Cases – Renal cell carcinoma with remote testicular metastases

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INTRODUCTION

The incidence of renal cell carcinoma (RCC) has more than doubled over the past 50 years in the developed world, accounting for 2% of cancer diagnoses and deaths worldwide.[1] Though historically associated with the triad of hematuria, flank pain, and palpable abdominal mass, diagnosis now occurs more commonly through incidental imaging findings.[1-3] Thus, delineating disease course and metastatic pattern is critical.

Common sites of RCC metastases include the brain, lung, bone, lymph nodes, adrenal gland, and liver; however, RCC is also notorious for its ability to metastasize to any organ.[2-5] Importantly, 20–40 % of patients with disease confined to the kidney who undergo nephrectomy will experience an RCC recurrence.[2] Cases of metastasis to the testicle have rarely been reported, with approximately 50 cases reported thus far.[3,6-8]

In this report, we present two cases of metastatic clear-cell RCC with spread to the testicle: a 68-year-old male with metastases to the contralateral testicle five years post-nephroureterectomy and systemic therapy, and an 80-year-old male with metastases to the ipsilateral testicle 39 years post-radical nephrectomy. All patient identifiers have been removed, conforming with institutional review board exemption standards.

CASE REPORT 1

A 68-year-old man was incidentally found to have a left testicular mass on contrast-enhanced surveillance computed tomography (CT) scan for previously treated RCC, which was diagnosed five years prior. He initially presented in March of 2017 with acute kidney injury. A 14.7 x 10.6 x 11.5 cm right renal heterogenous mass was found on ultrasound. Magnetic resonance imaging (MRI) confirmed a large, heterogenous, lower pole mass on the right kidney with a concomitant filling defect in the mid-right ureter and moderate right-sided hydroureteronephrosis.

The patient underwent a right nephroureterectomy in April of 2017 and was found to have clear-cell RCC (ccRCC), World Health Organization (WHO) grade 3, pT2bNX, with negative surgical margins. Tumor necrosis was focally present. Interestingly, a deposit ccRCC at the level of mid-to-distal ureter was appreciated on final pathology, which was considered synchronous metastatic disease (M1). He was deemed disease-free and was placed under surveillance with cross-sectional imaging and cystoscopy, per Canadian Urological Association (CUA) 2018 guidelines.[9]

In February 2019, he was found to have possible disease recurrence on MRI, with a hypoenhancing lesion of 0.4 x 1.2 cm in the lower pole of the left kidney. He was continued on surveillance until April 2020, when another MRI and CT scan showed a 34 x 32 mm lower left renal mass and multiple pulmonary metastatic nodules, as well as external iliac lymph nodes up to 7 mm on the left. Prior to commencing systemic therapy, brain imaging demonstrated three choroid plexus metastases.

The patient received gamma-knife treatment to the brain metastatic foci followed by 10 cycles of pembrolizumab and axitinib,[10] which was stopped in spring 2021 due to a lacunar infarction. He was then placed under surveillance with cross-sectional imaging.

In August 2022, surveillance CT scan suggested the presence of an enhancing left testicular mass. In retrospect, the mass can be seen on the two previous scans in March and May of 2022. The patient thus had a scrotal Doppler sonogram done September 29, 2022, confirming a hypervascular 1.7 x 1.2 cm mass (Figure 1). This was then reimaged and confirmed on repeat ultrasound in January 2023, showing a sustained 2.5 x 1.8 cm heterogenous mass arising from the mid-pole of the left testicle, with microcystic internal changes.

Given these findings, the patient was referred to the urology service for management of the testicular mass. Testicular germ cell tumor markers (alpha-fetoprotein [AFP], beta-human chorionic gonadotropin [hCG], and lactate dehydrogenase [LDH]) were within normal range. He was brought to the operating room in January

2023 for left radical inguinal orchiectomy. The operative and postoperative course were unremarkable.

On final pathology, the tumor was notably limited to the testis. A 2.1 x 1.9 x 1.8 cm dark tan to red-brown variegated tumor was easily circumscribed away from the uninvolved tissue that was spongy and dark tanned in composition (Figure 2). The tumor was composed of carcinoma cells positive for PAX8, CD10, CA IX, and RCC antigen, with a negative CK7 stain (Figure 3), suggesting metastatic ccRCC. The patient has been stable in followup and has not required systemic therapy since. He did receive gamma-knife treatment in January of 2024 for progressive central nervous system metastasis and had a good response.

