Secondary involvement of the gastrointestinal tract by renal cell carcinoma

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ABSTRACT

Secondary involvement of the gastrointestinal (GI) tract by renal cell carcinoma is rare. We undertook a retrospective review of our institution's pathology records from January 2006 to July 2017 and identified eight cases of GI tract involvement by renal cell carcinoma. Sites of involvement included stomach, duodenum, jejunum, ileum, and cecum. Pertinent clinical information was obtained from electronic medical records. The interval from primary resection to identification of GI involvement was often prolonged, averaging 6 years, and mimicked primary GI tract malignancies, with presentations including GI bleeding, abdominal pain, and obstruction. One case presented asymptotically on follow-up imaging. Histologic patterns of involvement varied from classic clear cell to purely sarcomatoid or complex unclassifiable morphology. Two patients with tumors exhibiting sarcomatoid morphology died within 2 years of primary resection and <1 year of GI involvement. The remaining patients survived a mean of 9 years (range, 5 to 22 years) at their last available follow-up.

KEYWORDS Gastrointestinal tract; renal cell carcinoma; secondary involvement

In 2018, cancers of the kidney and renal pelvis are projected to comprise 3.8% of new cancers and 2.5% of cancer deaths in the United States.¹ Renal cell carcinoma metastasizes in approximately 26% of cases.² Common sites of metastasis include lung (45%), bone (29.5%), lymph nodes (22%), liver (20%), adrenal gland (9%), and brain (8%).³ Involvement of the gastrointestinal (GI) tract is so rare that its incidence is difficult to approximate. For example, a systematic literature review of renal cell carcinoma involving the stomach compiled only 22 cases.⁴ A study of data from the Nationwide Inpatient Sample from 1998 to 2007 collected 11,157 cases of metastatic renal cell carcinoma and found that small bowel metastasis comprised 1.1% and large intestine metastasis 1.3% of that total, with other digestive sites comprising 2.9%.³

METHODS

Following approval by our institutional review board, we performed a retrospective review of cases of secondary involvement of the GI tract by renal cell carcinoma at our institution from January 2006 to July 2017. The pathological features were reviewed, including histologic type and pertinent immunophenotype of the tumor in the GI specimen. All immunohistochemical studies had been performed at the time of diagnosis, with no additional studies performed for this review.

Pathologic features of the primary renal cell carcinoma were also reviewed where available. Other pertinent information, including presentation, imaging, surgeries, and outcome, was collected utilizing our institution's electronic medical record.

RESULTS

Our search identified eight patients. Demographic, clinicopathologic, and outcome data are summarized in *Table 1*. The male to female ratio of the identified patients was 7:1, compared to the usual ratio of around 2:1 for kidney tumors.¹ At the time of primary resection, the mean patient age was 61 years (range, 46 to 76 years). GI involvement was discovered an average of 6 years after primary resection (range, 1 to 17 years), with symptomatic presentations in seven cases (including GI bleeding, obstruction, and pain) and one asymptomatic case detected on follow-up imaging. Sites of involvement included duodenum (three cases), jejunum (one), both duodenum and jejunum (one), ileum (one), cecum (one), and stomach (one). Histologically, three cases showed clear cell carcinoma, two showed clear cell carcinoma with eosinophilic features, two showed sarcomatoid, and one had a variable architecture, including glandular, papillary, and cribriform patterns.

Four patients developed local recurrences either at the resection or incision site, with two of these cases (case 3 and

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Table 1. Summary of patient demographics, clinicopathologic features of primary kidney tumors and gastrointestinal involvement, and outcome data

No.	Age (years)	Sex	R/L	Histo (grade)	Size (cm)	Extension	LVI (LN)	GI Int (years)	GI site	Presentation	Histo	LR	Other metastasis	Outcome (years)
1	52	M	R	Unknown	Unknown	Unknown	Unknown	17	Duodenum	GIB	CC	0	None	LTFU (22)
2	73	F	R	CCE (3)	4.5	Renal sinus	No	2	Ileum	Pain, diarrhea	CCE	+	None	LTFU (9)
3	48	M	R	Unknown	Unknown	Unknown	Unknown	10	Cecum	Image	CC	+	Liver	Alive (18)
4	70	M	L	Unknown	Unknown	Unknown	Unknown	4	Stomach	GIB	CC	0	Pancreas	LTFU (6)
5	66	M	L	CCS (4)	10.8	Renal vein	Yes	1	Duodenum, jejunum	GIB	S	+	Multiple	Died (2)
6	76	M	R	CCS (4)	4.5	None	Indeterminate	2	Duodenum	Obstruction	S	+	Liver	Died (2)
7	57	M	R	Variable (4)	3.8	Capsule, renal sinus, renal vein	Yes (6/42)	3	Duodenum	Pain	Variable	0	Unknown	LTFU (3)
8	46	M	R	Unknown	Unknown	Unknown	Unknown	10	Jejunum	GIB	CCE TC	0	None	LTFU (10)

