, Semir Vranic. Formal analysis, investigation, and writing – review and editing: Ana Paric, Dragana Karan-Krizanac, Ivan Saric, and Semir Vranic. Writing original draft: Ana Paric. Supervision: Semir Vranic.

Data Availability Statement

All data generated/analyzed in the study are included in this article. Further inquiries can be directed to the corresponding author.

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