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## Gallbladder's clear cell renal carcinoma metastasis: A case report



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## ABSTRACT

**INTRODUCTION:** Clear cell renal cell carcinoma (ccRCC) is well known for its propensity to metastasize to unusual sites, even after 10 years. Gallbladder metastases are extremely rare, being found in approximately 0.6% of cases, at autopsy.

**CASE PRESENTATION:** A 51-year-old man with a history of right ccRCC underwent total nephrectomy with extended lymphadenectomy, in another Hospital. Three years later, he was hospitalized at our Hospital, with gallbladder metastasis detected during a follow-up CT scan. At clinical examination, the patient did not present any symptoms or signs of gallbladder disease. Several imaging tests were performed to better characterize the lesion. A successful cholecystectomy and hepatic resection of 4b segment were performed, obtaining a R0 resection. The clinical course was uneventful, without any complications. After a 7-month follow-up, the patient is free from disease.

**DISCUSSION:** A typical metastases are those located in a site other than thoracic, skeletal, hepatic, adrenal or encephalic tissue. Cholecystectomy with R0 resection has demonstrated to be the only factor increasing survival, mainly in isolated cases of metastasis, providing an overall 35–60% survival rate at 5 years.

**CONCLUSION:** In the follow-up of patients with a positive history of renal cell carcinoma specially clear cell subtype, all new finding should be taken into account as possible metastases. We ought to consider US and CT-scan behavior of gallbladder metastatic disease in order to orientate our diagnosis. Surgery for metastatic gallbladder disease of renal origin seems to be a feasible therapy which is capable of increasing patients' overall survival.

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## 1. Introduction

Kidney cancer accounts for approximately 2% of the total human malignancies with approximately 190,000 new cases diagnosed each year world wide. Clear cell renal cell carcinoma (ccRCC) is well known for its propensity to metastasize to unusual sites, even after 10 years from diagnosis of primary lesion [1]. CcRCC accounts for about 70% of renal cell carcinoma (RCC) and approximately one third of these patients commonly develop metastases [2]. Gallbladder metastasis is extremely rare, being found in approximately 0.6% of cases, at autopsy [3]. In our paper, we report a case of gallbladder's clear cell renal cell carcinoma metastasis and introduce an overview of diagnostic imaging and treatment.

This paper has been reported in line with the CARE criteria (<http://www.care-statement.org>).

## 2. Case report

We present the case of a 51-year-old man with a history of right ccRCC. In July 2011, he underwent total right nephrectomy with extended lymphadenectomy. His specimen was classified as Führman pT2<sup>a</sup> N0 M0 grade 3, stage II. At that time, this pathology was considered of low-medium risk, with no indication for further therapy. During follow-up, in January 2013, a chest CT scan showed two pulmonary nodes (18 mm and 8 mm), which were treated with 7 cycles of bevacizumab and alfa 2-A interferon, and later on with sunitinib. After a 8-month therapy, a control chest CT scan was performed, showing an important reduction of the pulmonary nodes. In a further chest-abdomen CT scan performed in October 2014, the pulmonary nodes were too small to be characterized, but a 13 mm × 11 mm × 8 mm polyp lesion was found within the gallbladder lumen. At clinical examination, the patient did not present any symptoms or signs of gallbladder disease, such as abdominal tenderness or jaundice. Laboratory tests did not detect any alterations, and gave the following results: total bilirubin was 0.6 mg/dl (0.3–1.2 mg/dl), albumin was 4.28 g/dl (3.3–5.5 g/dl), AST was 25 U/L (2–40 U/L), ALT was 21 U/L (4–49 U/L), ALP was 152 U/L (70–290 U/L), GGT was 27 U/L (5–65 U/L) and LDH was 415 U/L

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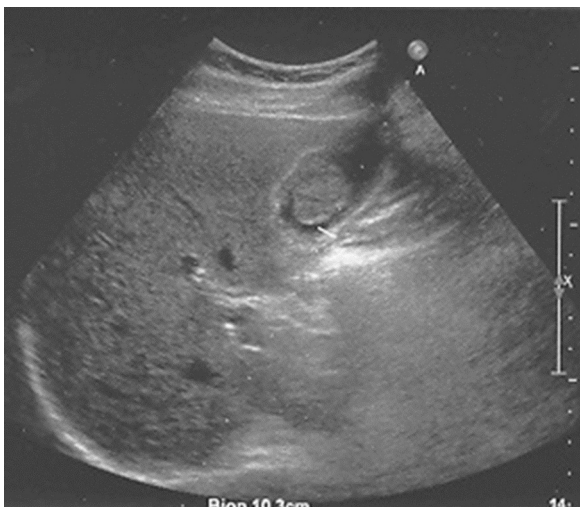


Fig. 1. Ultrasonography showing an hyperechoic mass within the gallbladder.

