

Case Report

Isolated Gallbladder Metastasis from Renal Cell Carcinoma: A Case Report and Review of the Literature

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Abstract

Isolated gallbladder metastasis from renal cell carcinoma is a very rare clinical entity with a significant male predominance. Until now, only 22 cases have been reported in the medical literature. Most cases occurred after very prolonged disease-free intervals. We report a case of metachronous isolated gallbladder metastasis of 15 mm size in a 72 yr old gentleman, 12 years after subtotal nephrectomy of the upper pole of the right kidney for clear cell renal cell carcinoma. At the time of diagnosis, the patient suffered from concurrent aggressive B-cell non-Hodgkin's lymphoma which was treated aggressively, including autologous bone marrow transplantation. Gallbladder resection was performed after treatment of the hematological malignancy. Small polypoid structures in the gallbladder of patients with antecedents of renal cell carcinoma should prompt surgical resection even if the size in ultrasound does not reach internationally accepted intervention thresholds for benign gall bladder polyps.

Keywords: Isolated gallbladder metastasis; Renal cell carcinoma; Surgical resection; B-cell-non-hodgkin-lymphoma

Abbreviations

RCC: Renal Cell Carcinoma; CNS: Central Nervous System; CT: Computed Tomography; NHL: Non-Hodgkin Lymphoma; FDG-PET: Fluorodeoxyglucose-Positron Emission Tomography

Introduction

Renal cell carcinoma (RCC) is the most common malignant disease of the kidney, representing more than 90% of all cancers affecting this organ, followed by urothelial carcinoma of the renal pelvis and rare cases of kidney lymphoma or sarcoma. Approximately 20%-30% of patients with RCC have metastatic disease at presentation. Close to 50% of patients with advanced disease will develop metastatic disease within 5 years of diagnosis. The most common histological type is clear cell tumor (70-75%). Papillary RCC and chromophobe RCC account for 15%-20% [1]. The most frequent sites of metastasis are lung (55%), regional lymph nodes (34%), liver (33%), bones (32%), adrenal (19%), contralateral kidney (11%) and CNS (6%) [2]. More than 230 cases of metastasis to the pancreas have been described. In contrast, the gallbladder is very rarely a target for metastasis of RCC, but was occasionally involved in malignant melanoma [1,3,4], stomach, pancreas, ovary, colon, biliary duct and breast carcinomas [1]. We report the case of a male patient who developed isolated renal cell carcinoma metastasis to the gallbladder which was incidentally found while he was being treated for aggressive non-Hodgkin's lymphoma.

Case Presentation

This 72 yr old gentleman was diagnosed in 2002 with renal cell carcinoma of the upper pole of the right kidney and underwent subtotal nephrectomy. 12 years later, in August 2014, he presented with rapid onset ascites and underwent diagnostic laparoscopy which revealed aggressive B-cell non-Hodgkin's lymphoma. The

initial CT staging showed a partly calcified, ovoid and polypoid mass measuring 15 mm within the gallbladder, thought to be a gallbladder calculus. The abdominal ultrasound examination also confirmed a 15 mm structure within the gall bladder, in keeping with a benign gall bladder polyp. The patient was treated with 6 courses of intensive polychemotherapy including methotrexate, anthracyclines, cyclophosphamide, vincristine, etoposide and cytarabine as described elsewhere [5]. In January 2015, the patient underwent autologous stem cell transplantation. During follow-up, the 15 mm polypoid mass within the gallbladder was reevaluated and operative removal scheduled to prevent malignant evolution. Histopathology revealed renal clear cell carcinoma of 23 mm diameter in the mucosal wall. Immunohistochemistry showed positivity for vimentin and pancytokeratin, and negativity for CK7, CEA, chromogranin, synaptophysin and CD68.

Morphological correlation with the initial tumor of 2002 corroborated the finding of late onset metastasis of RCC. The patient later relapsed of aggressive non-Hodgkin's lymphoma in 2015 and succumbed to this disease.

Discussion

Metachronous, isolated metastasis of renal cell carcinoma to the gallbladder is an extremely rare finding and only 22 cases have been reported in the literature so far [6]. The median disease free interval between primary operation for RCC and metachronous gallbladder metastasis (isolated or in the context of multiple other sites of metastasis) has been reported to be 3.1 to 7.4 years with the longest intervals spanning up to 27 years [6-8]. Table 1 summarizes cases of isolated metachronous metastasis to the gallbladder. These cases occur after long disease-free intervals (median time to diagnosis 6 years), with a strong male predominance (87%). The majority of the cases were diagnosed in asymptomatic patients (63%). Our case

Table 1: Solitary metachronous metastasis of renal cell carcinoma to the gallbladder.

