



Metachronous Isolated Splenic Metastasis in a Young Patient With Renal Cell Carcinoma: Case Report and Literature Review

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Splenic metastasis is uncommon and is usually associated with widespread disease.^{1,2} Isolated splenic metastases from renal cancer are also rarer and are often an incidental finding. This eventuality may turn into a dangerous scenario due to a spontaneous splenic rupture leading to sudden death.^{2,3} At the best of our knowledge, only few cases of metastasis from renal cell carcinoma (RCC) have been documented in the literature.⁴⁻¹¹ We hereby present a literature review of these cases and report a case of isolated splenic metastasis in a young man on active follow-up for a clear cell RCC clear cell Renal Cell Carcinoma (ccRCC). UROLOGY 127: 13–18, 2019. © 2019 Elsevier Inc.

CASE PRESENTATION

In June 2012, a 41-year old Caucasian male was admitted to our Department for a cT1b/N0/M0 renal mass of the right kidney and underwent a right laparoscopic nephrectomy. Postoperative course was uneventful and the patient was discharged on third postoperative day. According to the 2009 tumor nodes metastasis (TNM) staging system, postoperative staging was pT1b pN0 M0 (stage I). The pathology report showed ccRCC with a Fuhrman grade 3 and a 35% tumor necrosis (Fig. 1). The patient was routinely followed up with physical examination, blood tests, alternatively abdominal ultrasonography, and chest X-ray or computed tomography (CT) scan at 6 months intervals. His follow-up was uneventful for more than 4 years, until he presented to the routine follow-up visit with a 2-month history of general malaise, fatigue, night sweats, and 2 kg weight loss. A laboratory checkup revealed a normal value of hemoglobin (15 g/dL), hematocrit (40%), and platelets (350,000) but a raised erythrocyte sedimentation rate (63 mm/h); tumor markers, calcium, LDH, and b2-

microglobulin were found in normal ranges. A contrasted CT scan of chest, abdomen, and pelvis revealed an enlarged heterogeneous spleen with a focal enhancing nodularity measuring 3.5 × 3 × 2.5 cm endowed in the hilar region, confirmed also by an abdominal magnetic resonance imaging (Fig. 2).

A subsequent 18F-FDG PET-CT total body scan confirmed the small, isolated hypermetabolic mass inside the spleen with a standardized uptake value equal to 4. Brain magnetic resonance imaging and bone scintigraphy were negative. The case was discussed on Tumor Board meeting and a fine needle aspiration biopsy was excluded due to significant bleeding risks. The results of the radiological imaging excluded the differential diagnoses for splenic benign lesions such as hamartoma or inflammatory pseudotumor. A hematologic advice was also performed to rule out lymphoma or other hematologic malignancies, but extensive blood tests were in contrast with such hypothesis. Finally, the patient was admitted to our surgical department and a laparoscopic splenectomy was performed in October 2016. Perioperative course was uneventful and the patient was discharged on fourth postoperative day. He received pneumococcal, meningococcal, and H. influenzae vaccine as preventive infective protocol and resumed his scheduled oncological follow-up visits. At final pathologic report the diagnosis of metastasis was based on morphology and immunohistochemistry evaluations. On morphologic analysis, cells were round and/or polygonal with abundant clear cytoplasm and irregular nuclei with prominent and large nucleoli confirming a single splenic metastasis from means clear cell Renal Cell Carcinoma (ccRCC) with areas of necrosis, no infiltration of the spleen capsule, and of course free

