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Liver Metastases of Unknown Primary Renal Cell Carcinoma Treated With Immune Checkpoint Inhibitors Plus Tyrosine Kinase Inhibitors: A Case Report and Literature Review

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Abstract. *Background/Aim: Renal cell carcinoma (RCC) constitutes approximately 3% of all cancers. More than 60% of RCCs are detected incidentally; one-third of patients present with regional or distant metastases, and another 20-40% of patients develop metastases after radical nephrectomy. RCC can metastasize to any organ. In contrast, metastatic RCC (mRCC) without evidence of a primary tumor is extremely rare, with only a few reported cases. Case Report: We present a case of mRCC that initially presented with multiple liver and lymph node metastases but no primary renal lesion. An impressive response to treatment was achieved with a combination of immune checkpoint inhibitors and tyrosine kinase inhibitors. A clinical, radiological, and pathological diagnostic strategy, particularly in the context of a multidisciplinary team, are crucial for reaching a definitive diagnosis. This approach allows to select the appropriate treatment, making a huge difference for a mRCC due to its resistance to standard chemotherapy. Conclusion: There are currently no guidelines available for mRCC without primary tumor. Nevertheless, a combination of TKI and immunotherapy could be the optimal first-line treatment if systemic therapy is required.*

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Renal cell carcinoma (RCC), the most common form of kidney cancer, accounting for approximately 3% of all cancers (1). It affects about 300,000 people worldwide on an annual basis, resulting in over 100,000 deaths. Its incidence is still on the rise, but in recent years a positive trend in 5-year survival has been observed (1). More than 60% of RCCs are detected incidentally, and only 10% of patients exhibit the classic symptoms: hematuria, hip pain, and a distinct mass. Although a significant proportion of patients are considered cured after initial surgery, about 40% of patients will ultimately develop distant metastases (2, 3). Moreover, approximately 20% of patients will present with metastatic RCC (mRCC) at first diagnosis (2, 3). The lungs, lymph nodes, bones, and liver are the organs typically involved in metastatic disease. Moreover, the presence of bone and liver metastases is associated with a poor prognosis for survival (4, 5). In contrast, mRCC without evidence of a primary tumor in the kidney is extremely rare, and only a few cases have been reported in the literature, particularly with multiple upfront liver metastases (6-13).

Due to the rarity of occurrence, there are no guidelines for the clinical course and possible strategies, and its management is identical to that of neoplasms with a known primary mass. Several treatments have been indicated in case reports, including surveillance, surgical resection, radiotherapy, and systemic therapy. The clinical scenario for mRCC has dramatically changed over recent years with the emergence of treatments based on the combination of immunotherapy and tyrosine kinase inhibitors (TKIs). These therapies have led to a significant improvement in the response rate, progression-free survival, and overall survival (14).

We report the case of a man who presented without any evident primary renal tumor but with liver metastases, whose biopsy showed a clear cell carcinoma of the kidney.

Case Report

A 59-year-old patient presented with two days of worsening abdominal pain was referred to our Clinic in December 2021. He had no relevant past medical history. An abdominal ultrasound revealed several hepatic lesions. The patient underwent computer tomography (CT) scan of the thorax and abdomen, which indicated several hepatic lesions with a bulky mass of 13 cm and multiple lymph nodes near the pancreas and hepatic hilum (the largest with a short axis of 3.5 cm) (Figure 1A). A percutaneous needle biopsy was performed on one of the hepatic lesions. The pathologist's investigation revealed a carcinoma with an immunophenotypic profile consistent with kidney origin. The diagnosis was based on positivity for PAX8 and negativity for CDX2, HepPar-1, and CK7. The patient was referred to the Istituto Oncologico Veneto due to the absence of a renal mass and the disease's extensive diffusion to the liver and locoregional lymph nodes. A second liver biopsy revealed a clear cell carcinoma with immunohistochemistry (ICH) indicating positive staining for PAX 8, MNF-116, and CD10 and negative staining for HePpar-1, TTF-1, synaptophysin, HMB-45, Melan A, and vimentin (Figure 2). We also performed a somatic next generation sequencing (NGS) test (Foundation Medicine®, Cambridge, MA, USA), and the analysis revealed two genetic alterations in TET2 (T1959fs*20 mutations) and SETD2 (T2353fs*3), both of which were classified as potentially oncogenic in accordance with the ONCOKB database. All the laboratory cancer markers, such as CEA and CA19.9, were negative. All the patient characteristics upon admission are summarized in Table I.

