Renal Clear Cell Carcinoma with Unknown Primary: Is It Real Entity or Just Hypothesis?

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ABSTRACT

Renal cell carcinoma (RCC) is a common type of cancer, and about 25% of patients are diagnosed at an advanced stage. Bone metastasis is common in RCC, but instances of bone metastases without a primary kidney tumour have rarely been reported. Here, we report a case of a 56-year male patient who presented with extensive bone metastases. The biopsy was reported as clear cell RCC and no primary renal tumour was detected by positron emission tomography and magnetic resonance imaging. Pazopanib was initiated and progression was detected in the 6th month of treatment. Nivolumab was initiated as second line therapy. In the literature, primary unrecognised RCC cases are found only as case reports. This case highlights the importance of clinicians' consideration of possible metastatic RCC in a patient with pathologically diagnosed clear cell carcinoma, even if no primary renal tumour is identified.

Key Words: *Renal cell carcinoma, İmmunohistochemistry, Diagnosis, Kidney, Cancer.*

How to cite this article: Boru YE, Sutcuoglu O, Caliskan K, Gocun PU, Yazici O. Renal Clear Cell Carcinoma with Unknown Primary: Is It Real Entity or Just Hypothesis?. *J Coll Physicians Surg Pak* 2022; **32(JCPSPCR)**:CR200-CR202.

INTRODUCTION

Renal cell carcinoma (RCC) is a malignancy that originates from the renal cortex. At the time of diagnosis, 23% of patients have metastatic disease and 25% will develop metastases during the follow-up period after nephrectomy.[1] The most common sites of metastases are the lungs (45%), bones (30%), and regional lymph nodes (LN) (22%).[1] When metastatic RCC is diagnosed, there is often a primary tumour in the kidney. However, there are also rare cases of metastatic RCC without a renal primary.[2,3] In this report, a case is presented with multiple bone metastases, who was diagnosed with clear cell RCC without a primary mass in the kidney.

CASE REPORT

A 56-year man was admitted to the hospital with a complaint of thoracic pain for the past 3 months. On physical examination, there were no pathological findings except diffuse pain on palpation over bones. Laboratory findings including complete blood cell count, liver, and renal function tests were within normal limits.

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Received: November 02, 2020; Revised: May 18, 2021; Accepted: May 18, 2021
DOI: https://doi.org/10.29271/jcpsp.2022.JCPSPCR.CR200

Chest computed tomography (CT) revealed multiple lytic/sclerotic and calcified lesions with a maximum size of 13 mm in the sternum, ribs and thoracic vertebrae, which were reported as metastases. To localise the primary lesion, positron emission tomography – computed tomography (PET-CT) was performed. PET-CT revealed more than 20 lytic/sclerotic lesions, but no primary lesion. Prostate-specific antigen was normal. To rule out plasma cell disorders, specific blood and urine tests and bone marrow biopsy were performed. Serum and urine protein electrophoresis, immunoglobulins, and light chains were normal. In the bone marrow biopsy, among the bone marrow cells, a focus of medium-sized tumour cells with abundant clear cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli was seen in the desmoplastic stroma. Immunohistochemical staining showed pankeratin, keratin 8/18, EMA, vimentin, and PAX-8 positivity in tumour cells. Based on these findings, metastatic clear cell RCC diagnosis was considered (Figure 1). The body pain persisted during follow-up. To find a potential primary tumour, abdominal magnetic resonance imaging (MRI) was performed. The size of both kidneys was normal, and no mass was observed. Endoscopy and colonoscopy were performed to rule out a potential clear cell variant of gastrointestinal cancer. Bone marrow biopsy was re-evaluated, and additional immunohistochemistry was performed at our university's pathology department. CD10, PAX2 and kidney-specific cadherin were positive in tumour cells and the patient's diagnosis was confirmed again as metastatic clear cell RCC.

The patient was treated with pazopanib, thoracic radiotherapy, and zoledronic acid. After 3 months of pazopanib, PET-CT scan showed decreased metabolic activity in bone lesions. The pain

decreased almost fully and ECOG performance status was 0. However, in the 6th month of treatment, the patient presented with pain and shortness of breath. Imaging revealed new lesions in the lung, newly developed pleural effusion and progression of bone lesions. Nivolumab was initiated as the second-line therapy. The patient was at the second month of Nivolumab treatment and is being followed up.

