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Short Communication

Metastatic Renal Cell Cancer In The Absence Of Tumour In Primary Organ A Case-Based Review

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ABSTRACT

Background: to examine case reports that detail the presentation, diagnosis, and management of metastatic renal cell carcinoma (RCC) occurring in the absence of a detectable primary tumor in the kidneys. The most common presentation involves lymph nodes, with varying clinical manifestations such as pain, hematuria, confusion, mass, lymph node enlargement, or biochemical changes like hyperkalemia. Case reports illustrate clear cell RCC as the most common histopathology, often presenting as lymph node masses. Immunohistochemical staining is typically positive for Valentin, 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.

Objectives: To summarize and evaluate reported cases of metastatic RCC presenting without a primary renal tumor.

Methods: This Study Conducted in the Department of Urology, Whiston Hospital, Prescot, Liverpool, England. Targeted literature search was performed based on PubMed and Google Scholar (2013-2023) with such search terms as metastatic renal cell carcinoma without primary and CUP RCC. Case representations were embraced where they encompass specimens of histologically ascertained metastatic RCC isolated with no identifiable renal mass and also those that implicate affirmative immunohistochemistry (e.g., PAX8, CD10). The information on presentation, imaging, pathology, treatment and outcomes were extracted. A description analysis was made and the results coded in table form to bring out the trends of diagnosis and management.

Conclusions: Isolated metastatic lesions (established by immunohistochemistry (PAX8, CD10)) were found in all patients. Depending on the location of the lesion, targeted therapy (TKI/TF +/- immunotherapy) and surgeries were employed. Positive results were registered under individualized treatment regimens.
Confusion: CUP-mRCC is uncommon and can be treated with the multidisciplinary approach that should incorporate the following elements: imaging, IHC, targeted therapy, and surgical resection whenever possible.

Keywords. Carcinoma, Renal Cell, Neoplasm Metastasis, Neoplasms, Unknown Primary

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INTRODUCTION:

Carcinoma of unknown primary, also known as CUP, is a malignancy that has been recognised to have metastasised where the source of origin cannot able to be determined after all practice through clinical, radiological and pathological evaluation **[1]**. It constitutes approximately 3% of the total cancers reported worldwide **[2]**. CUP poses manifold diagnostic as well as therapeutic dilemmas due to its fierce biological nature and unpredictable expansion history **[3]**. The pathogenesis of CUP is reported to be linked to two major hypotheses: either a clinically silent primary tumour was present or regression of the primary lesion occurred after metastatic spread spontaneously **[4]**.This is a review of unusual manifestations of metastatic renal cell carcinoma (mRCC) without the presence of a palpable primary within the kidneys. The Metastatic Cancers that cannot have an ascertainable primary origin are divided into three groups according to the National Institute for Health and Care Excellence (NICE): Malignancy of Uncertain Primary Origin (MUO), Provisional Carcinoma of Unknown Primary (Provisional CUP), and Confirmed Carcinoma of Unknown Primary Origin (Confirmed CUP) **[5]**.The review aims to critically appraise and synthesise available published case reports on the clinical presentation, diagnostic workup, management strategies and outcomes of patients diagnosed with metastatic RCC. However, it shows no evidence of a primary renal tumour. PubMed and Google Scholar were used to conduct a literature search of case reports published between 2013 and January 2024, using the following terms: metastatic renal cell carcinoma, carcinoma of unknown primary, and renal metastases without primary. It identified nine pertinent, related case reports that met the inclusion requirement and were reviewed. Relevant information in these reports was removed and compiled into a summary table, which was used for comparing the data.