(125–243 U/L). In the light of such findings, the patient underwent several imaging tests, in order to better define the lesion.

Within the gallbladder's lumen (Fig. 1), ultrasonography showed an hyperechoic 18 mm × 24 mm mass, without significant color-doppler signal. Abdominal CT scan revealed the presence of an hyperdense 3 cm mass located over the gallbladder, without a clear dissection plane between this mass and the intra-luminal well known one (Fig. 2). Abdominal MRI confirmed a 18 mm solid node at the gallbladder's fundus, that presented contrast enhancement, with no signs of hepatic parenchyma infiltration. MRI was unable to identify the second mass previously detected by the CT scan (Fig. 3). In order to complete the pre-operative work-up, we requested a CEUS (contrast-enhanced ultrasonography) with the use of Sonovue®: the lesion within the gallbladder presented arterial enhancement and excluded hepatic involvement. PET (Positron Emission Tomography) showed high radioactivity in the gallbladder area (Fig. 4).

After case assessment by our multidisciplinary team, the patient underwent open cholecystectomy with 4b segmental hepatic resection; we performed an extemporaneous anatomopathological examination of the gallbladder wall, resulting in renal cell carcinoma metastasis. Our diagnosis was confirmed by the final histological examination. The final histological report defined the second lesion (described at CT scan) as benign gallbladder adenomyomatosis in a setting of chronic cholecystitis with no hepatic infiltration (Fig. 5).



Fig. 2. CT scan that confirms the hyperdense mass.

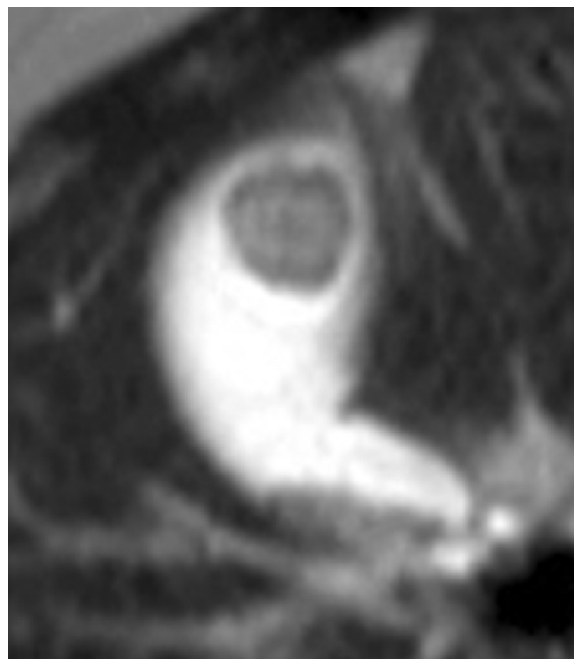


Fig. 3. MRI showing the lesion located at the fundus of the gallbladder.

Surgery was successful, obtaining a R0 resection. The patient resumed eating on the 4th postoperative day and the drainage tube was removed on the 8th postoperative day. The patient was uneventfully discharged on the 11th postoperative day. After 7 months, he is still free from disease, he is in good general conditions and undergoing follow-up at the oncological outpatient clinic.