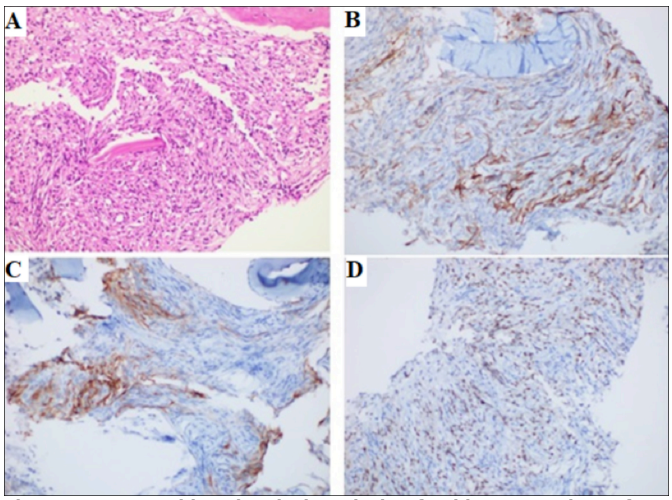

Figure 1: Immunohistochemical analysis of a biopsy specimen from patient. (A) Tumor cells have clear cytoplasm and small oval nucleus. (B) CD10 shows membranous staining in tumor cells. (C) Kidney-specific cadherin shows cytoplasmic staining tumor cells. (D) Pax-8 shows nuclear staining in tumor cells.

DISCUSSION

A very limited number of metastatic RCC cases without primary tumours have been reported in the literature. In this case, the patient presented with extensive bony metastases and pathological evaluation revealed RCC metastasis in the bone marrow. Immunohistochemical findings played a key role in the diagnostic process, and the diagnosis of the patient was accepted as RCC, although no mass was detected on imaging. Immunotherapy was initiated when progression was detected during pazopanib treatment.

On screening literature, primary unrecognised RCC cases were found only as case reports.[3] In these patients, the reason why the primary tumour could not be detected was not fully explained and different hypotheses were developed. Possible causes may be that the primary tumour is too small and cannot be detected by current imaging techniques.[3] On the other hand, it has been suggested that it may be a tumour originating from ectopic kidney tissue.[4] However, spontaneous tumour regression is seen in 1% of RCC, and spontaneous tumour regression occurring in the primary may explain this phenomenon.[5] When the cases in the literature were examined, it was observed that a primary renal mass was detected in a group of patients after a while and the disease did not recur after metastasis was removed in a group of patients.[3,6] Although the primary renal mass was still not detected in this patient, new metastatic lesions have developed in the lung. The small number of patients and their different progression make it difficult to understand the underlying mechanism. The data in the literature were insufficient to explain the pathophysiology. It is hoped that in future studies, the underlying pathophysiological mechanism of primary unknown RCC might be explained.

When a clear cell RCC patient with an undetected primary is encountered, the gastrointestinal and genitourinary systems should be examined. In this patient, both systems were examined and no pathological finding was detected. Imaging revealed no evidence in favour of the primary lesion, and the only solution for differential diagnosis was histopathological evaluation. Clear cell RCC consists of cells with clear cytoplasm and hyperchromatic, centrally localised round nuclei. This cell morphology can also be seen in other solid tumours. Therefore, immunohistochemical staining is needed in order to make an accurate diagnosis. Immunohistochemically, RCC marker and CD 10 are specific for metastatic RCC and have a high diagnostic value.[7,8] RCC marker has low sensitivity but high specificity. PAX-2 and PAX-8 are also important indicators of renal tumour origin.[9] Clear cell RCC usually stains with vimentin, keratin, EMA, CD10, PAX-2 and RCC marker.[9] Other markers such as Kidney injury molecule-1 (KIM-1) and anti-phosphorylated H2AX are suggested as potential markers to confirm metastasis.[9] An important differential diagnosis in female patients is clear cell ovarian carcinoma. Clear cell ovarian carcinoma stains with keratin 7 but does not stain with CD10. However, clear cell RCC stains with CD10 but not with keratin 7.[10]

In RCCs without an identifiable primary site, there is no well-defined treatment protocol. Published studies illustrate that in cases where surgical resection is possible, surgical resection and radiotherapy can be used as first-line treatment.[2,11] Tyrosine kinase and mTOR inhibitors can be used if the tumour is unresectable at diagnosis or if the tumour recurs after surgery.[12]

In this case report, it is emphasised that clinicians should consider metastatic RCC in cases of clear cell carcinoma without primary tumour mass. The diagnosis and staging process should be completed using histopathological evaluation and imaging techniques, and then oncological treatment should be started immediately.

