Metachronous Gallbladder Metastasis from Clear Cell Renal Cell Carcinoma with Atypical Immunohistochemical Profile: A Case Report and Comprehensive Literature Review

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Abstract

Background: Renal cell carcinoma (RCC) is a malignancy known for its high metastatic potential, commonly spreading to the lungs, bones, brain, liver, and adrenal glands. Gallbladder metastasis from RCC is exceedingly rare and poses significant diagnostic challenges due to its asymptomatic nature and nonspecific imaging findings.

Case Presentation: We report the case of a 58-year-old Persian man with a history of clear cell RCC treated with left radical nephrectomy 34 months prior. The patient presented with right upper quadrant abdominal pain. Imaging studies, including contrast-enhanced computed tomography and ultrasound, revealed two hypervascular polypoid lesions within the gallbladder. An open cholecystectomy was performed due to the suspicion of malignancy. Histopathological examination confirmed metastatic clear cell RCC invading the gallbladder wall. Notably, immunohistochemical analysis showed tumor cells positive for cytokeratin 19, alpha-methylacyl-CoA racemase, and vimentin, but negative for paired box gene 8, cytokeratin 7, cytokeratin 20, and cluster of differentiation 117 (C-Kit). The absence of paired box gene 8 expression is atypical for RCC metastasis and posed a diagnostic challenge. The patient had an uneventful postoperative recovery but unfortunately passed away two months later due to a cerebrovascular accident unrelated to his oncological condition.

Conclusions: This case underscores the importance of considering gallbladder metastasis in the differential diagnosis for patients with a history of RCC presenting with gallbladder lesions. The atypical immunohistochemical profile observed expands the known spectrum of metastatic RCC presentations and highlights the necessity for comprehensive diagnostic evaluation. Surgical intervention through cholecystectomy can lead to favorable outcomes and should be considered in similar cases.

Keywords: Renal Cell Carcinoma; Gallbladder Metastasis; Metachronous Metastasis; Immunohistochemistry; PAX8 Negativity; Cholecystectomy; Case Report

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Introduction

Renal cell carcinoma (RCC) constitutes approximately 3% of all adult malignancies, with the clear cell subtype accounting for about 70% of RCC cases. RCC is characterized by a high propensity for metastasis; around 30% of patients present with metastatic disease at diagnosis, and another third develop metastases during the follow-up period. The most common sites of metastasis include the lungs, bones, brain, liver, and adrenal glands. These metastatic events can occur either synchronously—

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at the same time as the primary tumor—or metachronously, arising months or even years after initial treatment [1,2].

Gallbladder metastasis from RCC is exceptionally rare and poses significant diagnostic challenges. Due to its infrequency and nonspecific clinical presentation, preoperative diagnosis is difficult, often requiring histopathological and immunohistochemical examinations for confirmation [3]. Although cases have been reported in the literature, many aspects of gallbladder metastasis from RCC remain inadequately understood, including optimal diagnostic strategies, treatment modalities, and prognostic factors.

In this report, we present a unique case of metachronous gallbladder metastasis from clear cell RCC, occurring 34 months after the patient underwent radical nephrectomy. We aim to shed light on this rare occurrence by providing a comprehensive review of existing literature (Table 1), focusing on clinical features, diagnostic approaches, management strategies, and patient outcomes. Additionally, we utilized Kaplan-Meier survival analysis and log-rank tests to estimate patient survival times, hoping to identify factors that may influence prognosis.

Patient Information

We report the case of a 58-year-old Persian man with a significant medical history of ischemic heart disease and previously treated clear cell renal cell carcinoma (ccRCC). The patient had undergone a left radical nephrectomy in December 2018 for ccRCC. Approximately 34 months post-nephrectomy, in July 2021, he began experiencing intermittent right upper quadrant abdominal pain. This symptom prompted evaluation at a private clinic, where initial investigations were unremarkable except for the persistent pain.

Advanced imaging studies were conducted, including an abdominopelvic computed tomography (CT) scan with and without contrast enhancement (Figure 1) and a complementary abdominal ultrasound. These imaging modalities revealed a semi-distended gallbladder containing two sizable polypoid lesions projecting from the gallbladder wall. The larger lesion measured 38 × 14 mm and was located in the fundal region, while the smaller lesion measured 15 × 14 mm on the mid-portion of the anterior wall. Notably, both lesions exhibited marked hypervascularity on contrast-enhanced imaging—a feature atypical for benign gallbladder polyps and more suggestive of neoplastic processes. Additionally, a 15 × 6 mm lymph node was identified in the mesenteric area of the right upper quadrant, raising concerns for possible lymphatic involvement.

Given the patient's history of ccRCC and the rarity of gallbladder metastasis, the differential diagnosis included primary gallbladder carcinoma, hypervascular polyps, and metastatic disease. The presentation of multiple hypervascular lesions in the gallbladder is particularly uncommon and posed a significant diagnostic challenge. Preoperative imaging did not conclusively differentiate between primary and secondary gallbladder tumors, highlighting the difficulty in diagnosing gallbladder metastasis from RCC preoperatively.

