

Synchronous Clear Cell Renal Carcinoma and Hepatocellular Carcinoma: A Rare Case of Dual Primary Malignancy

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ABSTRACT

Clear cell renal carcinoma (ccRCC) and hepatocellular carcinoma (HCC) are two distinct malignant neoplasms with different risk factors, pathogenesis, and clinical behavior. The synchronous occurrence of both tumors is extremely rare and poses significant diagnostic and therapeutic challenges. We present the case of a 48-year-old male patient with a history of poorly controlled type 2 diabetes mellitus and systemic arterial hypertension. He was diagnosed with left renal cell carcinoma after presenting with lumbar pain and hematuria. A radical nephrectomy was performed, and histopathological examination revealed a clear cell renal carcinoma, Fuhrman grade 3, with invasion into the perirenal fat and lymphovascular structures. A postoperative follow-up CT scan showed a small hepatic lesion, which was biopsied and confirmed as a well-differentiated hepatocellular carcinoma. Immunohistochemical studies demonstrated positivity for Hepar1 and CD34, and negativity for Glypican3, supporting a primary hepatic origin. The patient was started on pembrolizumab and axitinib, with good clinical response and stable renal function. This case highlights the importance of considering dual primary malignancies in patients with multifocal tumors and underscores the role of immunohistochemistry in distinguishing synchronous primary neoplasms from metastatic disease.

KEYWORDS: Clear cell renal carcinoma, hepatocellular carcinoma, synchronous tumors, dual primary malignancy, immunohistochemistry, pembrolizumab, axitinib.

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I. INTRODUCTION

The synchronous appearance of two histologically distinct primary malignant tumors, such as clear cell renal carcinoma (ccRCC) and hepatocellular carcinoma (HCC), is exceptionally rare. This unusual coexistence presents diagnostic challenges, particularly in distinguishing between primary neoplasms and metastases. Synchronous tumors are defined as two primary malignancies diagnosed simultaneously or within a six-month interval. To confirm a diagnosis of dual primary cancers, each tumor must exhibit its own malignant histological pattern and should not be the result of metastatic spread from the other. The incidence of such dual malignancies is expected to rise, partly due to

longer patient survival and improvements in diagnostic imaging².

Clear cell renal cell carcinoma is the most common histological subtype of kidney cancer, characterized by its origin in the proximal renal tubules, rich vascularity, and cells with optically clear cytoplasm. It typically presents with nonspecific symptoms such as hematuria, flank pain, or a palpable mass. In more aggressive forms, it can invade the renal vein and metastasize to distant organs. Histopathological confirmation and immunohistochemical staining for markers such as CD10 and EMA assist in diagnosis. The clear demarcation between renal origin and

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hepatic spread is essential when synchronous liver lesions are detected ⁹.

Hepatocellular carcinoma is the most frequent primary liver malignancy and represents the fifth most common cancer worldwide. Its incidence has increased dramatically in recent decades due to the rising prevalence of hepatitis C virus infection and metabolic syndrome. HCC is responsible for a large number of cancer-related deaths, particularly in patients with underlying cirrhosis, which is present in over 90% of cases. The male-to-female ratio is approximately 2–3:1, with a peak incidence at 65 years, although younger individuals are increasingly being diagnosed. Major risk factors include chronic hepatitis B or C infection, alcohol consumption, aflatoxin exposure, obesity, and diabetes ¹.

The pathogenesis of HCC involves chronic hepatic inflammation and a multistep carcinogenic process. Genetic mutations, microsatellite instability, and dysregulation of intracellular signaling pathways such as Wnt/ β -catenin and angiogenic factors contribute to malignant transformation. In cirrhotic livers, the annual incidence of HCC can reach 4%. Preventive strategies, such as hepatitis B vaccination, have helped reduce the burden of disease in some regions, but other risk factors like hepatitis C and metabolic syndrome remain difficult to control. Recent studies also highlight the regulatory role of microRNAs in hepatocarcinogenesis ¹.