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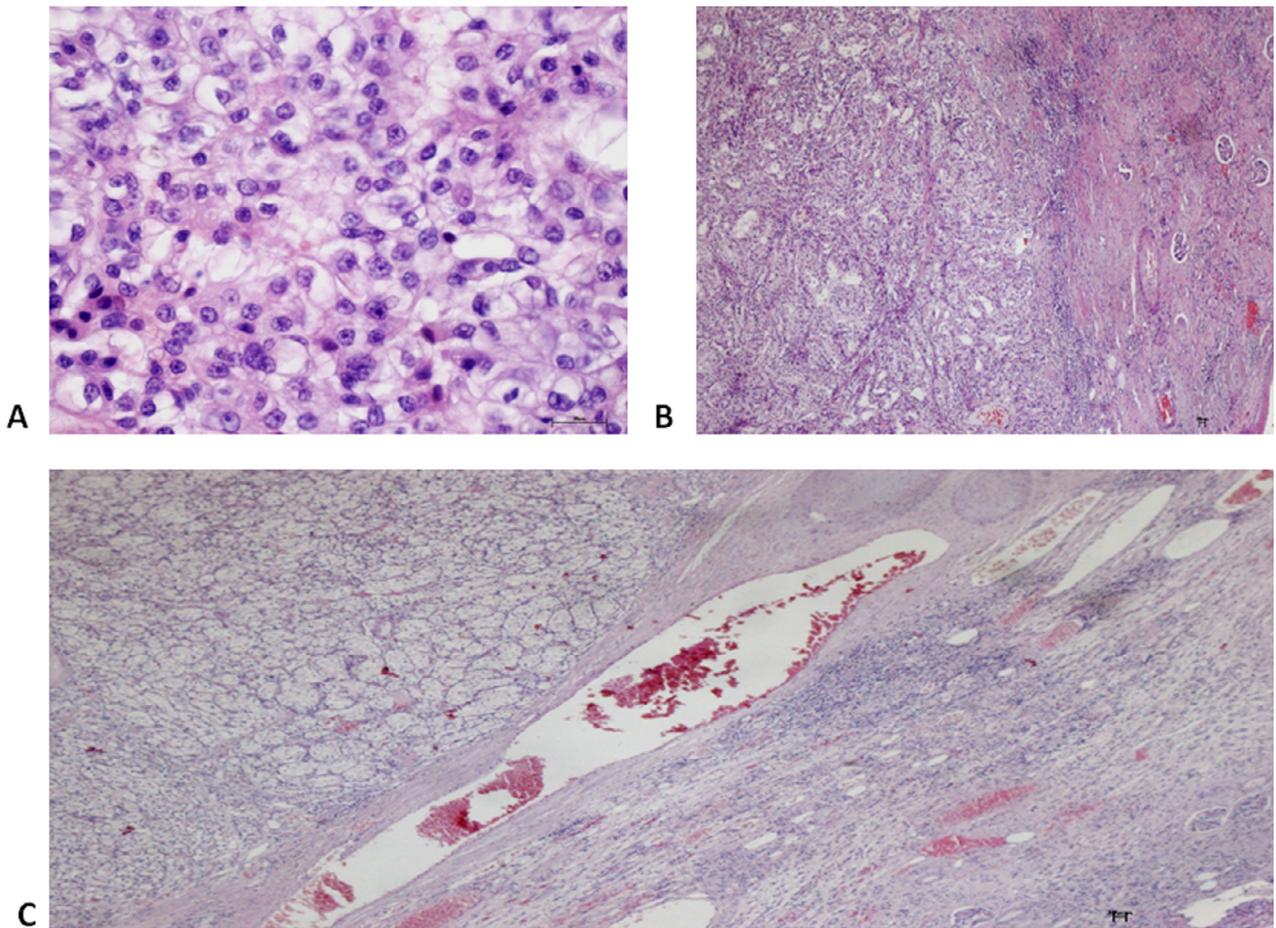


Figure 1. Primary renal tumor (respectively, A: 50 \times , B: 100 \times , and C: 400 \times). (Color version available online.)

surgical margins (Fig. 3A-C). Although there are no specific markers for RCC, the immunohistochemistry analysis showed positive staining for pancytokeratins, MNF116, and vimentin, while negative staining for CD31 and CD34, excluding a primary tumor of the spleen and

orienting for a secondary lesion from kidney. Moreover, we performed a PAX8 immunohistochemical stain to support the renal origin of the spleen metastasis. PAX8 staining resulted to be clearly positive (Fig. 3D,E), suggesting a metastasis from ccRCC. At last follow-up,