The case was discussed at a multidisciplinary meeting dedicated to genitourinary cancers. CT images were carefully evaluated, and no lesions were found in other organs. The pathology reports were discussed with the pathologists, and a clinical, radiological, and pathological correlation of the case was undertaken. The result confirmed diagnosis of clear cell mRCC. The patient was in good general condition with an ECOG performance status of 0 and normal laboratory tests. Therefore, the disease was classified as intermediate risk in accordance with the IMDC prognostic score (15). In January 2022, the patient began treatment with Axitinib 10 mg daily in combination with Pembrolizumab 200 mg every 3 weeks. After 3 months of treatment, a CT scan revealed an initial dimensional response in liver lesions and lymph nodes (Figure 1B). The patient reported experiencing G1 abdominal pain and G1 constipation as a result of the therapy, which were successfully treated with symptomatic treatment. After 6 months, all the lesions had shrunk further, with a total reduction of over 30%. No primary renal tumor or renal parenchymal alteration was observed. The last CT scan in November 2022 revealed a further reduction of the hepatic nodules with a large lesion of 3 cm (*vs.* 13 cm at baseline) and lymph nodes with short axes of less than 1 cm (Figure 1C). After one year, the patient is continuing treatment with Axitinib 10 mg daily and Pembrolizumab 400 mg every 6 weeks.

Informed consent for the publication of this case report was obtained from the patient.

Discussion

RCC can present with multiple clinical manifestations and has the propensity to metastasize to any organ, either through hematogenous or lymphatic spread. The lungs (75%), lymph nodes (36%), bones (20%), and liver (18%) are the most prevalent sites for metastases (4, 5). In contrast, cases of mRCC and non-identifiable kidney lesions are rare. How mRCC develops in the absence of a primary lesion is still unknown. The mass could remain hidden and undetectable through imaging, or the tumor may develop in ectopic renal tissue. In some cases, RCC may undergo spontaneous involution without therapy or may re-appear (6, 9, 11, 13).

In our case, liver lesions resembling a clear cell neoplasm necessitated a thorough evaluation to differentiate primary liver cancer from a different metastatic cancer. In fact, differential diagnoses in clear cell histotypes of malignant hepatic masses include at least primitive hepatocellular carcinoma and metastatic lesions such as adrenal cortical carcinoma, clear cell RCC, malignant melanoma, and clear cell sarcoma. Neoplasms originating from the liver are positive for Arginase-1, HepPar1, Glypican 3, villin, CD10, MNF116, CAM5.2 (CK8/CK18), and reticulin. RCC is positive for epithelial markers including RCC, PAX8, CAIX, and CD10 but negative for other markers such as CK7, CK20, HepPar-1, SF1, or Melan A. Adrenocortical gland-derived tumors are positive for steroidogenic factor 1 (SF1), calretinin, inhibin, MelanA/MART1, synaptophysin, neuron-specific enolase (NSE), IGF2, and vimentin. S100, MelanA, Sox10, and HMB45 are expressed in both malignant melanoma and clear cell sarcoma; however, only HMB45 exhibits EWSR1-ATF1 or EWSR1-CREB1 fusions. In certain instances, the genomic profile could support the diagnosis. Alterations in VHL, PBRM1, CDKN2A, SETD2, or the deletion of chromosomes 3p and 9p are associated with clear cell RCC (16-19). In our case, the alteration in SETD2 detected with the NGS test was essential to the final diagnosis. In fact, this is a classical truncating mutation that can lead to SETD2 loss, an alteration frequently related to RCC (20).

Our multidisciplinary team discussed all the pertinent facts in order to have a complete picture of the patient and to conduct an optimal clinical-pathological-radiological correlation. This