Immunohistochemistry plays a pivotal role in differentiating primary hepatic tumors from metastases. In HCC, positivity for HepPar-1 and CD34, along with negativity for Glypican 3 or PAX8, supports hepatic origin. Conversely, renal tumors typically express PAX8 and CD10. Identifying immunohistochemical profiles allows for accurate diagnosis, which directly impacts treatment decisions. In patients with coexisting ccRCC and HCC, surgery may include nephrectomy and liver resection when feasible. These cases underline the importance of a multidisciplinary approach in the evaluation of multifocal tumors ³.

II. CASE REPORT

A 48-year-old male, with a background of poorly controlled type 2 diabetes mellitus and systemic arterial hypertension, presented to the emergency department with persistent lumbar pain and hematuria. He reported no recent weight loss, anorexia, or fever. Physical examination revealed mild left flank tenderness without a palpable mass or other abnormal findings.

An abdominal CT scan revealed a left renal mass suggestive of malignancy. The patient underwent a left radical nephrectomy without perioperative complications. Histopathological analysis confirmed the diagnosis of clear cell renal cell carcinoma (ccRCC), Fuhrman grade 3, with invasion into the perirenal adipose tissue and lymphovascular structures. The surgical margins were reported as free of tumor infiltration.

Postoperatively, during routine imaging follow-up, a hepatic lesion was identified on abdominal CT. Further evaluation included a percutaneous liver biopsy. Histology reported a well-differentiated hepatocellular carcinoma (HCC). Immunohistochemical analysis showed positivity for Hepar-1 and CD34 and negativity for Glypican-3 and PAX8, confirming a primary hepatic origin rather than metastatic spread from the previous renal tumor.

Given the synchronous nature of both malignancies and the absence of metastases, the patient was started on systemic therapy with pembrolizumab and axitinib. This combination was selected based on current clinical guidelines for advanced or metastatic ccRCC and the potential therapeutic synergy in patients with preserved liver function. The patient showed a favorable clinical response, with radiologic stability of the hepatic lesion and no evidence of new metastases after several months of follow-up.

III. METHODS

The diagnostic approach began with a thorough clinical assessment focused on the patient's presenting symptoms of lumbar pain and hematuria. Initial evaluation included a complete physical examination and detailed medical history, with special attention to risk factors such as diabetes mellitus and hypertension. Routine laboratory tests were ordered, including complete blood count, serum creatinine, urea, electrolytes, glucose, and liver function tests to assess baseline systemic status.

Imaging played a crucial role in the diagnostic pathway. A contrast-enhanced abdominal computed tomography (CT) scan was performed, which revealed a suspicious mass in the left kidney. Based on these findings, the patient was scheduled for surgical intervention, undergoing a left radical nephrectomy. The resected specimen was sent for histopathological analysis to establish the definitive diagnosis and tumor characteristics, including grade and invasion.

Postoperatively, as part of standard surveillance, a follow-up CT scan of the abdomen was conducted. This imaging study revealed a hepatic lesion that had not been previously noted. To characterize this lesion, a percutaneous liver biopsy was performed under imaging guidance. The sample was subjected to histological and immunohistochemical evaluation to determine tumor origin. Staining included markers such as Hepar-1, CD34, Glypican-3, and PAX8.

Upon confirmation of dual primary malignancy, a multidisciplinary oncology team evaluated the patient. Given the diagnosis of synchronous clear cell renal carcinoma and hepatocellular carcinoma, and considering the absence of metastatic disease, systemic treatment with pembrolizumab and axitinib was initiated. The patient was monitored closely with clinical assessments and periodic imaging to evaluate therapeutic response and detect potential progression or adverse effects.

IV. RESULTS

On laboratory evaluation, the patient showed normal hemoglobin levels (16.3 g/dL), leukocytes at $8.2 \times 10^3/\mu\text{L}$, and a platelet count of 156,000/mm³. Renal function was altered with a creatinine level of 2.3 mg/dL and urea at 69.6 mg/dL, while glucose remained within normal limits at 95 mg/dL. Liver function tests reported gamma-glutamyl transferase (GGT) at 59 U/L, and the remaining hepatic enzymes were within reference ranges. Thyroid-stimulating hormone (TSH) was elevated to 7.6 $\mu\text{IU/mL}$, suggestive of subclinical hypothyroidism.