Laboratory investigations showed mildly elevated liver enzymes, with aspartate aminotransferase (AST) at 101 U/L and alanine aminotransferase (ALT) at 68 U/L. Other liver function tests, complete blood count, renal function tests, and tumor markers, including carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9), were within normal limits.

In October 2021, the patient was admitted for elective surgical intervention. An open cholecystectomy was planned due to the size and vascularity of the lesions, and the potential for malignancy. During surgery, extensive adhesions were encountered, necessitating adhesiolysis. The gallbladder appeared abnormal, consistent with the imaging findings. A cholecystectomy was performed without intraoperative complications. The patient had an uneventful postoperative course and was discharged home after 24 hours.

Gross examination of the formalin-fixed cholecystectomy specimen revealed a gallbladder measuring 7.5 × 3 cm with a smooth serosal surface. The wall thickness was 0.3 cm, and the mucosal surface was irregular. Multiple fragments of necrotic tissue totaling 3.5 × 3.5 × 1.5 cm were present. A necrotic mass measuring 2.5 × 2.5 × 2 cm was identified in the fundus, located 5.5 cm from the cystic duct.

Histopathological analysis demonstrated a neoplasm composed of clear cells with abundant cytoplasm and distinct cell borders, arranged in alveolar and nested patterns—a morphology characteristic of ccRCC. The tumor invaded the lamina propria and muscular layer but did not involve the lymphovascular system or perineural pathways. Surgical margins were free of tumor involvement, including the cystic duct margin.

Immunohistochemical (IHC) studies were pivotal for definitive diagnosis. The tumor cells showed strong positivity for cytokeratin 19, alpha-methylacyl-CoA racemase (AMACR), and vimentin. Surprisingly, the tumor cells were negative for paired box gene 8 (PAX8), cytokeratin 7, cytokeratin 20, and CD117 (C-Kit). The absence of PAX8 expression is particularly noteworthy, as PAX8 is commonly used as a sensitive and specific marker for renal epithelial tumors, including RCC. This atypical IHC profile

Table 1. Review of literature sorted out by year of publication

Author	Year	Country	Age/ sex	stage	Mode of metastasis	Interval from primary cancer	Presentation	Imaging	Macroscopic findings	Size	IHC	Treatment	Follow up period	Outcome
Fullarton et al.	1991	UK	43/F	N/A	Multiple	27 years	severe iron deficiency anemia	N/A	N/A	3cm	N/A	laparoscopic cholecystectomy	3 months	dead from metastasis
Satoh et al.	1991	Japan	71/M	N/A	Single	Synchronous	incidental	CT scan	polypoid lesion	3.8x2.6cm	N/A	extended cholecystectomy	19 months	recurrence-free
King et al.	1995	USA	64/M	N/A	Single	Synchronous	incidental	CT scan	polypoid lesion	N/A	N/A	cholecystectomy	26 months	disease-free
Pagano et al.	1995	Italy	62/M	N/A	Multiple	Synchronous	incidental	CT scan	round, firm parietal mass	3.5cm	N/A	cholecystectomy	3 years	disease-free
Lombardo et al.	1996	USA	77/M	N/A	Single	5 years	incidental	CT scan	polypoid lesion	3.2cm	N/A	laparoscopic cholecystectomy	N/A	N/A
Sparwasser et al.	1997	Germany	46/M	pT2N0 M0	Multiple	44 months	Abdominal pain	Abdominal ultrasonography	polypoid lesion	N/A	N/A	cholecystectomy	5 years	dead from metastasis
Aoki et al.	2002	Japan	63/M	N/A	Single	27 years	incidental	Abdominal ultrasonography	polypoid lesion	7.5x3cm	PAS, vimentin, and CD10	cholecystectomy	6 years	recurrence-free
Aoki et al.	2002	Japan	80/M	N/A	Multiple	7 years	incidental	Abdominal ultrasonography	polypoid lesion	4.5x2.5cm	PAS, vimentin, Leu-M1, and CD10	cholecystectomy	2 years	recurrence-free
Park et al.	2003	Korea	48/M	pT3cN0 cM0	Multiple	2 years	incidental	Abdominal ultrasonography	polypoid lesion	N/A	N/A	Adjuvant therapy + cholecystectomy	N/A	N/A
Ishizawa et al.	2005	Japan	73/M	T2N0M 0	Single	Synchronous	incidental	CT scan	polypoid lesion	3x2cm	vimentin	adjuvant therapy + laparoscopic cholecystectomy	2 years	recurrence-free
Hellenthal et al.	2007	USA	39/M	N/A	Single	Synchronous	incidental	CT scan	polypoid lesion	4cm	N/A	cholecystectomy	2 years	recurrence-free
Nojima et al.	2007	Japan	61/M	N/A	Single	Synchronous	Abdominal pain	Abdominal ultrasonography	polypoid lesion	15mm	Negative	cholecystectomy	10 months	recurrence-free
Moujahid et al.	2008	Morocco	56/M	N/A	Single	Synchronous	Abdominal pain	CT scan	polypoid lesion	9cm	EMA	cholecystectomy	8 months	recurrence-free
Ditah et al.	2008	USA	66/F	pT3aN0	Single	Synchronous	incidental	CT scan	N/A	2cm	CA-IX	adjuvant therapy + laparoscopic cholecystectomy	32 months	Stable disease
Patel et al.	2009	UK	64/F	N/A	Single	6 years	Abdominal pain	Abdominal ultrasonography	polypoid lesion	3cm	N/A	laparoscopic cholecystectomy	N/A	N/A
Sand et al.	2009	Germany	48/F	N/A	Single	5 years	Abdominal pain	Abdominal ultrasonography	polypoid lesion	2.5x2x1.5 cm	N/A	extended cholecystectomy	1 year	alive
Shoji et al.	2010	Japan	50/M	pT1aN0 M0	Multiple	3 years	incidental	CT scan	polypoid lesion	11x9mm	Vimentin	cholecystectomy	8 months	recurrence-free
Bolus et al.	2010	USA	50/M	N/A	Multiple	Synchronous	incidental	CT scan	polypoid lesion	13x21mm	N/A	open cholecystectomy	12 months	alive
Kawahara et al.	2010	Japan	73/F	T3bN0 M1	Multiple	Synchronous	incidental	PET/CT	polypoid lesion	10x8mm	N/A	cholecystectomy	N/A	N/A
Decoene et al.	2011	Belgium	47/F	N/A	Multiple	11 years	incidental	CT scan	polypoid lesion	N/A	N/A	cholecystectomy	N/A	N/A
Collin et al.	2012	Canada	68/M	pT3aN0 M0	Single	16 months	Abdominal pain	CT scan	cholelithiasis	0.2cm	CD10	endocholecystectomy	2 months	asymptomatic
Robledo et al.	2012	Spain	75/F	pT3N0 M0	Multiple	6 months	incidental	CT scan	nodular structure	2cm	Negative	laparoscopic cholecystectomy	4 months	recurrence-free
Chung et al.	2012	USA	63F	pT3N0 M0	Single	120 months	incidental	Abdominal ultrasonography	polypoid lesion	3.5x2x1.5 cm	N/A	cholecystectomy	84 months	alive
Chung et al.	2012	USA	52/F	pT4	Single	Synchronous	incidental	Abdominal ultrasonography	polypoid lesion	1.8x1.6x1.4cm	N/A	cholecystectomy	60 months	alive