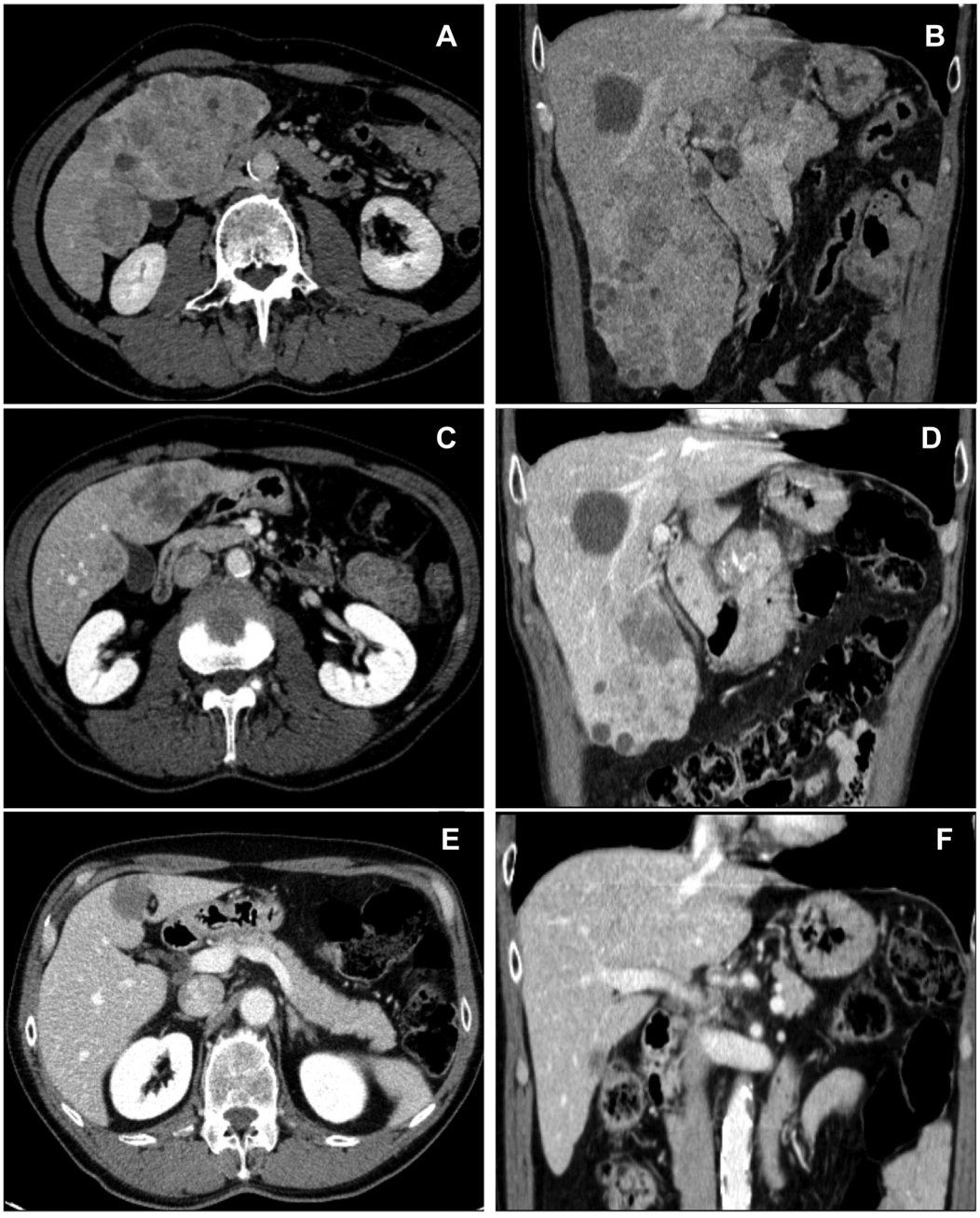

Figure 1. *Contrast enhanced CT scan axial (A) and coronal (B) view at the time of diagnosis; contrast enhanced CT scan axial (C) and coronal (D) view after 3 months of treatment; contrast enhanced CT scan axial (E) and coronal (F) view after 11 months. CT: Computed tomography.*

discussion allowed us to arrive at the definitive diagnosis of clear cell mRCC, which made a tremendous impact in determining the appropriate treatment.

An adequate and comprehensive diagnostic algorithm is crucial for several reasons. Cancers of unknown primary (CUP) are challenging due to their poor prognosis and limited treatment options, with a median survival of between 4 and 12 months. The use of gastroscopy and coloscopy is recommended in order to locate a primitive lesion. In addition, abdominal MRI could help in the search for small lesions in organs such as the liver, kidney, or soft tissue. Finally, whole-body PET/CT is the investigation of choice for proper staging, although the applicability of FDG PET/CT for RCC is limited due to physiological excretion