### 3. Discussion

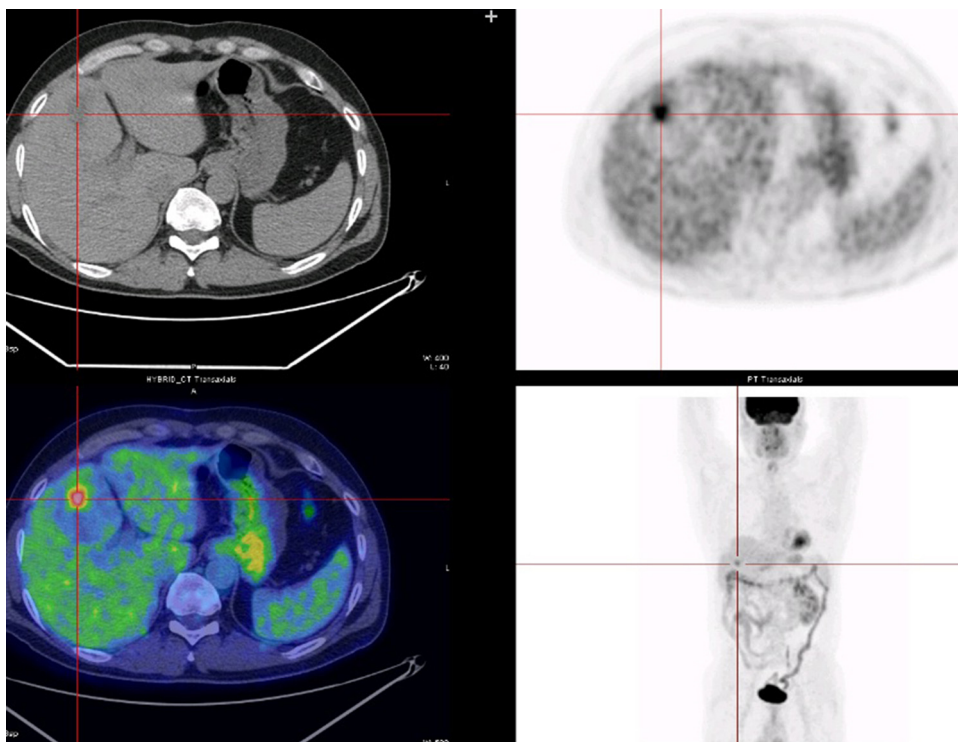
Renal cell carcinoma has a strong tendency to metastasize, mainly due to a complex and rich vascularization and its lymphatic drainage. The most common target organs are lungs (75%), bones (20%), lymph nodes (11%), liver (18%), and brain (8%) [4]. Atypical metastases are considered those located in a site other than thoracic, skeletal, hepatic, adrenal or encephalic regions [5]. Clear cell renal cell carcinoma most commonly metastasize hematogenously, via the vena cava, primarily to the lung, although lymphatic metastasis also may occur. Retrograde metastasis along the paravertebral veins, the vena testicularis/vena ovarii, intra renal veins, or along the ureter may also occur [6].

In our case, the metastatic disease presented at the gallbladder, which is a rather unusual metastatic area for ccRCC. Gallbladder metastases secondary to ccRCC are exceptional events and the world literature described only 41 such cases [3,4,6–10].

When gallbladder is affected by metastatic disease, it stems usually from melanoma, stomach, pancreas, ovary, small bowel, biliary duct and breast carcinomas [11,12]. Choi et al. found that the most common metastasis to the gallbladder was gastric cancer, followed by renal cell carcinoma [13].

The average time between radical nephrectomy and the onset of metastatic disease was 3.1 years, as stated by Leibovich et al. [14], as it was our patient's case.

Atypical metastases are an exceptional sign of metastatic renal cell carcinoma, but the role of surgery in this case is similar to that of surgery in pulmonary metastasis. In these cases, metastasectomy is accepted as possible treatment and in atypical metastases the cancer specific survival is similar [5].



**Fig. 4.** PET showing high radioactivity in the gallbladder area.

Due to low radiosensitivity, surgery is the preferred option if the tumor can be resected without unacceptable functional sequelae [15].

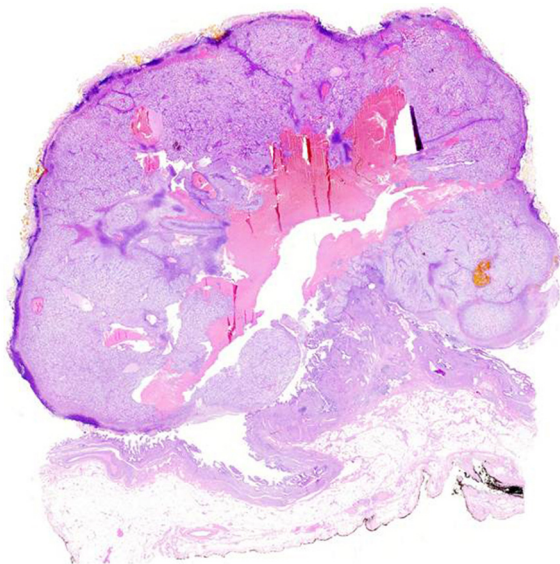
Gallbladder cancer patients can resemble those with chronic cholecystitis [16]. On the other hand, clinical findings are not specific enough to obtain a final diagnosis. Imaging may not be able to make a differential diagnosis between primary and secondary tumors of the gallbladder. US is the initial approach in the diagnosis of gallbladder tumors; metastases larger than 1 cm in diameter can appear under different hyperechoic masses, close to the gallbladder wall, without posterior acoustic shadowing. In primary tumors, one could observe a solid mass occupying the whole wall thickness,