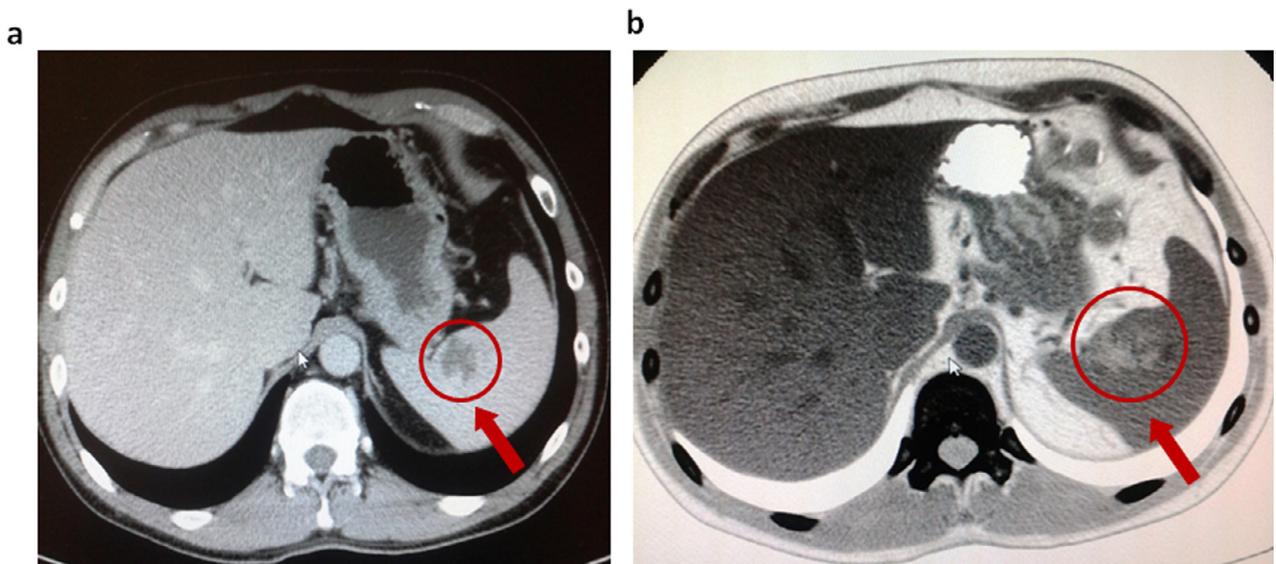


Figure 2. Abdomen CT scan (a) and RM (b), transverse plane. (Color version available online.)

