

## PAPER DETAILS

TITLE: Rare metastases of clear cell renal cell carcinoma to gastrointestinal tract: two case reports

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## EDİTÖRE MEKTUP / LETTER TO THE EDITOR

### Rare metastases of clear cell renal cell carcinoma to gastrointestinal tract: two case reports

Berrak hücreli renal hücreli karsinomun nadir görülen gastrointestinal sistem metastazları: iki olgu sunumu

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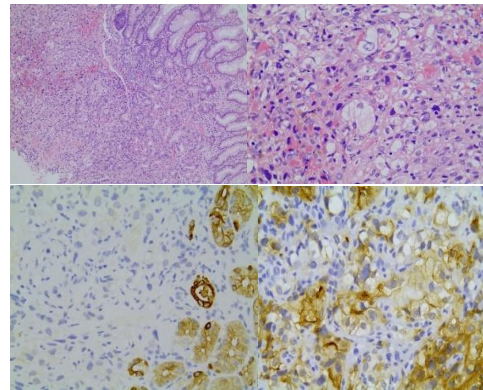
To the Editor,

Renal cell carcinoma (RCC) is among the most prevalent renal tumor, accounting for approximately 2-3% of adult malignancies. It was previously reported that approximately 20%-40% of patients would develop recurrence or distant metastasis after radical nephrectomy. It is known that RCC most commonly metastasizes to the lung, lymph nodes, bone, liver, adrenal glands, and brain in advanced stages<sup>1,2</sup>. The gastrointestinal tract (GI) is one of the rare and unusual sites of metastasis, and the literature reported few such cases. In this study, we presented two cases with rare gastrointestinal metastases of clear cell renal cell carcinoma (cRCC).

A 66-year-old male patient was admitted to the general surgery outpatient clinic with complaints of abdominal pain, bloating, constipation, and black, foul-smelling stools for the last two months. The patient's left radical nephrectomy and right adrenal gland excision in 2013 had been reported as cRCC. In the endoscopic examination, we observed about 1 cm diameter ulcerated area covered with fibrin in the stomach corpus and aphthous ulcers in the duodenum. On the colonoscopy, we observed an ulcero-vegetant mass filling the lumen in the descending colon. We performed multiple biopsies from the mass.

Microscopic examination of the materials from the stomach corpus revealed a tumor with pale

eosinophilic/clear cytoplasm, pleomorphic nuclei, and prominent nucleoli, forming solid island and tubule-like structures (Figure 1a,1b). In the immunohistochemical study, we observed that tumor cells were stained positively with vimentin and CD10, positively (focal) with RCC marker, and negatively with pan-cytokeratin (Figure 1c,1d). These findings were reported as consistent with cRCC metastasis.



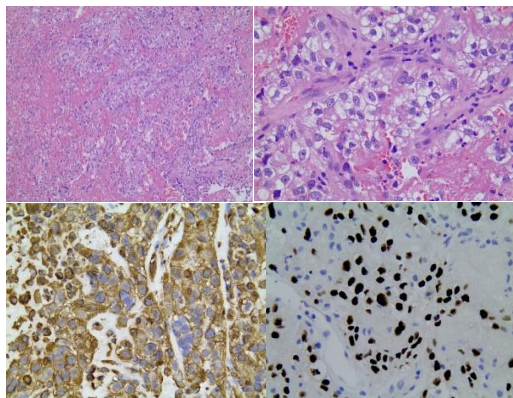
**Figure 1.** In the fundic type gastric mucosa material, we observed a tumor tissue with pale eosinophilic/clear cytoplasm, forming solid island and tubule-like structures (1a: HEX100, 1b: HEX400). Tumor cells showed positive staining with Panck (1c:X400) and CD10 (1d:X400).

We brought the patient to contrast-enhanced whole abdomen computed tomography (CT) and thorax CT

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for metastasis screening. On abdominal CT, we observed intra- and extra-abdominal extensive RCC metastases. On thorax CT, we encountered multiple metastatic nodules in the bilateral lung parenchyma and mediastinal bilateral hilar lymph nodes. In addition, we detected a subcutaneous implant in the old trocar entry site on the left inferolateral of the umbilicus due to the patient's previous operation. The hard-nature tumor implant of about 3x2 cm was excised.

The macroscopic examination of the material revealed a 3x2.5x2 cm adipose tissue. On the section surface, we observed a 2x8x2x1.5 cm sized off-white tumor formation with an irregular border with adipose tissue. In the microscopic examination, we detected a tumor consisting of atypical cells with an oval, round, slightly hyperchromatic nucleus, somewhat prominent nucleoli, and a wide pale eosinophilic transparent cytoplasm with clear borders, infiltrating the skin and subcutaneous soft tissues as masses (Figure 2a,2b). The tumor formed solid areas and tubular structures. In the immunohistochemical study, we discovered that the tumor was stained positively with vimentin and Pax8 (Picture 2c,2d). We also reported these findings as metastatic RCC.

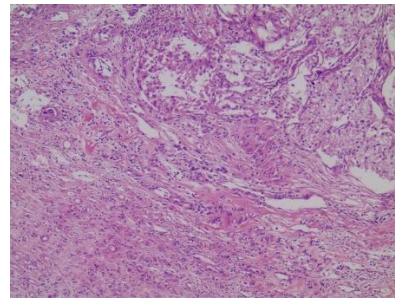


**Figure 2.** We observed a tumor tissue with pale eosinophilic/clear cytoplasm forming solid areas and tubular structures, infiltrating the skin and subcutaneous soft tissues as masses (2a: HEX100, 2b: HEX400). The immunohistochemical study showed that the tumor was stained positively with vimentin and Pax8 (2c-2d: HEX400).

