

Short Communication

## METASTATIC RENAL CELL CANCER IN THE ABSENCE OF TUMOUR IN PRIMARY ORGAN

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### ABSTRACT

**Summary.** This review aimed to search for case reports concerning the presentation, diagnosis, and management of metastatic RCC in the absence of a primary tumour in the primary organ, i.e., kidneys. The most common presentation involves lymph nodes, with varying clinical manifestations such as pain, haematuria, confusion, mass, lymph node enlargement, or biochemical changes like hypercalcemia. Case reports illustrate clear cell RCC as the most common histopathology, often presenting as lymph node masses. Immunohistochemical staining is typically positive for Vimentin, cytokeratin, and CD 10. The prognosis for mRCC CUP with Immunotherapy and Tyrosine Kinase Inhibitors (TKIs) has shown promising responses with or without surgery, better than metastatic RCC. The decision for treatment needs an individualized approach as recommended by the specific CUP MDT arranged.

**Keywords.** Metastatic Renal cell cancer (mRCC), Cancer of unknown primary (CUP), Renal cell carcinoma

### INTRODUCTION:

Carcinoma of unknown primary origin (CUP) refers to metastatic Cancer where the primary site remains unidentified despite standard investigations. It represents approximately 3% of diagnosed human cancers <sup>1</sup>Diagnostic and management challenges arise due to its aggressive spread and unpredictable metastatic pattern <sup>2</sup>. CUP is characterized by theories suggesting either undetectable primary lesions or regression of primary A Review of the Case Reports on Metastatic Renal Cell Cancer in the Absence of Tumour in Primary Organ Tumours <sup>3</sup>. NICE categorizes metastatic cancers into Malignancy of Uncertain Primary Origin/site/organ (MUO), Provisional Carcinoma of Undetermined Primary Organ/origin/site (Provisional CUP), and Confirmed Carcinoma of Unknown Primary Origin (Confirmed CUP). The objective of this review is a critical appraisal and thorough evaluation of cases of interest, examining their presentation, diagnostic processes, assessments, and treatment approaches, and ultimate outcomes as reported in various case studies. A literature search from 2013 to Jan 2024 was conducted on PubMed and Google Scholar using keywords related to metastatic renal cell cancers with an unknown primary organ. Nine relevant case reports were identified and included in the review. Data were extracted and presented in a Table.

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**Table. Case Reports And Outcome**

Cases Reported	Symptoms and Signs	Findings/Pathologies	Immunohistochemical Staining	Surgery Performed	Adjuvant Treatment	Outcome	Learning Outcomes
Shields and Kalebast, 2020	No symptoms. Absence of hematuria, pain, or urinary symptoms.	Left retroperitoneal lymph node measuring 1.8 cm	PAX 8, CK, AE1, and AE3	RPLND	No	No recurrence	Retroperitoneal lymph node dissection aids in diagnosing metastatic CUP RCC.
Kumar et al., 2014	Elevated calcium levels, cognitive confusion.	Bone lesions in the left scapula, right 7th rib, left 5th rib, and left SCJ joint. Pulmonary nodules on the left.	Positive staining for CAM5.2, Vimentin, and CD10	No surgery	Sunitinib and Zoledronic acid	Regression of pulmonary lesions and bone metastasis	Adjuvant therapy is beneficial in managing mCUP RCC.
Thamcharoen and Chaiwiriawong, 2013	Abdominal and chest symptoms, hilar lymphadenopathy	Reticular densities at right lung apex, masses at left neck and renal level.	CD10, Vimentin, and RCC	No surgery	Sunitinib	Stable disease	Immunohistochemical staining is crucial for accurate diagnosis.
Choi et al., 2012	Gradual mass emergence in the right supraclavicular region.	Right supraclavicular lymph node enlargement.	Positive for pan-cytokeratin, Vimentin, and CD10	No surgery	Radiotherapy with adjuvant Sunitinib	Regression of lesions	Combination of radiotherapy and adjuvant therapy is effective.
Wayne et al., 2010	Subcutaneous mass appearance.	Pancreatic body mass	CD10, AE1/AE3, PNRA, and Vimentin	Surgical excision, superficial parotidectomy, central pancreatectomy	No	Surgically excised metachronous oligometastatic lesion	Surgical excision is effective for managing isolated metastatic lesions.
Hlaing et al., 2022	Bronchitis	Lesions in T8, T7, T11, and L1	Positive for cytokeratins (AE1/AE3), CD10, PAX8; Negative for CK7, P40, and TTF	Palliative radiation therapy	No	-	Radiotherapy combined with immunohistochemical analysis enhances diagnostic accuracy.