Continued Table 1. Review of literature sorted out by year of publication

Author	Year	Country	Age/ sex	stage	Mode of metastasis	Interval from primary cancer	Presentation	Imaging	Macroscopic findings	Size	IHC	Treatment	Follow up period	Outcome
Chung et al.	2012	USA	51/M	pT4	Multiple	Synchronous	incidental	Abdominal ultrasonography	polypoid lesion	1.7x1cm	N/A	Adjuvant therapy + cholecystectomy	132 months	dead from metastasis
Chung et al.	2012	USA	42/M	pT4	Single	Synchronous	incidental	Abdominal ultrasonography	polypoid lesion	N/A	N/A	cholecystectomy	6 months	dead from metastasis
Jain et al.	2013	India	49/F	N/A	Single	6 years	Chronic cholecystitis	Abdominal ultrasonography	polypoid lesion	2x1.8x0.5 cm	pancytokeratin and vimentin	cholecystectomy	N/A	Alive
Hisa et al.	2013	Japan	73/M	N/A	Multiple	4 months	incidental	Abdominal ultrasonography	Sessile nodular mass	18mm	Vimentin	open cholecystectomy	8 years	alive
Whirter et al.	2013	UK	74/M	N/A	Single	14 years	Billiary colic	Abdominal ultrasonography	polypoid lesion	22x23x27 mm	vimentin, CAM 5.2, AE1/3, MNF116 and CD10	open cholecystectomy	N/A	alive
Ghaouti et al.	2013	Morocco	55/F	N/A	Multiple	Synchronous	Abdominal pain	Abdominal ultrasonography	pedunculated	2.6cm	CD10, vimentin and pancytokeratin	open cholecystectomy	N/A	N/A
Quiroz et al.	2014	Spain	55/F	N/A	Multiple	6 years	incidental	CT scan	nodular structure	2cm	N/A	cholecystectomy	N/A	N/A
Turner et al.	2014	New Zealand	55/F	N/A	Single	8 years	Abdominal pain	MRCP	polypoid lesion	2.7x1.8x1.4cm	N/A	laparoscopic cholecystectomy	N/A	N/A
Ricci et al.	2014	Italy	72/F	T1N0M0	Single	16 years	Billiary colic	Abdominal ultrasonography	N/A	3cm	N/A	laparoscopic cholecystectomy	N/A	N/A
Zaw Win	2014	USA	40/M	N/A	Multiple	21 years	Abdominal pain	PET/CT	N/A	4cm	N/A	laparoscopic cholecystectomy	N/A	N/A
Aoki et al.	2015	Japan	43/M	N/A	Single	1 year	incidental	CT scan	pedunculated	26mm	N/A	extended cholecystectomy	N/A	N/A
Cheng et al.	2015	Taiwan	65/M	N/A	Single	10 years	Abdominal pain	CT scan	polypoid lesion	3.5x2x1cm	EMA, vimentin, CD10	cholecystectomy	N/A	N/A
Neves et al.	2016	UK	60/F	pT1aN0	N/A	29 months	incidental	MRI	polypoid lesion	2.5cm	PAX8, Vimentin, CAM5.2, AMACR and EMA, focal E-cadherin	laparoscopic cholecystectomy	2 months	disease-free
Neves et al.	2016	UK	57/M	pT3bN0	Multiple	Synchronous	Abdominal pain	CT scan	polypoid lesion	22x15x8mm	AE1/AE3, Vimentin, CD10 and RCCAg	laparoscopic cholecystectomy	38 months	disease-free
Mrak et al.	2016	Austria	76/M	N/A	Single	12 years	incidental	CT scan	polypoid lesion	3cm	PAX-8	cholecystectomy	N/A	N/A
Ruiz et al.	2016	Italy	51/M	pT2aN0M0	Multiple	3 years	incidental	CT scan	N/A	18x24mm	N/A	open cholecystectomy	7 months	disease-free
Limani et al.	2016	Belgium	64/M	N/A	Single	1 year	incidental	CT scan	N/A	1.5cm	N/A	laparoscopic cholecystectomy	N/A	N/A
Kitaruma et al.	2017	Japan	68/M	T1aN0M0	Multiple	6 years	incidental	CT scan	polypoid lesion	1cm	N/A	laparoscopic cholecystectomy	5 months	alive
Shyr et al.	2017	Taiwan	80/M	pT1aN0M0	Single	14 years	incidental	Abdominal ultrasonography	polypoid lesion	4.2x3.4cm	N/A	open cholecystectomy	3.5 years	disease-free
Mitsimponas et al.	2017	Germany	72/M	N/A	Single	12 years	ascites	CT scan	polypoid lesion	15mm	vimentin and pancytokeratin	cholecystectomy	1 year	dead from metastasis