Table 1. Clinical Characteristics and Diagnostic Findings in Reported mRCC Cases

Author & Year	Clinical Presentation	Findings / Pathologies	Immunohistochemistry
Shields & Kalebasty, 2020	Asymptomatic; no hematuria, pain, or urinary complaints	Retroperitoneal lymph node (1.8 cm)	PAX8, CK, AE1/AE3 positive
Kumar et al., 2014	Hypercalcemia; cognitive dysfunction	Bone lesions (scapula, ribs, SCJ); pulmonary nodules	CAM5.2, Vimentin, CD10 positive
Thamcharoen & Chaiwiriyawong, 2013	Abdominal and chest symptoms; hilar lymphadenopathy	Masses in lung apex, neck, and renal area	CD10, Vimentin, RCC marker positive
Choi et al., 2012	Painless right supraclavicular mass	Supraclavicular lymphadenopathy	Pan-CK, Vimentin, CD10 positive
Wayne et al., 2010	Subcutaneous lump	Pancreatic and parotid mass	CD10, AE1/AE3, PNRA, Vimentin positive
Hlaing et al., 2022	Bronchitis-like symptoms	Vertebral lesions (T7–T11, L1)	AE1/AE3, CD10, PAX8 positive; CK7, P40, TTF negative

Table 2. Summary of Clinical Insights and Learning Points

Author & Year	Key Learning Point
Shields & Kalebasty, 2020	RPLND assists in diagnosing metastatic CUP RCC
Kumar et al., 2014	Systemic therapy is effective in bone-dominant mCUP RCC
Thamcharoen & Chaiwiriyawong, 2013	IHC is essential for accurate mCUP RCC diagnosis
Choi et al., 2012	Combined radiotherapy and targeted therapy can offer effective local control
Wayne et al., 2010	Surgery is beneficial for managing isolated oligometastatic lesions
Hlaing et al., 2022	Combined IHC and radiotherapy enhances diagnostic precision

Table 3: Clinical Presentations, Imaging, and Treatment Approaches in Metastatic Renal Cell Carcinoma without Primary Tumor: A Case-Based Analysis

Author & Year	Clinical Presentation	Imaging Findings	Histopathology / Immunohistochemistry	Treatment Administered	Clinical Outcome	Key Clinical Insight
Fayaz MS et al., 2017	Progressive left neck mass	4.7 × 3 × 3.3 cm mass in left supraclavicular and submandibular glands	Strong positivity for Cytokeratin (CAM 5.2), CD10, PAX8, and Vimentin	Targeted therapy with Pazopanib; no surgical intervention	Stable disease; no progression	Immunohistochemistry and genomic profiling are critical for accurate diagnosis
Bimbatti et al., 2023	Abdominal pain	Large hepatic mass (13 cm) and lymphadenopathy at pancreatic/hepatic hilum (up to 3.5 cm)	Positive staining for PAX8, MNF-116, and CD10	Axitinib (10 mg/day) + Pembrolizumab (200 mg every 3 weeks)	Over 30% reduction in tumor burden at 6-month follow-up	Combination of tyrosine kinase inhibitors and immunotherapy is effective as first-line care
Abian N. et al., 2024	Lumbar pain	Solitary vertebral lesion	Clear cytoplasm, oval nuclei; positive for PAX8, EMA, CAIX, CD10, and CK	Corpectomy, pedicle resection, tumor excision + Sunitinib (50 mg)	No evidence of renal tumor or disease progression	

Table 4. Clinical Presentations and Management of mRCC Without Primary Lesion

Author & Year	Presentation	Imaging Findings	IHC Profile	Treatment	Outcome
Fayaz MS et al., 2017	Left neck mass	4.7×3×3.3 cm supraclavicular/submandibular lesion	PAX8+, CAM5.2+, CD10+, Vimentin+	Pazopanib, no surgery	Stable disease
Bimbatti et al., 2023	Abdominal pain	13 cm liver tumor, 3.5 cm lymph nodes (pancreatic/hepatic hilum)	PAX8+, MNF-116+, CD10+	Axitinib + Pembrolizumab	>30% reduction at 6 months
Abian N. et al., 2024	Lumbar pain	Solitary vertebral lesion	PAX8+, EMA+, CAIX+, CD10+, CK+	Surgery + Sunitinib	No progression at 3-month follow-up

