CASE REPORT

Clear Cell Renal Cell Carcinoma with Unilateral Ovarian Metastasis: Report of a Rare Case and Review of Literature

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ABSTRACT

Renal cell carcinoma (RCC) is a common malignancy accounting for 2 to 3% of all adult malignancies, with a common occurrence in males in their 6th and 7th decades. Among histologic subtypes, clear cell carcinoma is the most common. In about 1/3 of patients, the tumour is first discovered when it has metastasized, and half of those initially diagnosed with RCC develop metastases during follow-up. Renal cell carcinoma metastasizes *via* the lymphatics and the haematogenous route. The most frequent sites are the lungs, followed by the lymph nodes, the bone, the liver, and the brain. However, renal cell carcinoma is notorious for metastases to any site. Although ovaries are considered the common site of metastases, the primary renal cell carcinoma metastasizing to the ovary is relatively uncommon, with only 41 cases reported in the literature. Of these cases, 11 involved bilateral ovaries. Metastatic tumours in the ovary can sometimes pose a diagnostic challenge, especially when they histologically resemble primary ovarian tumours. RCC can be misdiagnosed as primary clear cell carcinoma of the ovary. The distinction between the two is quite crucial for adequate management. We present a case of left renal clear cell RCC in a 44-year-old woman with metastasis to the left ovary.

Keywords: *Clear cell renal cell carcinoma, ovarian, metastases, unilateral.*

INTRODUCTION

Renal cell carcinoma (RCC) is a common malignancy accounting for 2 to 3% of all adult malignancies. Among histologic subtypes, clear cell carcinoma is the most common [1, 2]. Renal cell carcinoma metastasizes *via* the lymphatics and the haematogenous route. The most frequent sites are the lungs, followed by the lymph nodes, the bone, the liver, and the brain [3]. However, renal cell carcinoma is notorious for metastases to any site. Although ovaries are considered the common site of metastases, the primary renal cell carcinoma metastasizing to the ovary is relatively uncommon, with only 41 cases reported in the literature. Of these cases, 11 involved bilateral ovaries.

We present a case of left renal clear cell RCC in a 44-year-old woman with metastasis to the left ovary.

CASE PRESENTATION

We present a case of a 44-year-old woman who was diagnosed with clear cell RCC one year ago. There was no family history of any malignancy. The patient had a dull, persistent left flank pain for several months. Computerised tomography (CT) scan showed a large, well-defined, heterogeneous, enhancing mass in the left kidney measuring 10.3 x 6.5 x 7.5 cm. She underwent radical nephrectomy. On histopathological examination, the left renal mass was diagnosed as clear cell renal cell carcinoma, WHO grade 2. Tumour cells were positive for CD10, CAIX, and vimentin, and negative for CK7, CK20, TFE3, and CD117. The tumour was limited to the kidney, and no vascular invasion was identified. No sarcomatous or rhabdoid features were seen. Ureteric, renal artery, renal vein, perinephric fat, and renal sinus soft tissue margins were negative for tumour. The distance of the tumour from the renal capsule was less than 1 mm, and the distance from the perinephric fat was 2 mm. 4 left hilar lymph nodes were tumour-free (0/4). It was staged as PT2 N0 Mx.

The patient was seen after a year as part of follow-up. The patient had no abdominal pain, haematuria, heavy menstrual bleed, fever, or chills. Follow-up MRI performed after a year showed a solid enhancing left ovarian mass with peripheral cystic areas. It showed an intermediate signal on T2-weighted images and was minimally hyperintense on T1-weighted images. It showed avid enhancement and faint restriction on the diffusion images. It measured 2.9 x 2.4 x 2.9 cm. The right ovary showed a similar but smaller lesion measuring 0.8 x 0.8 x 0.7 cm. Tumour markers weren't done. No enlarged pelvic lymph nodes were seen. A trace of fluid was observed in the pelvis, likely physiological. Assessment of the abdomen showed a missing left kidney due to the nephrectomy. The right kidney was normal with no evidence of hydronephrosis. Differential diagnosis of the left ovarian mass included fibroma with atypical features

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probably related to ovarian torsion, struma ovarii, metastatic disease, *etc.* It was excised and sent for frozen section. A diagnosis of clear cell carcinoma, most likely metastases from renal clear cell carcinoma, was rendered at the time of frozen section. Additional sections submitted after formalin fixation showed similar morphologic features of a malignant neoplasm composed of sheets of clear cells with adjacent normal ovarian stroma (**Fig. 1**) Neoplastic cells were arranged in an alveolar pattern.