Saito et al.	2018	Japan	75/F	N/A	Multiple	15 years	incidental	CT scan	polypoid lesion	12mm	vimentin and cytokeratin 7	open cholecystectomy	3 years	recurrence-free
Ueda et al.	2018	Japan	72/F	T1bN0M1	Single	Synchronous	incidental	Abdominal ultrasonography	N/A	N/A	CD10	cholecystectomy	30 months	alive
Takenaka et al.	2018	Japan	70/M	N/A	Single	N/A	Abdominal pain	CT scan	N/A	5mm	N/A	laparoscopic cholecystectomy	N/A	N/A
Zouari et al.	2019	Tunisia	50/M	pT3N0M0	Multiple	4 years	incidental	CT scan	polypoid lesion	30x25mm	PAX8, Vimentin and CD10	laparoscopic cholecystectomy	18 months	disease-free

Continued Table 1. Review of literature sorted out by year of publication

Author	Year	Country	Age/ sex	stage	Mode of metastasis	Interval from primary cancer	Presentation	Imaging	Macroscopic findings	Size	IHC	Treatment	Follow up period	Outcome
Takagi et al.	2019	Japan	55/F	pT3a	Single	Synchronous	incidental	Abdominal ultrasonography	polypoid lesion	10mm	cytokeratin CAM 5.2, CD10, CD15 and vimentin	laparoscopic cholecystectomy	9 months	recurrence-free
White et al.	2019	Canada	59/F	N/A	Single	6 years	incidental	Abdominal ultrasonography	polypoid lesion	1.1cm	vimentin, and cytokeratin AE1/AE3	laparoscopic cholecystectomy	N/A	disease-free
Riberio et al.	2019	Brazil	74/M	T3BN0 M0	Single	9 years	incidental	CT scan	polypoid lesion	17x13mm	vimentin, AE1AE3, CD10, RCC and Racemase-focal	laparoscopic cholecystectomy	N/A	N/A
Liu et al.	2019	China	44/M	N/A	Single	Synchronous	Abdominal pain	Abdominal ultrasonography	N/A	2.4x1.8cm	PAX-8, RCC, CD10	laparoscopic cholecystectomy	N/A	N/A
Kinoshita et al.	2019	Japan	60/M	T1bN0 M0	Multiple	3 years	incidental	CT scan	polypoid lesion	N/A	CAM 5.2 and vimentin	laparoscopic cholecystectomy	12 months	recurrence-free
Oba et al.	2020	Japan	73/M	T1bN0 M0	Single	6 years	incidental	CT scan	polypoid lesion	6.4mm	CA9	laparoscopic cholecystectomy	6 months	recurrence-free
Oba et al.	2020	Japan	43/M	T2N0M 1	Multiple	1 year	incidental	CT scan	pedunculated	15x30mm	EMA	expanded cholecystectomy	7 years	alive
Cho et al.	2020	Korea	55/M	pT3	Single	Synchronous	incidental	CT scan	polypoid lesion	22mm	CK and CD10	laparoscopic cholecystectomy	10 months	disease-free
Patterson et al.	2021	USA	62/F	N/A	Single	Synchronous	incidental	CT scan	polypoid lesion	1.5cm	CD10	RAL cholecystectomy	1 month	in remission
Papalampros et al.	2021	Greece	71/F	pT2	Multiple	14 years	incidental	Abdominal ultrasonography	polypoid lesion	2.4cm	CD10, CAIX and PAX8	open cholecystectomy	6 months	recurrence-free
Kim et al.	2021	Korea	51/M	N/A	Single	Synchronous	incidental	CT scan	polypoid lesion	2.2cm	N/A	laparoscopic cholecystectomy	1 year	asymptomatic
Pierce et al.	2021	USA	60/M	pT3aNx M1	Single	Synchronous	Abdominal pain	CT scan	N/A	N/A	N/A	cholecystectomy	3 years	recurrence-free
Baloglu et al.	2022	Turkey	53/M	N/A	Single	Synchronous	incidental	PET/CT	N/A	2.3x2.6cm	PAX-2 and Vimentin	laparoscopic cholecystectomy	N/A	N/A
Harsha et al.	2022	India	50/M	pT2	Multiple	Synchronous	Abdominal pain	Abdominal ultrasonography	polypoid lesion	5x3x3cm	N/A	adjuvant therapy + open cholecystectomy	N/A	N/A
Akhtar et al.	2022	Pakistan	43/M	N/A	Multiple	Synchronous	incidental	CT scan	polypoid lesion	4.4mm	N/A	cholecystectomy	N/A	N/A