PATIENT'S CONSENT:

Informed consent from the patient was obtained prior to the writing of the manuscript.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

YEB: Material preparation, data collection, and data analysis.
OS, KC, PUG, OY: Manuscript writing.
YEB, OS, OY: Critical revision of the manuscript.
All the authors have approved the final version of the manuscript to be published.

REFERENCES

1. Bukowski RM, Novick AC. Clinical practice guidelines: renal cell carcinoma. *Cleveland Clinic J Medicine* 1997; **64**:SI1-44; quiz SI5-7. DOI: 10.3949/ccjm.64.s1.4.
2. Choi YR, Han HS, Lee OJ, Lim SN, Kim MJ, Yeon MH, *et al*. Metastatic renal cell carcinoma in a supraclavicular lymph node with no known primary: A case report. Cancer research and treatment. *J Korean Cancer Association* 2012; **44(3)**:215. Doi: 10.4143/crt.2012.44.3.215.
3. Kumar R, Aziz T, Jamshaid H, Gill J, Kapoor A. Metastatic renal cell carcinoma without evidence of a primary renal tumour. *Current Oncology* 2014; **21(3)**:e521. Doi: 10.3747/co.21.1914.
4. Terada T. Extra-renal clear cell renal cell carcinoma probably arising from mesodermal embryonic remnants. *Pathology Int* 2012; **62(4)**:291-3. Doi10.1111/j.1440-1827.2011.02780.x.
5. Lokich J. Spontaneous regression of metastatic renal cancer: Case report and literature review. *American J Clinical Oncology* 1997; **20(4)**:416-8. Doi: 10.1097/00000421-199708000-00020.
6. Fayaz MS, Al-Qaderi AE, El-Sherify MS. Metastatic renal cell carcinoma with undetectable renal mass presenting as lymphadenopathy. *CEN Case Rep* 2017; **6(1)**:36-8. Doi: 10.1007/s13730-016-0239-9.
7. Ortiz-Rey J, Gómez CDM, Peláez EB, Fernández AC, Barbosa MB, Antón IB. Expression of CD10 and renal cell carcinoma marker in clear cell renal cell carcinoma: Analysis on tissue arrays. *Actas Urologicas Espanolas* 2006; **30(3)**:281-6. Doi: 10.1016/s0210-4806(06)73440-4.
8. Zhou M, Roma A, Magi-Galluzzi C. The usefulness of immunohistochemical markers in the differential diagnosis of renal neoplasms. *Clinics Laboratory Medicine* 2005; **25(2)**:247-57. Doi: 10.1016/j.cll.2005.01.004.
9. Ramos-Vara J, Edmondson E, Miller M, Dusold D. Immunohistochemical profile of 20 feline renal cell carcinomas. *J Comparative Pathology* 2017; **157(2-3)**:115-25. Doi: 10.1016/j.jcpa.2017.06.004.
10. Cameron R, Ashe P, O'Rourke D, Foster H, McCluggage W. A panel of immunohistochemical stains assists in the distinction between ovarian and renal clear cell carcinoma. *Int J Gynecological Pathology* 2003; **22(3)**:272-6. doi: 10.1097/01.PGP.0000071044.12278.43.
11. Wayne M, Wang W, Bratcher J, Cumani B, Kasmin F, Cooperman A. Renal cell cancer without a renal primary. *World J Surgical Oncology* 2010; **8(1)**:1-3. Doi: 10.1186/1477-7819-8-18.
12. Mihály Z, Sztupinszki Z, Surowiak P, Gyorffy B. A comprehensive overview of targeted therapy in metastatic renal cell carcinoma. C*urr Cancer Drug Targets* 2012; **12(7)**: 857-72. Doi.10.2174/156800912802429265.