Alveoli were lined by cells with abundant clear cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli (**Fig. 2**). No necrosis was seen. Adjacent ovarian stroma was oedematous and showed multiple cortical cysts. Tumour cells demonstrated diffuse and strong positivity for CD10 (**Fig. 3**), CAIX (**Fig. 4**), and PAX-8, which were

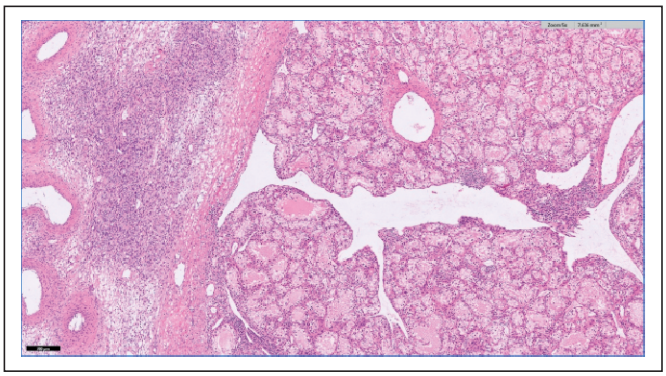

Fig. (1): High power magnification showing transition area of clear cell carcinoma with ovarian parenchyma (H&E 10 x).

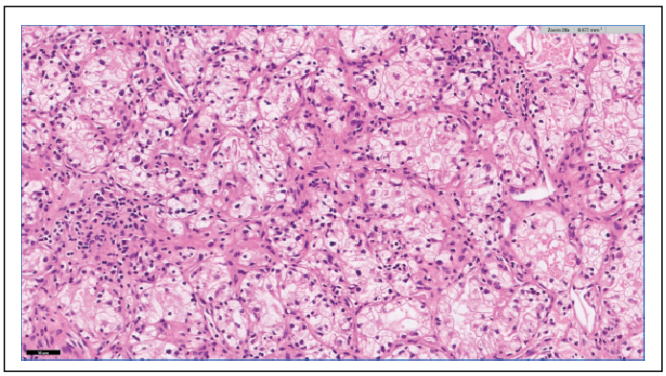

Fig. (2): Tumor exhibiting clear cell configuration. Neoplastic cells are arranged in alveolar pattern with hyperchromatic nuclei and inconspicuous nucleoli (H & E 10 x).

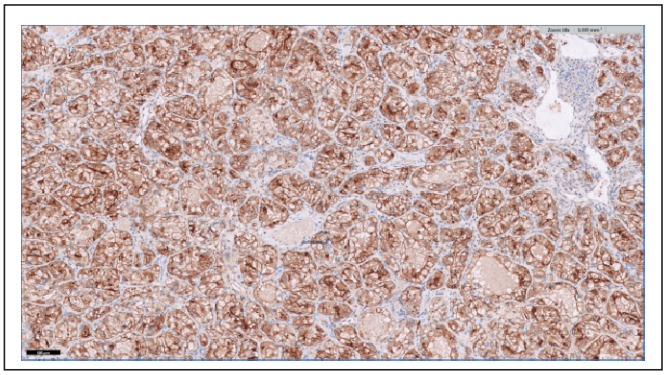

Fig. (3): Tumor cells exhibiting positive staining for CD10 (H& E 40x).