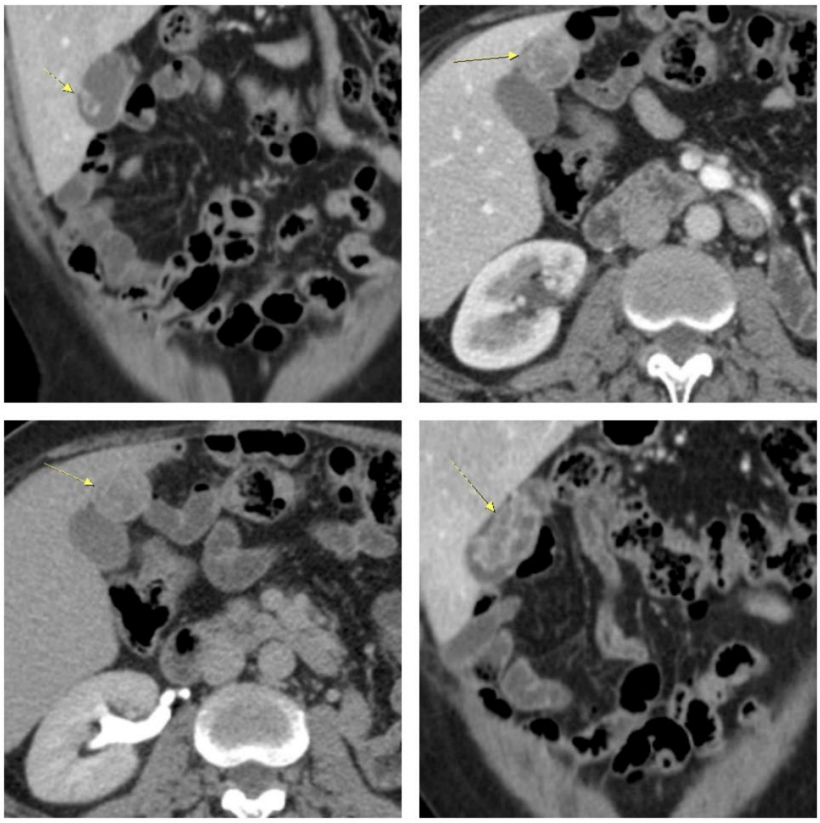

Fig. 1. Contrast-enhanced CT scan showing hypervascular polypoid lesions in the gallbladder.