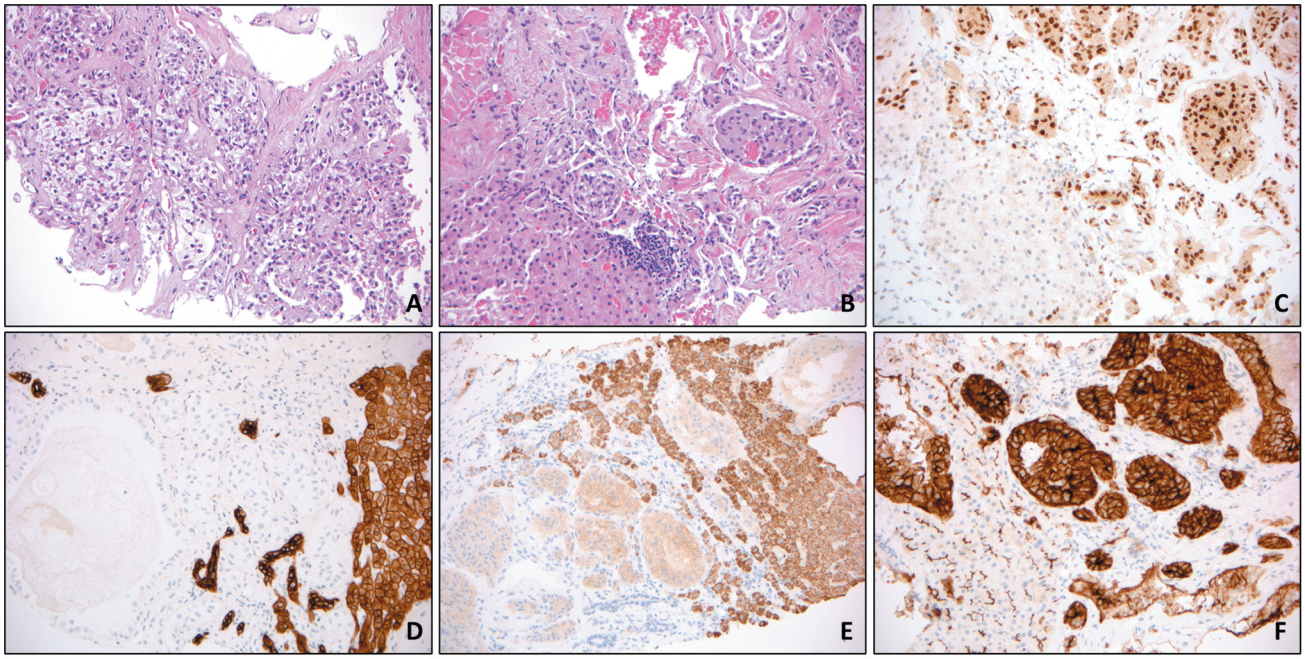

Figure 2. *Morphological and immunohistochemical features of the hepatic lesion. Following hematoxylin and eosin staining, the lesion exhibited a solid alveolar growth pattern and was composed of nucleated cells with large, clear, and eosinophilic cytoplasm (A). Numerous microscopic blood vascular invasions were present (B). Immunohistochemical analysis revealed that the neoplasm had strong nuclear positivity for PAX8 (C), negativity for expression of cytokeratin MNF-116 (D) and HePpar-1 (E) relative to the surrounding liver parenchyma, and strong positivity for CD10 (F) at 200× magnification.*

from the kidneys (21). Nevertheless, recent data suggest that PSMA PET/CT is a promising imaging modality for RCC, and in the near future, it may aid in the detection of a primary renal tumor and the evaluation of the therapeutic response (22). In our case, due to the pathological and laboratory reports, as well as the high load of hepatic disease, we decided to forego these tests in order to avoid wasting time and commence active treatment immediately.

In certain CUP series, approximately 8% resulted in RCC (23, 24). These patients often have high-risk features or non-clear cell histology and must be referred for RCC-specific treatments as opposed to the chemotherapy typically used for CUP or gastrointestinal cancer. Furthermore, RCC is highly resistant to systemic chemotherapy and is a highly angiogenic and immunogenic disease (25). Anti-VEGFR TKIs and ICIs are currently the cornerstone treatments for RCC (14).

First-line treatment options for patients with advanced clear cell RCC depend on the prognostic risk class to which the patient belongs. In fact, multiple independent prognostic factors including performance status, time from the diagnosis of metastatic disease to treatment, corrected calcium value, platelet and neutrophil counts, and hemoglobin value, are combined in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score, which classifies patients as favorable, intermediate, or poor risk (15). Other important factors include performance status, comorbidities, the presence of disease symptoms, histological type, the presence of sarcomatoid differentiation, tumor burden, and the sites involved.

