The Unusual Presentation of a Single Case of Synchronous Metastatic Clear Cell Renal Cell Carcinoma to the Gallbladder: A Case Report and Literature Review

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ABSTRACT: Clear cell renal cell carcinoma, accounts for approximately 70% of all adult renal tumors. This disease is well known for its high metastatic potential, with estimates of 25-50% of patients reporting metastasis to distant structures. However, there have only been several reported cases in medical literature describing hematogenous spread to the gallbladder, with the majority occurring metachronously, in males, and with multiple metastases. This case report follows an extremely unique presentation in a 60-year-old female. Although the patient did not exhibit the usual signs and symptoms or meet the typical demographics seen with metastatic renal cell carcinoma, it should find a place on the differential diagnosis list when a gallbladder lesion is detected on imaging during the initial staging and/or restaging in patients with renal-cell carcinoma.

KEYWORDS: Clear cell, renal, carcinoma, metastatic, synchronous, gallbladder.

Introduction

Clear cell renal carcinomas are among the most common adult renal cancers, comprising around 90% of renal neoplasms [1].

It is well known that renal cell carcinomas have a high metastatic potential, with the lungs, liver, contralateral kidney, bones and adrenal glands being the most likely sites for metastasis [2,3].

In caveat, metastatic spread to the gallbladder has been an exceedingly rare destination, accounting for as little as 0.58% of RCC positive patients [4].

Those exhibiting gallbladder metastases from RCC often present metachronously, often exhibiting a mean time to presentation of 5 years post nephrectomy [5].

In addition, this rare condition has a high propensity of effecting males at twice the rate seen in females.

Here, we report on an extremely unique case in which a 62-year-old female patient presents with a synchronous clear cell renal cell carcinoma (ccRCC) with metastasis to the gallbladder.

Information pertaining to the patient’s initial presentation, diagnostic imagining, histologic findings, and treatment modalities used are reported in order to expand the literature pertaining the presentation of this rare condition.

Case Presentation

In December, 2017, a sixty-year-old female presented to the clinic complaining of a several month history of right flank pain, and a single episode of hematuria occurring several months prior.

Pertinent medical history included being immunocompromised and having a significant familial history of cancer.

Therefore, a contrast enhanced Computerized tomography (CT) scan was performed where a centrally necrotic, heterogeneously enhancing mass (12.4x8.1x11.1cm) arising from the inferior pole of the right kidney was found showing imaging criteria consistent with renal cell carcinoma (Figure 1.1).

Incidentally, an enhancing polyp projecting into the lumen of the gallbladder was noted (Figure 1.2-1.4).
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Figure 1. Contrast-enhanced CT scan of the abdomen and pelvis. (1) Axial image shows heterogeneous enhancing right renal mass consistent with renal cell carcinoma. (2) Axial image showing an enhancing polyp projecting into the lumen of the gallbladder. (3) Sagittal and (4) Coronal images showing the polyp (white arrow) and stalk (red arrow) attached to the anterosuperior wall of the gallbladder.

This measured approximately 1.5cm.

The patient was referred to a surgical oncologist and subsequently underwent a combined robot assisted laparoscopic (RAL) right nephrectomy with RAL cholecystectomy.

Histology of the polypoid mass in the gallbladder revealed sheets of polygonal cells with clear cytoplasm and small round nuclei surrounded by thin-walled vasculature, with similar structures being noted within the kidney parenchyma (Figure 2.1, 2.2, 2.3).

Furthermore, based on morphology and immunohistochemical staining with CD10, the diagnosis of metastatic clear cell renal cell carcinoma was rendered (Figure 2.3).

The patient had an uneventful recovery and was discharged several days later.

One month later PET scans revealed metastasis to right adrenal gland and was put on Optiva and Carbozantunib to prevent further spread.

As of writing, she is now in remission and in good health condition. Care was given at an academic institute, thus patient written consent is taken during provision of care.
Figure 2. Gallbladder & Kidney.
(1) Low magnification image of clear cell RCC metastasis to gallbladder involving muscular wall.
(2) High magnification image showing polygonal cells with clear cytoplasm, characteristic of clear cell RCC.
(3) An encapsulated lesion with clearing of cytoplasm, characteristic thin-walled vasculature (green arrow), and an identifiable glomerulus (blue arrow). Hematoxylin and Eosin staining.

Discussion
Metastases to the gallbladder are an extraordinarily uncommon event, with malignant melanomas being the most common cause in Western country populations [6].