or a polypoid lesion with an increased blood flow. A CT scan signal which could be of some help in differentiating between primary and metastatic gallbladder tumors is represented by the invasion of the mucosal layer; in case the mucosa is not infiltrated, indicating an invasion from the serosa layer, the primary gallbladder tumor can be excluded [11]. Doppler ultrasonography has been successful in demonstrating the vascularity of renal cell carcinoma in other locations [17].

Furthermore, in contrast CT scan, metastases from ccRCC are hypervascular, whereas primary gallbladder cancer does not present an hypervascular pattern; another peculiarity is represented by the fact that gallstones do not usually accompany metastatic gallbladder tumors from RCC, though primary cancer often coexists with gallstones [3]. Metastatic renal cell carcinoma tends to have a polypoid morphology instead of a cholecystic mass, with early wash-in and wash-out [13]. It is important to know whether we face a primary gallbladder tumor or a metastatic disease, because of gallbladder cancer propensity for early metastasis and direct invasion of the liver [18]. This might modify surgical approach, requiring—if necessary—a much larger hepatic resection.

Cholecystectomy with R0 resection has proved to be the only factor that increases survival, mainly in isolated cases of metastasis. The latest case reports showed that solitary metastasis of renal cell gallbladder carcinoma (with no evidence of involvement of other anatomic sites) correlates with better survival [19]. In metastatic gallbladder cancer, an R0 resection is the only factor associated with prolonged survival. The presentation of the metastatic disease with acute cholecystitis was associated to poor survival, because of overall tumor metastasizing to the gallbladder [9].

Metastasectomy provided an overall 35–60% survival (OS) at 5 years in patients who underwent metastasectomy of a solitary lesion, but its benefit is highly correlated with the metastasis site. It is important to keep in mind some good prognosis criteria, that might help in selecting patients who are supposed to benefit from surgery: metachronous metastasis with a recurrence-free period longer than 12 months, solitary metastasis, good health



**Fig. 5.** Hystological staining of the lesion, that diagnosed clear cell renal cell carcinoma metastasis.



condition, and patients aged under 60 years [20]. It was reported that a Fuhrman grading that increases between the primary tumor and the metastasis is detrimental [21].

At present, according to European Association of Urology guidelines, nephrectomy combined with alpha-IFN is recommended for patients with metastatic renal cell carcinoma, who are suitable for surgery and have a good performance status. In patients with synchronous metastatic spread, metastasectomy should be performed if the metastatic spread is resectable and the patient has a good performance status. Clinical prognosis is worse in patients who underwent surgery for metachronous metastasis [19].

#### 4. Conclusion

All new findings during follow-up in patients with a positive history of RCC (in particular clear cell subtype) should be considered as possible metastases. We have to consider US and CT-scan behavior of gallbladder metastatic disease, in order to orientate our diagnosis. Metastatic gallbladder tumor is very difficult to diagnose, because it is easily mistaken with benign disease during common imaging. In a patient with positive history of RCC we have to rule out any possible metastasis, before judging a gallbladder lesion as benign. Up to date, surgery for metastatic gallbladder disease of renal origin seems to be a feasible treatment, capable of increasing patients' overall survival.

#### Conflicts of interest

All the authors of this paper disclose any financial and personal conflict of interest of any sort.

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#### Ethical approval

No ethical approval was required.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### Author disclosure

M.D. Castro Ruiz Carolina, M.D. Pedrazzoli Claudio, M.D. Bonacini Stefano. All 3 authors contributed to the study concept, data collection, data analysis and interpretation, as with the writing of the paper.

#### Guarantor

M.D. Claudio Pedrazzoli.

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