DISCUSSION:

Many of the clinical presentations and histopathological features reported in metastatic renal cell carcinoma (mRCC) cases lacking an identifiable primary lesion are demonstrated in Table 1. Clinical manifestations included painless lymphadenopathy pain caused by skeletal lesions and liver mass **[6]**. Typical diagnostic studies included contrast-enhanced CT scans, PET scans, and applicable serum markers, which helped identify metastatic locations. Immunohistochemical stains were primarily used to confirm histologically, especially when PAX8, CD10, Vimentin, and CAM5.2 showed a strong positive result, indicating that it is a clear cell RCC**[7]**. These indicators were crucial in determining the treatment plan Therapy was tailored to the specific disease site and area. Surgery, including retroperitoneal lymph node dissection and resection of isolated metastases, has been reported to yield positive results in select patients **[8]**. Significant responses were observed with systemic treatments, specifically tyrosine kinase inhibitors (such as pazopanib and axitinib) and immune checkpoint inhibitors (such as Pembrolizumab) [6,7].Although in all the large databases analysis, like the SEER registry, metachronous RCC patients generally

have a poor median survival of around 7 months in lung and bone metastases, 5 months in brain, and 4 months in the liver **[9],** treatment based on individualized histopathological and immunological profiling may have much improved results.This evaluation highlights the Importance of immunohistochemistry in diagnosing carcinoma of unknown primary (CUP) of renal origin and in providing proper management in terms of treatment. In addition, it emphasises the significance of a multidisciplinary approach among urologists, oncologists, pathologists, and radiologists in the management of mCUP RCC **[10]**.

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REFERENCES.

1. Aragon-Ching JB. Rapidly evolving first-line therapy using checkpoint inhibitors in metastatic renal cell cancer. Future medicinal chemistry. 2022;14(11):767-70.

2. Aweys H, Lewis D, Sheriff M, Rabbani RD, Lapitan P, Sanchez E, et al. Renal Cell Cancer - Insights in Drug Resistance Mechanisms. Anticancer research. 2023;43(11):4781-92.

3. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M, Mafakher L. Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment. Giornale italiano di nefrologia : organo ufficiale della Societa italiana di nefrologia. 2022;39(3).

4. Chen YW, Wang L, Panian J, Dhanji S, Derweesh I, Rose B, et al. Treatment Landscape of Renal Cell Carcinoma. Current treatment options in oncology. 2023;24(12):1889-916.

5. Dizman N, Meza L, Bergerot P, Alcantara M, Dorff T, Lyou Y, et al. Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. Nature medicine. 2022;28(4):704-12.

6. Dudani S, de Velasco G, Wells JC, Gan CL, Donskov F, Porta C, et al. Evaluation of Clear Cell, Papillary, and Chromophobe Renal Cell Carcinoma Metastasis Sites and Association With Survival. JAMA network open. 2021;4(1):e2021869.

7. El Kaddissi A, Ducleon GG, Lefort F, Mezepo G, Frontczak A, Goujon M, et al. Metastatic renal cell cancer and first-line combinations: for which patients? (focus on tolerance and health-related quality of life). Bulletin du cancer. 2022;109(2s):2s19-2s30.

8. Garje R, Elhag D, Yasin HA, Acharya L, Vaena D, Dahmoush L. Comprehensive review of chromophobe renal cell carcinoma. Critical reviews in oncology/hematology. 2021;160:103287.

9. Silver JA, Roy CF, Lai JK, Caglar D, Kost K. Metastatic Clear Renal-Cell Carcinoma Mimicking Anaplastic Thyroid Cancer: A Case Report. Ear, nose, & throat journal. 2024;103(7):Np407-np10.

10. Yanagisawa T, Mori K, Katayama S, Mostafaei H, Quhal F, Laukhtina E, et al. Hematological prognosticators in metastatic renal cell cancer treated with immune checkpoint inhibitors: a meta-analysis. Immunotherapy. 2022;14(9):709-25.

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