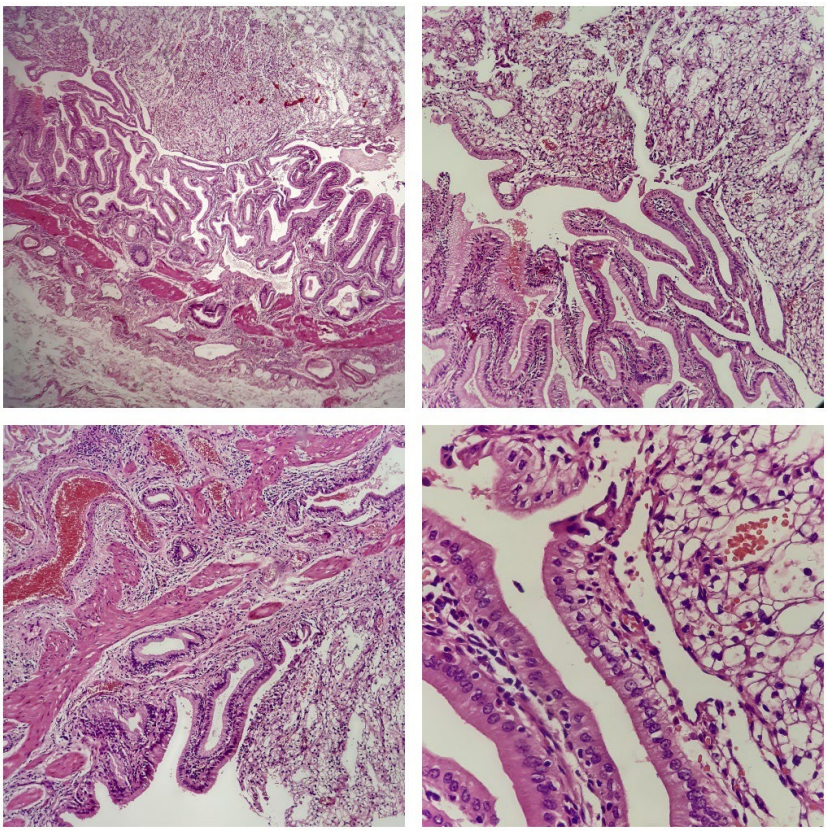

Fig. 2. Histopathological examination revealing clear cell morphology consistent with metastatic renal cell carcinoma.

presented a diagnostic dilemma and emphasizes the heterogeneity of metastatic ccRCC, underscoring the need for a comprehensive panel of immunomarkers in such cases.

The unique combination of IHC findings, along with the patient's history and morphological features, confirmed the diagnosis of metastatic ccRCC to the gallbladder. This case is remarkable due to the metachronous presentation of multiple hypervascular gallbladder lesions, the atypical negative PAX8 staining, and the diagnostic challenges posed by these factors.

Two months after surgery, in December 2021, the patient suffered a cerebrovascular accident (CVA) and unfortunately passed away. At the time of his death, there was no clinical or imaging evidence of recurrent or residual metastatic disease, suggesting that the gallbladder was the sole site of metastasis.

Discussion

Gallbladder metastasis from renal cell carcinoma (RCC) is an extremely rare clinical phenomenon, with only a limited number of cases documented in the literature. Recognizing this rare metastatic site is crucial due to its potential impact on patient management and prognosis. Our comprehensive review of 67 reported cases (summarized in Table 2) provides valuable insights into the clinical characteristics, treatment modalities, and outcomes associated with this condition.

Demographics and Clinical Presentation

The analysis of reported cases reveals a male predominance, with 66% of patients being male and 34% female. The age of patients ranged from 39 to 80 years, with a mean age of 59.6 ± 11.4 years. This suggests that gallbladder metastasis from RCC tends to occur in middle-aged to older adults, which is consistent with the typical age distribution of RCC.

In terms of metastatic patterns, single metastasis to the gallbladder was more frequent, occurring in 58.2% of cases, whereas multiple metastases were reported in 40.3% of cases. Additionally, metachronous metastasis—defined as metastasis occurring more than six months after the primary tumor—was observed in 59.7% of patients, while synchronous metastasis accounted for 40.3%. The interval between the initial RCC diagnosis and the

Table 2. Summary of review of literature of gallbladder metastasis from RCC

Sex, n = 63	
Male	42 (66%)
Female	21 (34%)
Age (years), n = 63	
Median (range)	60 (39-80)
Mean	59.6 ± 11.4
Gallbladder metastasis timing, n = 62	
Synchronous	25 (40.3%)
Metachronous	37 (59.7%)
Metachronous metastasis Interval (months), n = 37	
Median (range)	72 (4-324)
Mean	97.0 ± 82.1
Presentation, n = 63	
Incidental	43 (68.2%)
Abdominal pain	15 (23.8%)
Biliary colic	2 (3.1%)
Severe anemia	1 (1.5%)
Chronic cholecystitis	1 (1.5%)
Ascites	1 (1.5%)
Imaging method, n = 62	
CT scan	34 (54.8%)
Ultrasound	23 (37.0%)
MRI	2 (3.2%)
PET/CT	3 (4.8%)
Tumor size (cm), n = 55	
Median (range)	2.0 (0.2-9.0)
Mean	2.2 ± 1.5
Macroscopic findings, n = 52	
Polypoid lesion	44 (84.6%)
Other	8 (15.4%)
Treatment, n = 63	
With adjuvant therapy	5 (7.9%)
Without adjuvant therapy	58 (92.1%)

detection of gallbladder metastasis varied widely, ranging from synchronous presentation to as long as 27 years (324 months), with a mean interval of 97.0 ± 82.1 months. This significant variation underscores the necessity for prolonged surveillance in RCC patients, as late metastatic presentations are possible even decades after nephrectomy.

Most patients were asymptomatic at the time of diagnosis, with incidental findings accounting for 68.2% of cases. Symptomatic presentations included abdominal pain (23.8%), biliary colic (3.1%), severe anemia (1.5%), ascites (1.5%), and chronic cholecystitis (1.5%) [5-49]. The high rate of incidental detection highlights the diagnostic challenge, emphasizing the importance of considering gallbladder metastasis in patients with a history of RCC who present with gallbladder lesions.