Table I. *Patient characteristics upon admission.*

Characteristics	Value (Normal range)
Age	59
Comorbidity	None
Karnofsky Performance Status	90
Hemoglobin	16 g/dl (14-17.5)
Corrected calcium	9.6 mg/dl (8.4-10.2)
Neutrophils	5.7 10^9/l (1.8-7.8)
Platelets	380 10^9/l (150-450)
Site of metastasis	Liver, retroperitoneal lymph nodes

First-line treatment options for subjects classified as intermediate or poor risk are Axitinib plus Pembrolizumab, Cabozantinib plus Nivolumab, Lenvatinib plus Pembrolizumab, or Ipilimumab plus Nivolumab (14).

Due to the presence of large hepatic metastases and the absence of sarcomatoid differentiation, we chose to initiate

Table II. *Summary of previous case reports of mRCC without a primary tumor.*

Author	Histological type	Sites of metastasis	Local treatment	Systemic treatment	mPFS
Kumar *et al*. (6)	Clear cell	Bone, Lung	NO	Sunitinib	>18 months
Wayne *et al*. (7)	Clear cell	Cutaneous (Back)	Surgery	NO	9 months
Bathia *et al*. (8)	Clear cell	Cutaneous (Nose)	Surgery	NO	>9 months
Choi *et al*. (9)	Clear cell	Supraclavicular LN	RT	Sunitinib	>20 months
Thamcharoen *et al*. (10)	Papillary	Supraclavicular LN, Lung	NO	Sunitinib	>4 years
Fayaz *et al*. (11)	Clear cell	Cutaneous (Neck), Supraclavicular LN	NO	Pazopanib	>1 year
Walton *et al*. (12)	Clear cell	Cutaneous (Arm)	Surgery	NO	>27 months
Costantino *et al*. (13)	Clear cell	Adrenal glands, Liver	Surgery	Sunitinib	>12 months

LN: Lymph nodes, RT: radiotherapy.

a treatment based on a TKI–ICI combination for our patient, who was classified as an intermediate-risk patient according to the IMDC classification. This decision was taken because we preferred to achieve disease control while eliminating the risk of an initial progression. In fact, the patient presented an immediate disease response, which is ongoing. These results are consistent with data derived from the KEYNOTE 426 study, where the objective response rate was 59.3%, the disease control rate was 83.8%, and the median progression-free survival was 15.1 months (26). In addiction these results are confirmed in a real-world study where the combination therapy significantly improved the PFS especially in patients with intermediate and poor risk disease (27).

Nine cases of mRCC patients without primary lesions have been reported in the literature (Table II). An analysis of the results of existing case reports reveals that clear cell (8 cases) is the most prevalent histology compared to papillary (only 1 case). The most frequently involved sites were the skin and lymph nodes.

With regards to treatment, five patients underwent local therapy involving surgical resection or radiotherapy, facilitated by the limited number and size of the lesions, particularly in three cases with skin metastasis. Four cases started systemic therapy with TKIs and had a long PFS, probably due to the low burden of disease and the involvement of organs with a favorable prognosis, such as the lymph nodes and lungs (4, 5). Two patients who underwent initial surgery subsequently relapsed at a new distant site of disease and resumed systemic treatment with good disease control. To the best of our knowledge, this is the second reported case of hepatic metastases with a poor prognosis and one of the few with a high burden of disease and sites involved. This is the first case in which a combination treatment was successfully initiated, and a remarkable radiological response has been achieved.

One year after the diagnosis of multiple large hepatic lesions of clear cell RCC without an evident primary cancer, the patient is currently in optimal clinical condition with an excellent tumor response.

Conclusion

We report a single case of mRCC with metastases to the liver and lymph nodes but no primary lesion. RCC presenting with an unidentified primary is rare but should be considered in select cases. Modern immunohistochemical and molecular techniques are necessary for an accurate diagnosis, which is essential for selecting the proper treatment. A multidisciplinary team provides the opportunity for a comprehensive evaluation of the patient. There are currently no guidelines available for such clinical cases. Nevertheless, it is reasonable to conclude that a combination of TKI and immunotherapy is the optimal first-line treatment if systemic therapy is required. In the future, the accumulation of new cases and their follow-up over the years may provide additional evidence for the management of these patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

All Authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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