An unenhanced abdominopelvic CT scan revealed postoperative changes in the left abdomen and a hyperdense tubular image in the left renal fossa, consistent with prior nephrectomy. No retroperitoneal lymphadenopathy or hepatic focal lesions were identified. Additionally, osteoarthritic changes with anterior osteophytes were observed in the lumbar spine at L1–L2, and a left-sided pleural effusion with basal consolidation and air bronchogram was noted.

Histopathological analysis of the nephrectomy specimen confirmed a clear cell renal cell carcinoma (ccRCC), ISUP/WHO grade 3, with tumor invasion into Gerota's fascia and presence of lymphovascular invasion. Tumor necrosis was also documented. The surgical margins, including hilar vessels, were free of neoplastic infiltration.

Subsequent liver biopsy revealed a 1.5 cm well-differentiated hepatocellular carcinoma (HCC). There was no evidence of lymphovascular invasion. Immunohistochemical staining was positive for Hepar1 and CD34 in blood vessels, while markers Glypican 3 and PAX8 were negative, confirming primary hepatic origin of the lesion.

V. DISCUSSION

The simultaneous presentation of clear cell renal cell carcinoma (ccRCC) and hepatocellular carcinoma (HCC) as two independent primary tumors is a highly unusual clinical entity. This rarity is evidenced by the limited number of published case reports documenting such occurrences. While the diagnosis of multifocal neoplasms often raises suspicion of metastatic disease, it is essential to consider the possibility of synchronous primary malignancies, particularly when both tumors exhibit distinct histological and immunohistochemical profiles. In one report, a similar case presented with liver and kidney tumors initially presumed to be metastatic, but later confirmed as two separate malignancies through biopsy and immunohistochemistry⁵.

Accurate diagnosis of synchronous primary tumors relies heavily on the application of immunohistochemical markers. Renal cell carcinoma typically expresses PAX8 and CD10, while hepatocellular carcinoma is marked by Hepar1 and CD34. In our case, the liver lesion was negative for Glypican-3 and PAX8, further supporting the diagnosis of a primary HCC rather than a metastasis from the renal tumor. These findings align with published literature highlighting the

pivotal role of immunohistochemistry in resolving diagnostic ambiguity in complex oncologic cases⁶.

The Barcelona Clinic Liver Cancer (BCLC) staging system is widely used to assess prognosis and therapeutic options in HCC. It incorporates tumor size and number, liver function, and performance status to stratify patients. Early-stage HCCs are candidates for surgical resection, ablation, or transplantation, whereas intermediate and advanced stages are approached with locoregional or systemic therapy. In the present case, the hepatic lesion was small and well-differentiated, favoring a good prognosis. However, the presence of two synchronous malignancies necessitated a systemic therapeutic approach⁷.

On the renal side, ccRCC accounts for 70–80% of renal cancers and is characterized by variable aggressiveness depending on histological features such as nuclear grade, necrosis, and vascular invasion. The presence of lymphovascular invasion and perirenal fat infiltration, as seen in our patient, suggests a higher risk of recurrence or metastasis. Nevertheless, the absence of distant disease and negative surgical margins offered a favorable context for systemic therapy rather than immediate additional surgery¹¹.

From a molecular perspective, ccRCC is associated with alterations in the VHL gene and dysregulation of the PI3K/AKT/mTOR pathway, among others. These molecular characteristics have paved the way for targeted therapies such as tyrosine kinase inhibitors and immune checkpoint inhibitors. Recent *in silico* studies have identified multiple potential therapeutic targets in ccRCC, reinforcing the rationale for systemic approaches combining pembrolizumab and axitinib in selected patients⁸.