Pathological Findings

Macroscopic examination most commonly revealed polypoid lesions within the gallbladder (84.6%), followed by pedunculated masses (5.7%), nodular structures (3.8%), cholelithiasis (1.9%), sessile nodular masses (1.9%), and submucosal nodules (1.9%). The size of gallbladder metastases ranged from 0.2 cm to 9 cm, with a mean size of 2.2 ± 1.5 cm. These lesions can mimic benign gallbladder polyps or primary gallbladder carcinoma on imaging studies, making preoperative diagnosis challenging.

Immunohistochemical (IHC) analysis was reported in 24 cases and showed variable expression of markers. Positive staining was observed for periodic acid-Schiff (PAS), vimentin, cluster of differentiation 10 (CD10), differentiation antigen in human myelomonocytic cells (Leu-M1), epithelial membrane antigen (EMA), carbonic anhydrase IX (CA-IX), pancytokeratin, CAM 5.2, AE1/3, MNF116, PAX8, and alpha-methylacyl-CoA racemase (AMACR). The variability in IHC profiles underscores the heterogeneity of RCC metastases and highlights the necessity for comprehensive immunohistochemical panels to achieve an accurate diagnosis.

Our case is particularly noteworthy due to the atypical IHC findings. The tumor cells were negative for PAX8, a marker commonly positive in RCC and used to confirm renal origin. This negative result posed a diagnostic challenge, as PAX8 negativity is unusual in metastatic RCC. However, the tumor was positive for cytokeratin 19, AMACR, and vimentin. Along with the patient's clinical history and histopathological features, these findings supported the diagnosis of metastatic clear cell RCC. This atypical IHC profile expands the known spectrum of metastatic RCC presentations and emphasizes the need for a broad immunohistochemical approach when evaluating gallbladder lesions in patients with a history of RCC.

Treatment and Outcomes

Surgical intervention remains the primary treatment modality for gallbladder metastasis from RCC. In our review, cholecystectomy was the most common procedure performed, either alone or with regional lymphadenectomy (38.8% of cases). Laparoscopic cholecystectomy was conducted in 32.8% of cases, while other treatments included cholecystectomy with adjuvant therapy (7.5%), endocholecystectomy (1.5%), and robot-assisted laparoscopic cholecystectomy (1.5%). The choice between open and laparoscopic approaches often depended on tumor size, location, and the presence of adhesions or other complicating factors.

The follow-up period among reported cases ranged from 1 to 132 months, with a mean duration of 27 ± 29.3 months. Outcomes were reported for 46 patients (68.7%). Of these, 7 patients (10.5%) died from metastasis or other causes, while 39 patients (58.2%) remained recurrence-free, disease-free, had stable disease, were asymptomatic, or were in remission at the time of their last follow-up. The favorable outcomes observed in the majority of patients suggest that surgical resection of gallbladder metastasis can lead to prolonged survival and potential cure.

Our patient underwent open cholecystectomy due to the size and vascularity of the lesions and the presence of extensive adhesions from previous surgery. Despite the diagnostic challenges and the rarity of this metastatic presentation, the surgical intervention was successful, and the patient did not show evidence of recurrent disease in the immediate postoperative period. Unfortunately, he passed away two months later due to a cerebrovascular accident unrelated to his cancer, preventing long-term follow-up.

Prognostic Factors

According to the study by Shyr et al. [4], survival rates for patients with gallbladder metastasis from RCC were 91.5%, 76.2%, and 59.3% at 1, 3, and 5 years, respectively, with a median survival time of 26.5 months. Interestingly, survival was not significantly influenced by factors such as the number of metastases, the interval from RCC diagnosis, the presence of symptoms, tumor size, or the type of cholecystectomy performed. However, our analysis revealed that asymptomatic patients had significantly better survival rates, with a p-value of 0.004 in the log-rank test, suggesting that incidental detection may

confer a survival advantage due to earlier intervention (summarized in Table 3 and Figure 3).

Clinical Implications

Our case highlights several important clinical considerations:

1. **Long-Term Surveillance**: Given the potential for late metachronous metastasis—even decades after initial RCC treatment—long-term follow-up is essential. Clinicians should maintain a high index of suspicion for metastatic disease in RCC survivors presenting with new abdominal symptoms or imaging findings.
2. **Diagnostic Approach**: The variability in IHC profiles necessitates the use of comprehensive immunohistochemical panels when evaluating gallbladder lesions, especially in patients with a history of RCC. Relying on a limited set of markers may lead to misdiagnosis.
3. **Treatment Strategy**: Surgical resection via cholecystectomy offers a significant opportunity for prolonged survival and potential cure. The decision between open and laparoscopic approaches should be individualized based on tumor characteristics and surgical expertise.
4. **Prognosis**: The generally favorable outcomes observed suggest that gallbladder metastasis from RCC, when managed appropriately, does not carry the same poor prognosis typically associated with metastatic RCC to other sites.