R/L indicates right or left; Histo (grade), primary tumor histology with Fuhrman nuclear grade in parentheses; LVI (LN), lymphovascular invasion with number of positive over total lymph nodes in parentheses; GI Int, interval from primary tumor resection to gastrointestinal involvement; Histo, histology of gastrointestinal involvement; LR, local recurrence; GIB, gastrointestinal bleeding; LTFU, lost to follow-up; CCE, clear cell with eosinophilic features; CC, clear cell; CCS, clear cell with focal sarcomatoid features; S, sarcomatoid features; TC, tubulocystic.

case 6) ultimately involving the GI tract (cecum and duodenum) by direct extension. These recurrences occurred an average of 3 years (range, 1 to 7 years) after the primary resection. Four cases had documentation of other metastases, including to liver, lungs, pancreas, contralateral adrenal and kidney, and lymph nodes. Additionally, three cases exhibited other primary tumors including high-grade urothelial carcinoma (case 2, 4 years after kidney resection), melanoma (case 3, 6 years after kidney resection), and lung adenocarcinoma and leiomyoma (case 6, both 2 years after kidney resection). As part of pathologic workup, immunohistochemical stains had been performed in a subset of cases. Notably, PAX8 was only positive in two of five stained cases and RCC in one of four; CD10 and vimentin were positive in three of three and four of four cases, respectively. CK7 was negative in all five of the stained cases.

Four cases had primary pathology available for review. The mean primary tumor size was 5.9 cm (range, 3.8 to 10.8 cm). Primary histology showed two cases of clear cell renal cell carcinoma with focal sarcomatoid features, one of clear cell carcinoma with eosinophilic changes, and one of unclassified renal cell carcinoma with a variety of patterns (including solid, reticular, micropapillary, papillary, and tubuloductal). Only one case was limited to the kidney; the others all showed extrarenal extension, including renal sinus invasion, renal vein invasion, and capsular invasion. All four cases were negative for invasive tumor at margin.

Two patients died within 2 years of primary resection. Both exhibited sarcomatoid features in their primary tumors, and their GI involvement was composed entirely of the sarcomatoid component, underscoring its aggressiveness. One of these initially presented with lung metastases and subsequently developed metastases in the contralateral adrenal gland, kidney, lymph nodes, liver and separate metastases to the duodenum and jejunum. The other case was without evident disease following surgery but developed recurrent tumor in the nephrectomy bed that directly extended into surrounding soft tissue to involve other structures, notably duodenum and hepatic hilum (with a separate metastasis to liver). The remaining patients were lost to follow-up at varying dates but survived a mean of at least 9 years (range, 5 to 22 years).

DISCUSSION

It is notable that the two patients who died of their disease in our series had sarcomatoid histology. Though not part of tumor staging, sarcomatoid change has been incorporated into the International Society of Urologic Pathology's grading system, in which tumors exhibiting rhabdoid or sarcomatoid features are placed in grade 4 alongside tumors with marked nuclear pleomorphism.⁵ This is motivated by the prognostic implications of sarcomatoid change. A study of 77 patients with sarcomatoid renal cell carcinoma without metastases at presentation found that only 50% survived 2 years and 77% of patients without evidence of disease upon resection went on to develop metastases or local recurrences with a median interval of

26.2 months.⁶ In this study, the most common site of involvement was the lung (45%) followed by local recurrence (25%), as seen in our case. Another study of 108 patients with sarcomatoid change found a 77% rate of initial metastasis, with a shortened median overall survival of 7 months versus 17 months in patients with localized disease.⁷

An actuarial analysis of a set of 172 renal cell carcinomas without initial metastatic disease projected a 7-year rate of local recurrence of only approximately 5%.² Interestingly, in this study, the observed mortality was from distant metastasis or complications of treatment, and the study did not find persuasive evidence that local recurrence meaningfully increased the likelihood of distant metastasis. Therefore, the typical prognosis of a patient with only local failure would be expected to be favorable. The fact that one of our patients with local recurrence died so quickly might be due to tumor aggressiveness, indicated by sarcomatoid histology.

The differential diagnosis of a GI tumor includes GI stromal tumors, neuroendocrine tumors, lymphoma, and melanoma.⁸ Classically, RCC and PAX8 staining would suggest renal origin, because these markers have been previously shown to stain 98% and 72% to 85% of clear cell renal cell carcinomas, respectively.⁹ However, PAX8 can be positive in other tumor types such as carcinoma of Mullerian origin.¹⁰ Vimentin has been found to stain 87% of clear cell carcinoma and CD10 has been found to stain 94% to 100%, whereas CK7 is negative in 63% to 100% of cases.⁹ Although this combined immunophenotype is supportive of the diagnosis, none of these markers is independently specific.

Ultimately, accurate diagnosis of renal cell carcinoma involving the GI tract can best be rendered by correlating

histomorphological features with clinical history, radiological findings, and judicious use of immunohistochemistry.

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