In Latin America, including Mexico, the epidemiological landscape of both HCC and RCC is evolving. While hepatitis C and metabolic syndrome remain prominent risk factors for HCC, ccRCC is increasingly associated with obesity and hypertension. The coexistence of both malignancies in the same patient—particularly one with diabetes and hypertension—raises important questions about shared metabolic pathways or inflammatory mechanisms that may contribute to carcinogenesis in multiple organs^{1,10}.

Prognostically, patients with synchronous malignancies may fare better than those with metastatic disease, provided that each tumor is diagnosed and treated according to its biological behavior. Some reports describe long-term survival in patients undergoing curative resection of both lesions, while others highlight the utility of systemic treatment in advanced or multifocal presentations. This case reinforces the value of personalized, multidisciplinary care in complex oncology scenarios¹⁰.

Lastly, consensus guidelines from international associations such as AEEH, AEC, SEOM, SERAM, SERVEI, and SETH emphasize the need for standardized diagnostic criteria and integrated imaging-pathology correlation in HCC. Such structured frameworks are essential when multiple tumors coexist, and decisions must be made

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regarding their origin and clinical significance. This patient benefited from a precise diagnostic process that avoided misclassification, enabling the implementation of targeted and effective treatment ¹².

CONCLUSIONS

The synchronous development of clear cell renal cell carcinoma (ccRCC) and hepatocellular carcinoma (HCC) in a single patient is an extraordinarily rare event that poses significant clinical challenges. This case demonstrates the importance of maintaining a high index of suspicion for multiple primary malignancies in patients presenting with multifocal tumors, especially in the context of metabolic comorbidities such as poorly controlled diabetes mellitus and hypertension, which may predispose to multiorgan carcinogenesis. The coexistence of two anatomically and histologically distinct tumors, each with its own pathophysiological pathways and clinical behavior, reinforces the critical need for individualized diagnostic approaches.

The diagnostic process in this case illustrates the pivotal role of histopathology and immunohistochemistry in distinguishing synchronous primary tumors from metastatic disease. Relying solely on imaging findings may lead to erroneous conclusions regarding tumor origin. The immunohistochemical profile in this patient—PAX8 positivity in the renal tumor and Hepar1/CD34 positivity with Glypican-3/PAX8 negativity in the hepatic lesion—was essential to confirm the diagnosis of two distinct primary malignancies. This diagnostic accuracy enabled the formulation of an effective, personalized treatment plan tailored to the biological characteristics of both tumors.

Therapeutically, the case highlights the utility of targeted therapy and immunotherapy in complex oncology scenarios where surgical management is not immediately indicated or feasible for both lesions. The decision to initiate pembrolizumab and axitinib was grounded in current evidence supporting their efficacy in advanced or multifocal ccRCC, and potentially beneficial effects in patients with synchronous malignancies when hepatic function remains preserved. The initial positive response further supports the role of systemic therapy in managing select patients with multiple primaries, offering clinical stability without compromising organ function.

This report contributes to the limited body of literature on synchronous ccRCC and HCC and serves as a reminder of the importance of multidisciplinary collaboration in the diagnostic and therapeutic journey of cancer patients. It also underscores the necessity of ongoing clinical vigilance and periodic reassessment in oncologic follow-up, as the potential for additional primary neoplasms cannot be excluded in high-risk patients. From an epidemiological perspective, the increasing prevalence of metabolic syndrome, obesity, and viral hepatitis in Latin America suggests a potential rise in

similar complex oncologic cases, making awareness and preparedness essential for early recognition and management.

In conclusion, this case not only exemplifies the complexity of diagnosing and treating synchronous primary malignancies but also serves as a model of precision medicine in action. It emphasizes the value of comprehensive clinical evaluation, integration of diagnostic modalities, and evidence-based therapeutic decision-making. Future research is warranted to better understand the molecular mechanisms that may link seemingly unrelated tumors and to establish clear guidelines for the optimal management of patients with multiple synchronous cancers.

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Synchronous Clear Cell Renal Carcinoma and Hepatocellular Carcinoma: A Rare Case of Dual Primary Malignancy

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