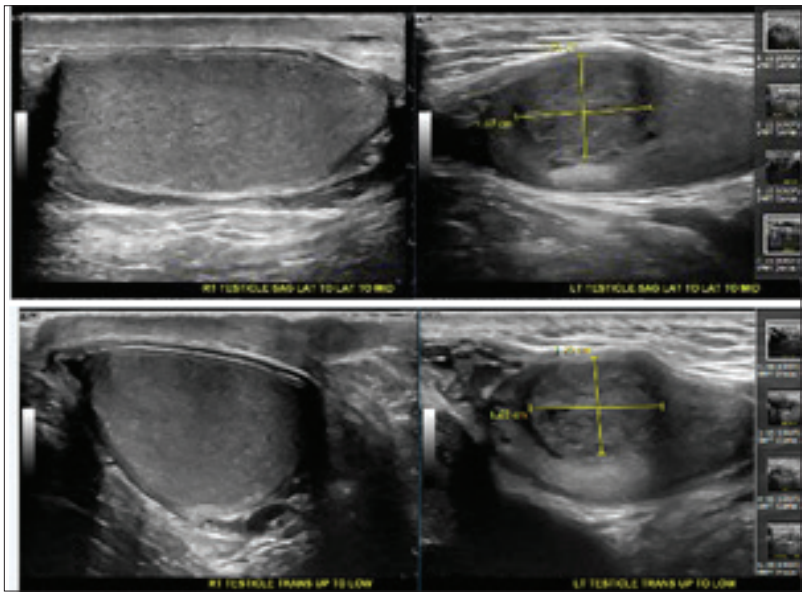

Figure 1. September 29, 2022: Scrotal Doppler sonogram revealed an undescended left testicle in the inguinal canal with a solid and heterogeneous mass measuring 1.7 x 1.2 cm with increased color Doppler blood flow. The left side shows a transverse view and the right side shows a sagittal view, demonstrating the heterogenicity and difference between both testes.

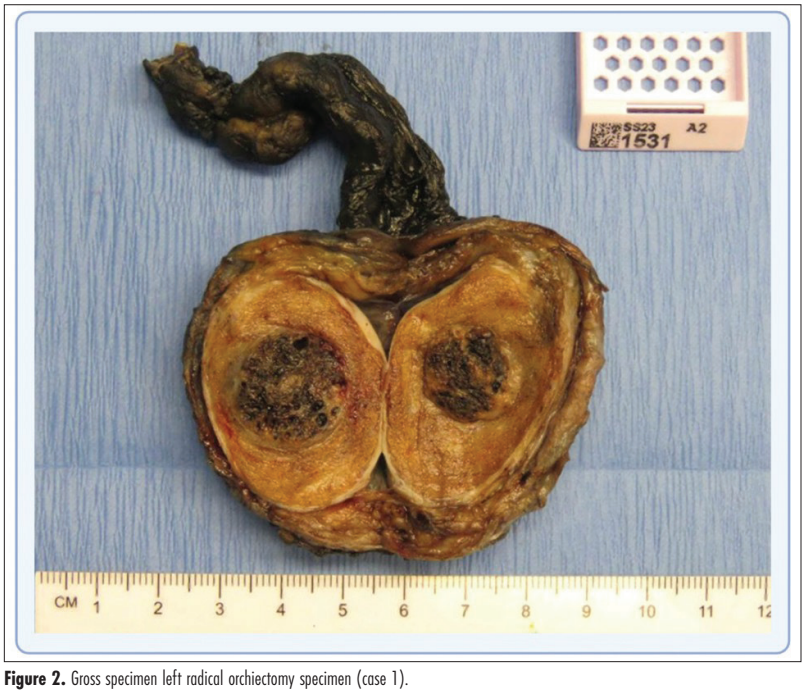

Figure 2. Gross specimen left radical orchiectomy specimen (case 1).

CASE REPORT 2

An 80-year-old male was seen by urology for followup of a mildly complex right renal cyst in the context of remote left nephrectomy for a ccRCC in 1985. Pathology from the previous nephrectomy specimen was unavailable due to the remote nature of the surgery. He noted that he has been having left-sided orchalgia, and on physical exam, had some left-sided testicular tenderness and a palpable left-sided hydrocele. There was no inguinal adenopathy and genital exam was otherwise unremarkable. He underwent an ultrasound exam of his scrotum, which revealed a 1.2 x 1.3 x 1.2 cm solid, isoechoic mass in the mid-pole of the left testicle and a 1.6 x 1.8 x 1.4 cm solid, isoechoic mass in the lower-pole of the left testicle, concerning for solid malignancy (Figure 4).