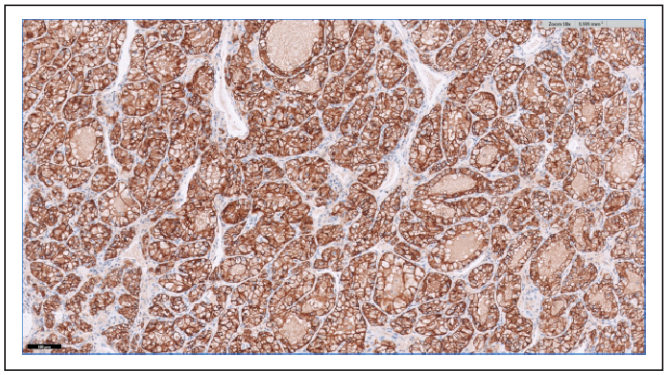

Fig. (4): Tumor cells showing strong membrane staining for CAIX (H& E 40x).

negative for Napsin-A and CK7. The final diagnosis on the permanent section, based on morphological and immunohistochemical profile, was metastatic clear cell carcinoma consistent with a known primary renal origin. The left fallopian tube was unremarkable. No treatment-related changes were present. The right ovary was tumour-free and showed benign ovarian parenchyma with cortical cysts and a ruptured haemorrhagic corpus luteum cyst.

DISCUSSION

Ovarian metastases are found in 0.5% of renal cancers. A review study was undertaken by Young and Hart in 1992, which included the clinical and pathological features of the renal cell carcinoma metastases to the ovary. They personally observed three cases, and six cases were previously reported. They emphasized the importance of distinguishing it from the primary ovarian clear cell adenocarcinoma. The primary renal tumours in all nine cases were well-differentiated RCC, clear cell type. In five cases, the ovarian tumour was diagnosed, whereas in two cases, it was initially misdiagnosed as primary ovarian clear cell carcinoma. Two cases showed bilateral ovarian metastases. In two instances, metastasis occurred 8 and 11 years after nephrectomy for RCC [4].

Similarly, Adachi *et al.* [5] reported a case of ovarian metastasis to both right and left ovaries from a primary left-sided RCC diagnosed three years after radical nephrectomy. The patient was alive without any residual disease, three years after bilateral salpingo-oophorectomy at the time of publication of the case report [5]. Shinojima *et al.* [6] reported a case of a 47-year-old female patient who underwent left radical nephrectomy for a primary clear cell RCC. On routine check-up four years later, abdominal CT revealed a 9 cm predominantly solid and partially cystic tumour in the pelvic cavity. She underwent hysterectomy and bilateral salpingo-oophorectomy for a left ovarian tumour, which on histopathological examination was reported as metastatic RCC [6]. Similarly, Valappil *et al.* [7] reported a case in which ovarian metastasis from primary RCC occurred seven years after diagnosis of renal primary.

The above examples show that ovarian metastases from primary RCC can occur several years following initial diagnosis and surgery for RCC [7]. Sometimes, ovarian metastases of RCC may be the first sign of a renal tumour, without a prior history of primary RCC. RCC is notorious for metastasising to rare sites anywhere in the body. He also recommended that it is crucial to consider the possibility of metastasis from renal cell carcinoma as a potential differential diagnosis in cases of ovarian tumours with clear cells by imaging to discover occult RCC [7].

With regards to the therapeutic and prognostic implications, it is essential to differentiate between the two entities, *i.e.,* primary ovarian and clear cell carcinoma of the kidney metastases to the ovary, for the adequate management of the cases.

Histological differentiation between the two may be difficult. However, certain histological features, such as the hobnail appearance of the epithelium, are more typical of ovarian clear cell carcinoma. Apart from histology, immunohistochemistry (IHC) is very important in differentiating between the two. The RCC monoclonal antibody is expressed in 80-90% of RCCs but is negative in ovarian clear cell carcinoma. Conversely, keratin seven and CA125 are represented in primary ovarian carcinoma, including clear cell carcinoma, whereas clear cell renal cell carcinoma does not show immunoreactivity. CD 10 is positive in RCC but negative in primary ovarian cancers [7, 8]. Also, the following immunohistochemical stains, CK 7, CK 20, Vimentin, ER, and CA 125, are shown to help distinguish primary ovarian cancers from metastatic RCC [9].