Author	Age	Sex	DFI	Symptoms	Size (mm)
Botting, et al. 1963 [26]	66	M	1.5	NA	42x20
Golbey, et al.1991 [27]	84	M	13	None	35
Nagler, et al. 1994 [28]	82	M	5	None	30x30
Lombardo, et al. 1996 [2]	77	M	5	None	30x30
Sparwasser, et al. 1997 [3]	46	M	3.7	Abdominal pain	27x21
Aoki, et al. 2002 [21]	63	M	27	None	75x30
	80	M	8	None	45x25
Miyagi, et al. 2003 [29]	53	M	10.5	None	25x15
Park, et al. 2003 [30]	48	M	2	None	NA
Itoh, et al. 2004 [20]	53	M	11	None	25x25
Ishizawa, et al. 2006 [23]	73	M	5	None	30x20
Pandey, et al. 2006 [31]	46	M	1	Abdominal pain	NA
Patel, et al. 2009 [32]	64	F	6	Acute biliary syndrome, upper back pain	30
Biolchini, et al. 2009 [33]	77	F	13	None	115x5
Fang, et al. 2010 [19]	54	M	7	None	15x10
Mazzei, et al. 2010 [34]	73	M	5	Acute biliary syndrome	NA
Collin, et al. 2012 [35]	68	M	NA	None	NA
Vaziri, et al. 2012 [36]	57	M	NA	Abdominal pain	22
McWhirter, et al. 2013 [37]	74	M	14	Acute biliary symptom	22x23
Jain, et al. 2013 [38]	49	F	6	Right upper quadrant abdominal pain	20x18
Win, et al. 2014 [13]	62	M	21	Acute biliary syndrome	40
Ueda, et al. 2015 [39]	43	M	1	None	26
Current report	72	M	12	None	23

was an incidental finding during staging for aggressive NHL and asymptomatic regarding the gallbladder. Abdominal ultrasound is a convenient and reliable tool in the diagnosis of gallbladder tumors. Metastases can appear as hyperechoic masses bigger than 1 cm in diameter, close to the gallbladder wall without posterior acoustic shadowing [9-12]. A CT sign that can help in the differentiation between primary gallbladder tumors and metastases is the invasion of the mucosal layer. When the mucosal layer is not infiltrated, a primary gallbladder tumor can be excluded [6]. Moreover, the majority of cases of metastatic renal cell carcinoma to the gallbladder reported in the literature presented themselves as polypoid masses [6]. Therefore, in patients with a history of renal cell carcinoma and a polypoid gallbladder mass in computed tomography, a metastasis of the RCC should be included in the differential diagnosis. The role of PET-CT in the diagnostic of the gallbladder metastases of RCC remains questionable. While Robeldo, et al. denied any benefit from using PET-CT to detect gallbladder metastasis [6], Win et al. claimed that FDG-PET is a useful and good diagnostic tool in mRCC because it can detect cancers before anatomic changes are perceptible [13]. Removal of gall bladder polyps in otherwise healthy subjects is usually advocated for sizes exceeding 10 mm [14,15]. For polyps between 6 and 10 mm regular follow-up with ultrasound is usually recommended [15-17]. In patients with a history of RCC, a more active approach seems prudent. As a matter of fact, the median tumor size at diagnosis of gall bladder metastasis of RCC in the literature

was 3 cm (range, 1.1–7.5). The case reported here had a very long interval from diagnosis of RCC metastasis to operation (12 years), and the removed specimen measured 2.3 cm. RCC metastases to the gallbladder have a low incidence of concomitant gallstone disease [8,18,19]. There is certain variability in the histological findings of gallbladder metastasis from RCC. The majorities of metastases has a polypoid or pedunculated morphology and often begin as a submucosal nodule that eventually becomes pedunculated [8,18,20]. In this case metastatic gallbladder carcinoma may resemble primary carcinoma of the gallbladder. Metastasis may be limited to the muscle layer and perimuscular connective tissue and doesn't necessarily involve the mucosa [6,8,18,21]. In immunohistochemistry, primary carcinoma of the gallbladder is positive for CK7 and CEA, while metastatic RCC is negative for these antigens [22]. In contrast RCC metastasis would be positive for vimentin, pancycotocerin and CD10 but negative for CEA, CK7, chromogranin, synaptophysin and CD68, which indeed happened with our patient [1,19,23]. Isolated metastasis of RCC is preferentially treated with surgical resection after multidisciplinary review, especially for solitary or easily accessible pulmonary metastases, solitary resectable intra-abdominal metastases, especially if there is a long disease-free interval after nephrectomy, or a partial response of metastases to immunotherapy or targeted therapy [24]. In fact, in all patients with metastatic renal cell cancer, those deriving the largest benefit from surgery were patients with a recurrence-free interval of above 12 months vs. less

than 12 months (55% vs. 9% 5 year survival, $p < 0.0001$), solitary versus multiple sites of metastasis (54% vs. 29% 5 year survival, $p < 0.001$), and age < 60 years (49% versus 35% 5 year survival, $p = 0.05$) [25]. Overall survival rates of patients with solitary metachronous gallbladder metastasis exceeded 90% in two series [7,19]. Renal cell carcinoma is considered a chemotherapy resistant entity and, in our patient, 6 courses of intensive polychemotherapy followed by autologous stem cell transplantation failed to significantly reduce the size of the tumor. On the other hand, the profound immune suppression inflicted by aggressive chemotherapy did not lead to any relevant growth of the tumor, which remained almost stable in size as measured by non-invasive radiological imaging throughout the therapy for NHL.

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