**Table 02: Clinical Presentations, Imaging, and Treatment Approaches in Metastatic Renal Cell Carcinoma without Primary Tumor: A Case-Based Analysis**

Author & Year	Presentation	Imaging Findings	Histopathology & Immunohistochemistry	Treatment	Outcome	Key Takeaway
Fayaz MS et al., 2017	Neck mass (Left side) progressively increasing	4.7 × 3 × 3.3 cm mass in left supraclavicular and submandibular gland observed	Strong positivity for Cytokeratin (CAM 5.2), CD10, PAX8, and Vimentin	No surgery, Pazopanib	No progression of the disease	Genomic profiling and immunohistochemical staining are critical for diagnosis.
Bimbatti et al., 2023	Abdominal pain	Liver lesions with a 13 cm large tumor and pancreatic/hepatic hilum lymph nodes (largest 3.5 cm)	Affirmative staining for PAX8, MNF-116, and CD10	Axitinib 10 mg/day, Pembrolizumab 200 mg every 3 weeks	6-month CT showed >30% reduction in tumor size	Combination of Tyrosine Kinase Inhibitors and immunotherapy is effective as first-line treatment.
Abian N. et al., 2024	Lumbar pain	Vertebral mass	Clear cytoplasm, oval nuclei with positive reactivity for PAX8, EMA, CAIX, CD10, and CK	Corpectomy, pedicle resection, and tumor removal, Sunitinib 50 mg	3-month follow-up CT showed no renal tumor or disease progression	Surgery combined with Sunitinib is a viable option in CUP-mRCC with solitary bone lesion.

Table 1 shows the diversity of presentation of different reported cases and histological findings for immunohistochemical staining and outlines the outcomes that are with or without surgery for the lesion. Clinical presentations varied, mostly including lymph node masses <sup>4</sup>, bone lesions <sup>5</sup>, and liver involvement. Investigations involved CT scans, PET imaging, and serum marker tests. Histological examinations confirmed mostly clear cell RCC through immunohistochemical staining. Treatments ranged from surgery to targeted therapies, with positive outcomes observed in terms of regression or stable disease. The cases highlight the importance of personalized treatment strategies based on individual patient characteristics and disease biology. Management includes surgery, targeted therapies, immunotherapy, and radiation therapy, depending on the extent of the disease and patient factors. Immunohistochemical staining plays a crucial role in diagnosis and treatment planning. An important finding is that the response to treatment shows either regression or stable disease in

the case of metastatic RCC Carcinoma of Unknown primary. While an analysis based on the SEER database shows, the median survival for patients with lung, bone, or brain metastasis was 7 months, 7 months, 4 months, and 5 months, respectively <sup>6</sup>. In conclusion, this review of reported cases underscores the diverse clinical presentations and treatment modalities in metastatic clear cell renal cell carcinoma (mCUP RCC). Immunohistochemical staining played a crucial role in confirming diagnoses and guiding treatment decisions. Surgical interventions such as retroperitoneal lymph node dissection and excision of metastatic lesions demonstrated favourable outcomes, while adjuvant therapies, including targeted agents and immunotherapy, showed promising results in controlling disease progression. These findings emphasize the importance of a multidisciplinary approach, incorporating both surgical and medical interventions, in the management of mCUP RCC and highlight the significance of immunohistochemical staining in diagnosis and treatment planning.

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**Final Approval of version:** All Manton above

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