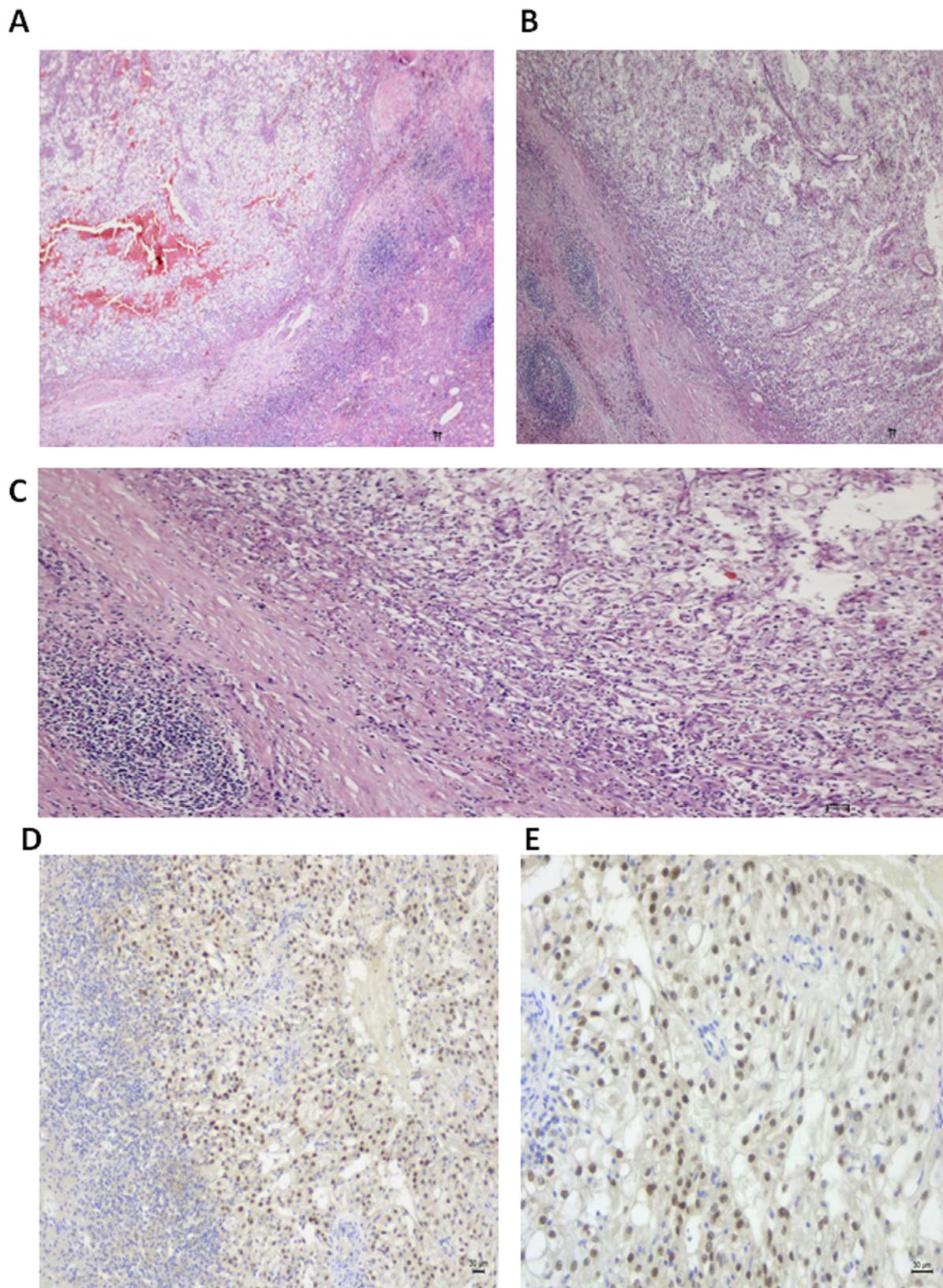


Figure 3. Splenic metastasis from clear cell renal carcinoma (A, 50 \times , B, 100 \times , C, 200 \times , D and E, PAX8 positive immunohistochemical staining, respectively, 10 \times and 20 \times). (Color version available online.)

27 months after splenectomy, the patient had no evidence of disease on total body CT scan.

DISCUSSION (PRESENTED BY GIUSEPPE SIMONE M.D., PH.D., CONSULTANT UROLOGIST AT REGINA ELENA NATIONAL CANCER INSTITUTE OF ROME)

RCC is the most common malignant neoplasm of the kidney. It accounts for a 3% of all solid adult malignant neoplasms. At time of diagnosis, as many as one-third of the patients may have a metastatic disease and about 25% of the all patients operated will have a relapse metastasizing mainly in lungs, bones, surgical sites, adrenal glands, liver, brain, and contralateral kidney.¹²⁻¹⁴

In these metastatic cases, adjuvant therapy is effective in only about 10% of patients.¹⁵ Despite the unpredictable natural history of RCC, including very late metastases and metastases to unusual sites, splenic metastasis from ccRCC is a very rare entity and it is usually a part of multiorgan metastatic disease, synchronously or shortly after primary tumor revealed during follow-up imaging studies.¹⁶⁻¹⁸ The reported incidence of metastatic tumors in spleen varies from 0.3% to 7.3%, but it is generally linked to hematological malignancies. Usually, primary tumors with common metastatic spread to the spleen include melanoma, breast, and lung cancers.^{19,20} An internal review of our Institutional Renal Database including 1995 RCCs treated between 2001 and 2017 at the Department of Urology, Regina Elena National Cancer Institute of Rome, documented only 7 cases (0.35%) of splenic metastases, always as part of a multimetastatic disease, except for the presented case. Notably, in autopsy series, the incidence of occult micrometastatic splenic spread from cancer patients has been quoted to be about 4%-7%.^{20,21} The spleen is considered to be resistant to cancerous implantation. As reported in Literature, potential reasons for the rarity of splenic metastasis in nonhematologic malignancies include: the sharp angle at the origin of splenic artery that prevent large tumor emboli from entering the artery, the rhythmic contraction by splenic sinusoids, the constant blood flow through the organ, the paucity of afferent lymphatic vessels, the protective role of the splenic capsule, and the microenvironment that prevent the growth of neoplastic cells.^{1,3,22-24} Furthermore, phagocytosis and its physiological immunological antineoplastic action may be other factors preventing tumor seeding in spleen. Despite that, the pattern of metastatic deposit in the spleen is very heterogeneous and ranges from macroscopic (solitary nodule, multiple nodules, miliary, or diffuse replacement) to microscopic implants and the neoplastic cells may be located to the venous sinuses, red pulp, white pulp, or trabecular vessels.²¹⁻²³ Probably, the late occurrence of solitary splenic metastases may depend on early blood-borne micrometastasis in spleen after a clinical latency period.^{16,21,24} Rarely, the metastasis is confined to the trabecular lymphatics of the spleen, probably this is