Toquerto *et al.* [10] reported a similar case report. In his study, the patient presented with weight loss, lethargy, and a palpable mass. Toquero *et al.* [10] reported a review of 14 cases. In his observations, a delay in the diagnosis of primary renal cell carcinoma was observed in approximately 1/3 of cases. There was confusion with presenting symptoms, which corresponded to the metastatic site rather than the primary.

Younes *et al.* [11] reported a similar case of ovarian metastases from the primary clear cell renal cell carcinoma.

Based on the available evidence, they suggested that surgical extirpation of both the primary and metastatic tumours may lead to long-term disease-free survival [10]. Another case of bilateral ovarian metastasis from primary RCC was reported by Guney *et al.* [12]. They also emphasised that early diagnosis and prompt treatment of this metastatic tumour can lead to prolonged patient survival [12]. Luychx *et al.* [13] noted that most cases of metastatic spread to the ovaries are discovered during follow-up of RCC treatment. They also noted that surgical excision of ovarian metastasis improves the prognosis if the lesions are completely excised [13].

A case with bilateral ovarian metastasis was reported by Holody-Zareba *et al.* in 2013 [14]. A similar case of bilateral metastases was also reported by Synder *et al.* in 2021 [15].

Further regarding the duration, Bauerová *et al.* [16] reported the development of ovarian metastasis from primary RCC 21 years later. Although literature reports 41 cases of RCC showing ovarian metastases, only 11 cases involved the ovaries bilaterally [17, 18].

Distinguishing a primary ovarian tumour from metastatic RCC to the ovary is essential because of differences in treatment and prognosis.

Uruc *et al.* [17] reported a case in a 48-year-old female that has similarities to our case. She presented with right flank pain and haematuria. The patient underwent right radical nephrectomy for suspected RCC, which was confirmed on histological examination as clear cell RCC. Almost 2 years after the nephrectomy, ultrasonography showed a haemorrhagic cystic mass in the left ovary, which was reported as a malignant clear cell neoplasm on frozen section [17]. Histopathology of the permanent sections confirmed metastasis from primary RCC. Hence, it was emphasised that both the primary ovarian carcinomas and the metastatic renal cell carcinomas should be treated by radical surgical procedures for long-term disease-free survival [17].

Table **1** below highlights the total number of cases reported in the literature to date.

Table 1: Authors with unilateral/bilateral ovarian metastasis with publication year.

Author	Year	Unilateral or Bilateral Ovarian Metastases
Young RH *et al.* [4]	1992	Bilateral
Adachi *et al.* [5]	1994	Bilateral
Shinojima *et al.* [6]	2001	Unilateral
Valappil *et al.* [7]	2004	Unilateral
Toquero *et al.* [10]	2009	Unilateral
Guney *et al.* [12]	2010	Bilateral
Luychx *et al.* [13]	2011	Unilateral
Holody-Zareba *et al.* [14]	2013	Bilateral
Bauerová L *et al.* [16]	2014	Unilateral
Kostrzewa M *et al.* [18]	2015	Bilateral
Uruc F *et al.* [17]	2017	Unilateral
Synder *et al.* [15]	2021	Bilateral
Younes *et al.* [11]	2023	Unilateral
Present Study	2025	Unilateral

CONCLUSION

Renal cell carcinoma (clear cell type) can rarely metastasize to one or both ovaries in females. Such metastases can occur several years after the diagnosis and surgical treatment of the primary renal tumour. In some cases, ovarian metastasis may be the first sign of the primary renal tumour. It is essential to distinguish between a primary ovarian clear cell carcinoma and metastatic RCC since management is different. However, very rare metastatic RCC should be kept in the differential diagnosis of a unilateral or bilateral clear cell ovarian tumour. Surgical resection of metastatic RCC in the ovaries improves the prognosis if it is completely excised.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for the publication of her anonymized information in this article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

AUTHORS' CONTRIBUTION

N.Y, Z.A, AN, A.P.S., and A.T, as pathologists, made pathological diagnoses and wrote the manuscript. M.B., a gynaecologic surgeon, and H.AR., a urologic surgeon, followed the patient and performed surgery. All authors approved the final version of the manuscript.

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