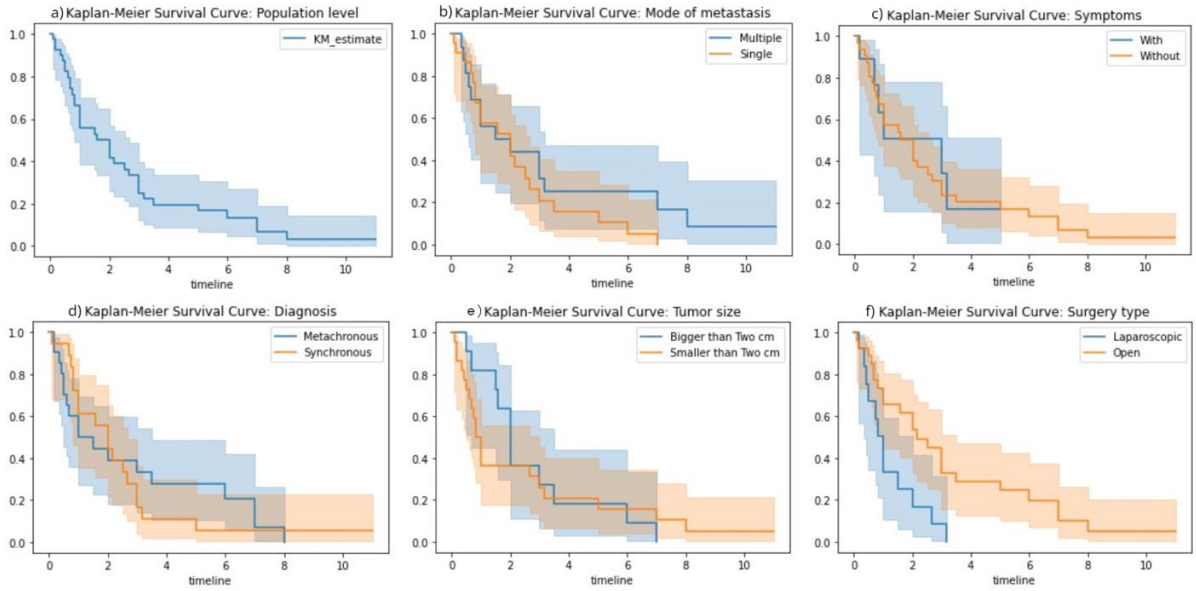

Fig. 3. Kaplan-Meier survival curves comparing survival rates based on clinical presentation (asymptomatic vs. symptomatic)

Table 3. Survival results of RCC metastatic to the gallbladder based on the literature review

	Mean ± SD, year	1-year survival	3-year survival	5-year survival	p-value
Overall, n = 40	2.33 ± 2.50	62.5%	30.0%	17.5%	
Mode of metastasis					**0.905**
Single, n = 22	2.84 ± 2.03	50.0%	31.8%	18.1%	
Multiple, n = 17	3.15 ± 1.88	82.3%	29.4%	17.6%	
Presentation					**0.004**
Asymptomatic, n= 31	1.67 ± 1.65	64.5%	29.0%	19.3%	
Symptomatic, n = 9	2.52 ± 2.69	55.5%	33.3%	11.1%	
Timing of metastasis					**0.399**
Synchronous, n = 19	2.36 ± 2.62	68.4%	26.3%	10.5%	
Metachronous, n = 21	2.30 ± 2.43	57.1%	33.3%	23.8%	
Tumor size					**0.562**
≤2cm, n = 22	2.23 ± 2.94	91.6%	50.0%	33.3%	
>2cm, n = 12	2.50 ± 2.10	40.9%	18.1%	9.0%	
Surgery technique					**0.824**
Open, n = 27	2.91 ± 2.81	70.3%	40.7%	25.9%	
Laparoscopic, n = 13	1.12 ± 0.95	46.1%	7.6%	0.0%	

Conclusion

Gallbladder metastasis from RCC, although rare and often asymptomatic, should be considered in the differential diagnosis for patients with a history of RCC who present with gallbladder lesions. Our case adds to the growing body of evidence that surgical intervention through cholecystectomy can lead to favorable outcomes and potentially long-term survival. The atypical immunohistochemical profile observed emphasizes the need for comprehensive diagnostic evaluation. Increased awareness and reporting of such cases will enhance understanding, aid in early detection, and improve management strategies for this rare metastatic occurrence.

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Conflict interests

There are no conflicts of interest related to the research, authorship, or publication of this article.

Abbreviations

RCC: Renal Cell Carcinoma
ccRCC: Clear Cell Renal Cell Carcinoma
CT: Computed Tomography
AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
CEA: Carcinoembryonic Antigen
CA 19-9: Cancer Antigen 19-9
IHC: Immunohistochemical
PAX8: Paired Box Gene 8
CVA: Cerebrovascular Accident
PAS: Periodic Acid-Schiff
CD10: Cluster of Differentiation 10
Leu-M1: Differentiation Antigen in Human Myelomonocytic Cells
EMA: Epithelial Membrane Antigen
CA-IX - Carbonic Anhydrase IX
CAM 5.2: Cytokeratin Antibody Marker 5.2
AE1/3: A Cytokeratin Marker (specific antibodies for cytokeratins)
MNF116: A Cytokeratin Marker (specific to certain epithelial tumors)
AMACR: Alpha-Methylacyl-CoA Racemase

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