Others possible sites where metastases to the gallbladder are most frequently seen include lung, renal, pancreatic and colorectal cancers [6-8].

Therefore, cases of gallbladder metastases arising from renal cell carcinoma patients are an extremely rare finding, with few cases having been reported in medical literature to date [6].

A review of literature published within the last ten years was conducted on PubMed, with keywords “renal cell carcinoma metastasis gallbladder” as search criteria.

A total of 23 published articles, describing 29 patients, were discovered and determined eligible for analysis.

The addition of one patient from our institution was included as well (Table 1).

Table 1. Case reports of Renal Cell Carcinoma with metastasis to gallbladder published in the last 10 years.

| Parameter                   | No. of Patients (%) | No. of Patients Used in analysis |
|-----------------------------|---------------------|----------------------------------|
| Median Age (Years)          | 62 yo               | 30                               |
| Sex                         |                     |                                  |
| - Male                      | 20 (66%)            | 30                               |
| - Female                    | 10 (33%)            | 30                               |
| Presentation                |                     |                                  |
| - Synchronous               | 7 (23%)             | 30                               |
| - Metachronous              | 23 (77%)            | 30                               |
| Metastasis                  |                     |                                  |
| - Gallbladder only          | 13 (43%)            | 30                               |
| - Gallbladder+other metastasis| 17 (57%)          | 30                               |
| Pathology                   |                     |                                  |
| - Clear cell                | 30 (100%)           | 30                               |
| - Other or not specified    | 0 (0%)              | 30                               |
| Recurrence of Disease       |                     |                                  |
| - Yes                       | 10 (48%)            | 21                               |
| - No                        | 11 (52%)            | 21                               |
Although RCC is known for its high metastatic potential, with reports indicating 25 to 50% of patients exhibiting some form of metastasis, hematogenous spread to the gallbladder has been shown to occur in as little as 0.58% of cases [4].

Our literature review showed a clear male predominance with infections occurring at a 2:1 male to female ratio, and a median age of diagnosis at 62 years old.

Similar results were found in the literature review performed by Neves et al. which looked at cases dating back to 1963 [1].

Although RCC metastasis to the gallbladder can present in either a synchronous or metachronous fashion, our review illustrated a clear bias for metachronous presentation (77%).

Shyr et al. also reached that same conclusion and found that patients were diagnosed with a median time to presentation of 5 years post nephrectomy [9].

Furthermore, clear cell type was responsible for 100% of the cases of gallbladder metastasis.

It was also determined that metastasis to other sites, in addition to gallbladder, occurred in 57% of cases compared to just 43% of cases exhibiting spread solely to the gallbladder.

Diagnosis of gallbladder metastasis of RCC is often done through the use of radiographic imaging as well as histological analysis.

The majority of cases included in the literature review utilized contrast enhanced CT scans, often displaying hyper-vascular and strongly enhancing lesions within the tumor [10,11].

However, final diagnosis is made on specimen analysis. cCRCC metastasis often stains positive for markers such as vimentin, carbonic anhydrase IX (CAIX), CD117, CD10 and stain negative for cytokeratin 7 [10,12,13].

Due to the rarity of the disease, there have been no definitive treatment strategies for gallbladder metastasis of RCC to date.

However, cholecystectomy was the treatment option of choice in our literature review and has generally been shown to improve outcomes in patients.

Chung et al. conducted a study following 33 patients and ultimately found a five-year survival rate of 35%-50% following the procedure.

He also concluded that prognosis was significantly decreased if multiple metastatic sites had occurred [12,14].

In our review, we found 21 cases with follow up information pertaining to the patient post treatment.

Of which, a disease recurrence rate of around 48% was calculated.

This is in line with other previously published studies [1,6,11].

Conclusion
Gallbladder metastasis from RCC is an extremely rare event.

This condition most often presents in an asymptomatic, metachronous fashion, with a high predilection of affecting male patients around 62 years old.

Although the patient presented in the current study did not meet the usual demographics and presentation for the disease, it should still find a place on the list of potential diagnoses when a gallbladder lesion is detected on imaging during initial staging and/or restaging of renal-cell carcinoma patients.

Competing Interest
The authors declare that they have no competing interests

Authors’ Contributions
GTP was responsible for organizing and writing the manuscript;
IE was responsible for providing the analysis of radiology images;
AU was responsible for providing the analysis of pathological specimens;
AK was the supervisor and helped in editing and revising the manuscript.
All authors read and approved the final manuscript.

Conflict of Interest
None to declare.

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