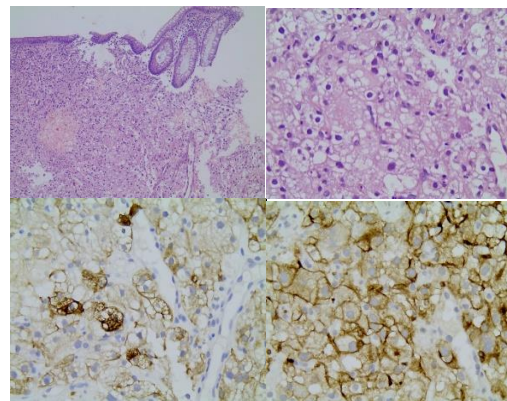
About two years later, the patient was admitted to the pulmonology clinic for a dyspnea complaint. We were informed that the patient did not complete his/her oncological treatment for a previous RCC. We brought the patient to contrast-enhanced thorax CT

because of atelectasis and pleural effusion on the right on the chest radiography. During follow-up, we observed progressed multiple metastatic nodules and mediastinal hilar LAPs in the lung parenchyma on CT.

A 55-year-old male patient was admitted to the general surgery outpatient clinic with complaints of fatigue and anemia for a week. We were informed that the patient was diagnosed with cRCC after the left radical nephrectomy in 2019 (Figure 3). The patient was not followed up in oncology and did not receive any treatment. In the colonoscopic examination, we observed an ulcero-vegetant mass of 5 cm at the junction of the descending colon and the rectosigmoid colon, narrowing the lumen by 60%.



**Figure 3.** We detected a tumor tissue with clear pale eosinophilic cytoplasm, slightly pleomorphic nuclei, and somewhat prominent nucleoli, forming solid islands and tubular structures in the kidney tissue (HEX100).



**Figure 4.** In the colon mucosa material, we observed a tumor consisting of atypical cells with clear cytoplasm, large nuclei, and prominent nucleoli, forming solid islands under the epithelium (2a: HEX100, 2b: HEX400). Tumor cells showed positive staining with Panck and CD10 (2c-2d: HEX400).

Microscopic examination revealed ulceration in the colonic mucosa and a tumor consisting of atypical cells with clear cytoplasm, large nuclei, and prominent nucleoli, forming solid islands under the surface epithelium (Figures 4a,4b). In the immunohistochemical study, we observed that the tumor cells were stained positively with pan-cytokeratin, Pax8, and CD10, and negatively with CDX2 (Figures 4c,4d). These findings were reported to be consistent with cRCC metastasis. Contrast-enhanced abdominal CT for screening metastasis showed metastatic mass lesions and intra-abdominal LAPs in the left kidney operation site-left psoas muscle and the entire mesocolon. On the thorax CT, we observed a nonspecific nodule in the right lung parenchyma and emphysematous alterations in the bilateral lung parenchyma.

RCC is the most common kidney tumor in adults and generally more common in males in the sixth and seventh decades (M/F: 2/1). GT is among the rare, unusual metastasis sites of RCC. The relevant literature revealed 13 metastatic RCC to the colon after curative nephrectomy between 1999 and 2019<sup>2</sup>. RCC cases reported as gastric metastasis mostly applied with the complaints of microcytic anemia and melena-like gastrointestinal bleeding. In advanced stages, acute bleeding develops due to diffuse mucosal ulcerations<sup>3</sup>. RCC cases reported as colon metastases mostly applied with complaints of hematochezia, abdominal pain, and anemia<sup>2</sup>.

The recurrence rate of RCC after curative surgical treatment is 20-40%. Although it tends to recur within the first five years after surgery, about 5-10% of patients may have late recurrences following this 5-year period<sup>2</sup>. Metastases to the stomach are more common in the trunk and fundus and more likely to be single rather than multiple<sup>4</sup>. The splenic flexure and transverse colon are most commonly involved in the colon<sup>2</sup>.

Gastric metastasis of RCC is usually detected after a much longer interval from the diagnosis of primary RCC, compared to other metastatic gastric tumors<sup>4</sup>. Accordingly, although we observed late recurrence (7 years) in the first case with gastric metastasis, there was early recurrence (1 year) in the second case with colonic metastasis.

Gastric metastases can be distinguished from primary gastric carcinomas microscopically by the absence of cellular atypia in the gastric glands suppressed by the metastatic tumor<sup>3</sup>. The most common type of RCC

is cRCC; it is also the most common variant of gastric metastatic RCC cases reported in the literature<sup>5</sup>. Therefore, it is essential to distinguish cRCC metastasis histopathologically from other important lesions, such as gastrointestinal stromal tumors (GISTs), that have epithelial differentiation and can fake the histology<sup>6</sup>.

Although primary clear cell adenocarcinoma of the colon is sporadic, it is imperative to suggest a differential diagnosis of cRCC from colonic metastasis<sup>7,8</sup>. Both types of tumors contain large numbers of clear cells, round or polygonal, with abundant clear cytoplasm. However, in clear cell adenocarcinoma, one can observe back-to-back gland structures composed of clear cells and periodic acid Schiff (PAS) positive intraluminal and intracellular mucin. Immunohistochemistry is helpful in diagnosis in cases that cannot be distinguished histopathologically. cRCC is stained positively with CD10, PAX8, and Vimentin but negatively with CK20 and CDX2. Yet, CK20 and CDX2 stain positively in colorectal carcinomas<sup>1,7,8</sup>. Thus, the identification of the tumor source may influence the formulation of the therapeutic strategy.

Overall, recurrent metastases of RCC may develop after many years of curative nephrectomy. GT is among the rare sites of metastasis. GT metastasis of RCC should be kept in mind in the presence of abdominal pain, anemia, or gastrointestinal bleeding, especially in patients with a history of radical nephrectomy.

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