Testicular tumor markers (AFP, beta-hCG, and LDH) were negative, and the patient underwent a left inguinal orchiectomy for treatment of his testicular masses. Pathology revealed a tumor mass of atypical clear cells with nested architecture and alveolar capillary pattern (Figure 5). Tumor nuclei showed focally prominent nucleoli and there was involvement of the testis, epididymis, and tunica albuginea. The tumor cells were diffusely positive for pan-CK (AE1/3), PAX8, CAIX, CD10, and vimentin, and minimally focally positive for CK7 (Figure 6). The cells were negative for CD117, GATA3, and AMACR (racemase). These immunophenotype findings led to a diagnosis of metastatic clear-cell carcinoma in keeping with RCC.

The patient underwent staging imaging approximately five months following his surgery. An infused CT scan of his chest, abdomen, and pelvis revealed no evidence of disease recurrence or metastatic disease. The patient was also seen by medical oncology following his orchiectomy and will be followed with repeat imaging for a period of two years. There is currently no plan for systemic therapy due to the current imaging findings and remote nature of his disease.

DISCUSSION

Testicular metastasis from RCC represents a rare and diagnostically challenging pathology. Final staging and

diagnosis depends on cross-sectional imaging findings and pathologic report post-removal.[2] The first case of testicular metastasis from RCC was described in 1946 by Bandler and Roen.[3,11] Since that time, approximately 50 cases have been studied, revealing the median time between primary renal tumor diagnosis and testicular metastasis to be 33.5 months.[3] Our cases present significant outliers, with metastasis detected 65 months and 39 years after initial diagnosis. While primary testicular cancer, lymphoma, and metastatic disease are possible culprits of testicular malignancy, to our knowledge, our first case is the first documented case of testicular metastasis after a course of systemic therapy of an already defined site of mRCC.

It is important to distinguish these cases from primary clear-cell carcinoma of the testis, which is also a rare entity, with approximately 100 cases reported in literature. Based on case series, clear-cell carcinoma of the testis has distinct morphologic and immunohistochemical features. CK7 positivity and negative RCC markers, along with clinical history and imaging, may be helpful to distinguish between this entity and testicular metastasis from RCC.[12]

Testicular metastatic RCC most classically presents as a palpable mass within the scrotum and may result in release of proinflammatory cytokines inducing a systemic-sickness syndrome that leads to a cluster of symptoms including fatigue, insomnia, and irritability.[1,2,13] This highlights the need for a physical exam and repeated review of patient symptomatology in addition to imaging in RCC followup.

Still, metastatic RCC to the testis remains a rare clinical entity, with less than 50 documented cases.[3] Hence, in the absence of any patient complaint with an otherwise challenging exam or limited physical exam, diagnosis poses a challenge that relies almost entirely on imaging. In this case, this was evidenced by two concurrent CTs showing the development and steady growth of a testicular mass, further elucidated and confirmed on ultrasound imaging.

CONCLUSIONS

The nature of testicular metastatic RCC and its rarity pose a diagnostic challenge, furthered by a patient's possible asymptomatic presentation. These cases act to raise clinical suspicion and emphasize the importance of both followup and a detailed radiologic review.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

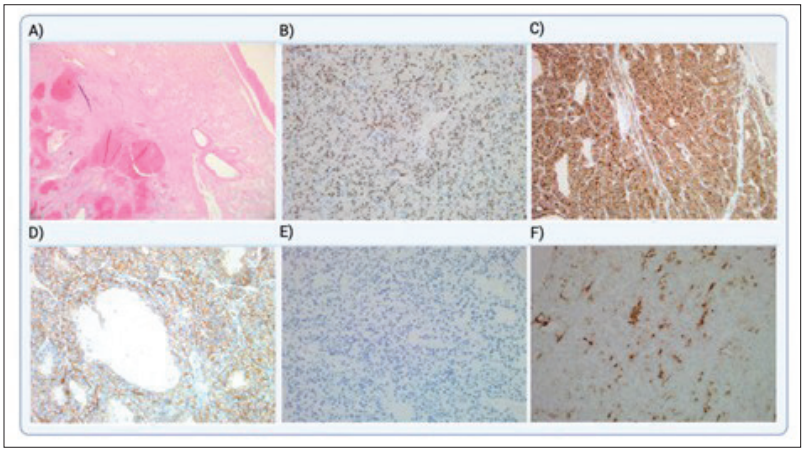

Figure 3. A left radical orchiectomy specimen. (A) H&E stain 4x; (B) PAX 8 (positive) 20x; (C) CD10 (positive) 20x; (D) CAIX IHC (positive) 20x; (E) RCC antigen (positive) 20x; (F) Ck7 (negative) 20x.