due to a retrograde permeation of splenic lymphatics that usually originates from malignant deposits in the hilum.²² So, although extremely unusual, isolated splenic metastasis may occur in patients previously treated for RCC. At the best of our knowledge, only 11 cases of splenic metastasis from RCC have been reported in literature⁴⁻¹¹ (Table 1); all but 1 had left sided primary renal tumor. Considering the presented case, the entire population was represented by 10 men with the exclusion of 2 women, confirming the expected gender distribution. According to the Vancouver ISUP classification system and the past Heidelberg classification, histologic subtypes of primary renal tumors included 6 ccRCC, 1 unclassified RCC with mixed cc and tubulo-papillary features, 1 papillary RCC, and unspecified RCC histologic variant for the remaining 4 cases. Clinical stages at presentation of these 11 reported cases plus the present case were: 3 stage I, 3 stage II, 2 stage III, 3 stage IV, and unknown in 1 case. The mean onset time from surgery for primary tumor was 64.1 months (ranged 0-264 months), while the median age was 60.7 years (ranged 41-72 years). Most of them were treated only with surgery while 4 patients received further treatments (surgery plus radiation or medical treatment). The reported prognosis was variable: 2 patients died within 1 year, 8 survived for a 6 months-9 years range, and in 2 cases the life status was not reported.⁴⁻¹¹ In this report, we described the second case of solitary splenic metastasis from right RCC but with the youngest age at the time of metastasis; the previous one died 6 months following splenectomy and was reported by Strum in 1984. Direct extension from a left sided renal tumor has been well widely reported in literature,⁷⁻⁹ probably due to topographic relation to the spleen, but in the present case, the side of primary tumor was right and a solitary spleen relapse occurred 51 months after primary tumor surgery; furthermore, the splenic capsule was intact, still suggesting a metastatic spread through blood diffusion, to be considered as a real metachronous metastatic event. To date, metastasectomy has been considered a standard of care when a nonevident disease status is achievable.²⁵ Obviously, site and disease volume of metastasis may influence the prognosis and consequently the treatment options.²⁶ In the presence of multiple metastases, the prognosis is very poor, while single site metastasis is associated with better outcomes and complete surgical resection has been considered the best treatment for any isolated lesion, providing significant survival benefits.^{26,27} Therefore, metastasectomy maintains a key role in the management of RCC metastases, especially in the presence of following clinical conditions: limited number and volume of metastases and realistic expectancy of surgical radicality (nonevident disease status), long interval from nephrectomy >12-24 months, good performance status, and clear cell histology without sarcomatoid compound.²⁸ Eventually, there is not sufficient evidence to support any use of tyrosin-kinase inhibitors in the adjuvant setting following surgical resection of spleen metastasis from RCC^{15,29,30}; given the small number of reported cases in Literature,

Table 1. Literature review of splenic metastasis originating from renal cell carcinoma

Author	Primary Histotype and Stage	Primary Kidney	Patient Age/Sex	Time to Metastasis (mo)	Splenic Met Size (cm)	Met Treatment	Clinical Outcomes
Strum 1984	RCC unknown	Right	55 M	264	Whole spleen	Surgery + radiation	Died, 6 mo
Murao 1987	RCC stage I	Left	72 M	120	5 cm	Surgery	Alive, 1 y
Pal 1995	RCC stage IV	Left	54 F	Synchronous	Small nodule	Surgery	Unknown
Suzuki 1996	RCC stage I	Left	43 M	84	5 cm	Surgery	Alive, 9 y
Tatsuta 2001	ccRCC stage II	Left	69 M	22	6 cm	Surgery	Alive, 5 y and 7 mo
Kugel 2001	ccRCC stage II	Left	72 M	24	7 cm	Surgery + INF	Died, 1 y
McGregor 2003	p-RCC stage IV	Left	65 M	Synchronous	8 cm	Surgery	Unknown
Ielpo 2010	ccRCC stage II	Left	68 M	168	6 cm	Surgery	Alive, 1 y and 3 mo in remission
Moir 2011	ccRCC stage III	Left	70 F	11	7 cm	Surgery	Alive, 2 y in remission
Zhang 2015	Unclassified RCC stage III	Left	67 M	24	10 cm	Surgery + radiation	Alive, 5 mo in remission
Grewal 2016	ccRCC stage IV	Left	53 M	2	Multi-focality	Surgery + sunitinib	Alive in remission
Present case	ccRCC stage I	Right	41 M	51	3,5 cm	Surgery	Alive, 27 mo in remission

ccRCC, clear cell renal cell carcinoma; RCC, renal cell carcinoma.

it is reasonable to apply same rules than for other RCC metastasectomy, where adjuvant treatment should not be considered a standard of care outside from clinical trials.

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