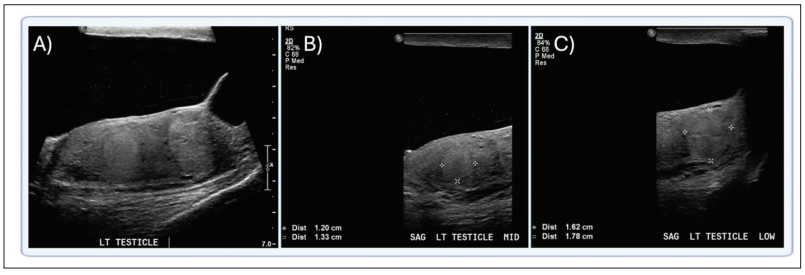

Figure 4. February 23, 2024: (A) Scrotal ultrasound revealed two left testicular masses: (B) 1.2 x 1.3 x 1.2 cm solid isoechoic mass of the mid pole; and (C) 1.6 x 1.8 x 1.4 cm solid isoechoic mass of the lower pole left testicle.

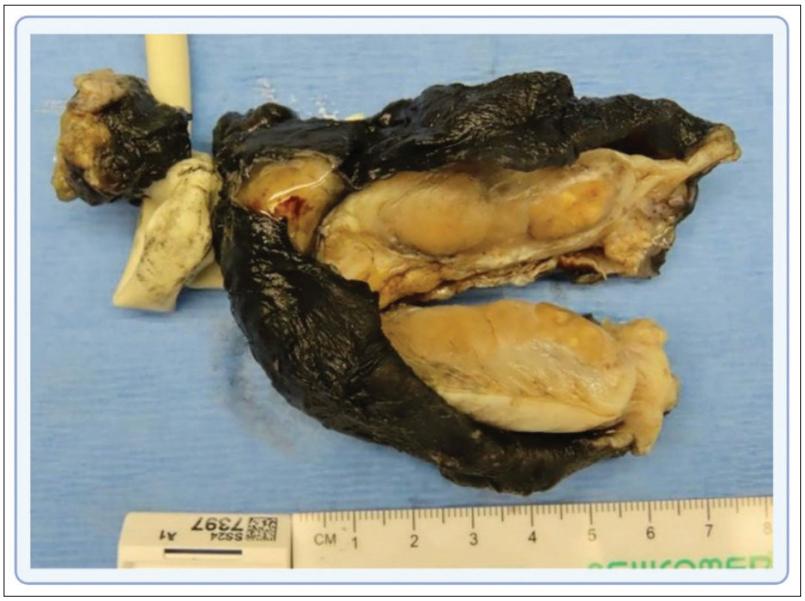

Figure 5. Gross specimen left radical orchiectomy specimen (case 2).

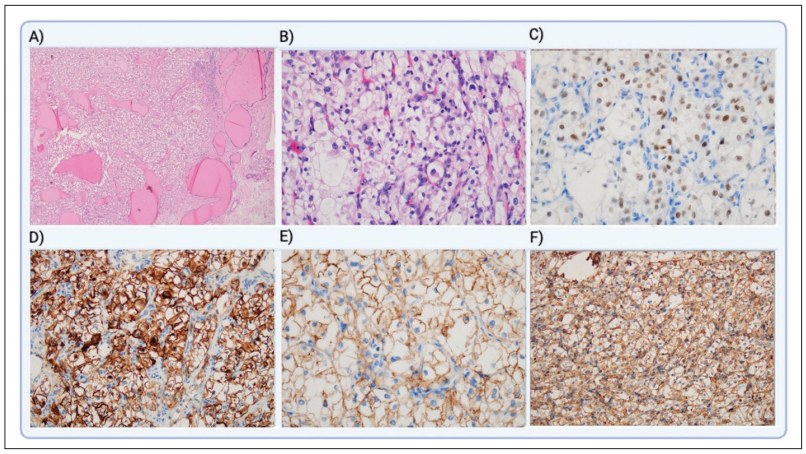

Figure 6. A left radical orchiectomy specimen: (A) H&E stain; (B) H&E stain further magnified; (C) PAX 8 (positive); (D) CD10 (positive); (E) CAIX (positive); (F) Vimentin (positive).

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