Local Recurrence of Renal Cell Carcinoma Causing Massive Gastrointestinal Bleeding: A Report of Two Patients Who Underwent Surgical Resection

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We report two cases of local recurrence of renal cell carcinoma, which invaded the gastrointestinal tract. The intervals to local recurrence after primary nephrectomies were 5 and 13 years. Both cases developed massive gastrointestinal bleeding. Blood transfusions and arterial embolization were performed; however, continuous melena prevented improvement in their general condition. Although distant metastases were observed in both cases, tumor resections combined with intestine invasion were performed. Although this surgical approach does not significantly improve the prognosis, even in patients who have remaining metastatic lesions, it may provide palliation and improve the quality of survival.

Key words: renal cell carcinoma – local recurrence – gastrointestinal bleeding – surgical resection

INTRODUCTION

Local recurrence of renal cell carcinoma (RCC) at the renal fossa often appears with no manifestations until the tumor invades adjacent structures or forms massive growths (1–3). Because RCC is rich in blood flow, gastrointestinal bleeding due to invasion of the tumor often represents a difficult management problem. We present two cases of local recurrence of RCCs causing massive gastrointestinal bleeding that were uncontrollable by conservative therapies and underwent surgical resection.

CASE REPORTS

CASE 1

A 62-year-old man underwent a left nephrectomy for RCC with lung metastases in February 1990. He had a history of diabetes mellitus and myocardial infarction. Although an adjuvant immunotherapy with interferon-α, 600 × 10^4 I.U. for 8 weeks, was given, the sizes of the metastatic lung tumors did not change. Subsequently, partial resections of the bilateral lung were performed for multiple lung metastases in May 1990. The postoperative course was uneventful and immunotherapy and chemotherapy had been continued for 2 years including interferon-α, 5-fluorouracil and mitomycin C. However, in 1992, the patient developed bilateral lung metastases and liver metastasis. Consequently, resection of multiple lung metastases was performed in June and a hepatectomy in August. After that, he had been followed as an outpatient by his family doctor without adjuvant therapy. He had been doing well without major clinical symptoms, but sudden massive gastrointestinal bleeding occurred in March 1995. Local recurrence of RCC was determined, presenting as a large mass located at the left renal fossa with multiple lung metastases. Conservative treatment, including blood transfusions, was given, but his general condition gradually deteriorated and he presented with symptoms of ileus. The patient was referred to our hospital on August 3, 1995. On admission, the performance status (PS) of the patient according to the criteria of the World Health Organization (WHO) was Grade 4, due to his long-standing history of disease. Abdominal computed tomography showed a huge, well-enhanced mass, 11.5 × 6.0 × 5.0 cm in size, which had invaded the left psoas muscle and the fourth portion of the duodenum, occupying the whole lumen (Fig. 1). On upper gastrointestinal endoscopic examination, a large elevated irregular shaped tumor, which had a bleeding tendency, was observed. The intestine was completely obstructed by the tumor. Angiography was performed on August 15, revealing a tumor stain having both a jejunal artery and a lumbar artery as feeders (Fig. 2). To control continuous intestinal bleeding, arterial embolization of the lumbar artery was done, but the first jejunal artery could not be embolized.
Two days later, the patient developed a hemorrhage shock with massive hematemesis. In spite of systemic care, there was no improvement in his poor condition and a laparotomy was performed on September 11.

On exploring the abdominal cavity, no evidence of peritoneal dissemination or liver metastasis was present. The tumor was palpable as a large mass located at the left renal fossa, fixed to the retroperitoneum and invading the left psoas muscle and duodenum. The tumor was resected along with part of the duodenum and the jejunum, but the retroperitoneal surgical margin was macroscopically positive. Considering the general condition of the patient, further surgical intervention was abandoned and a duodenojejunostomy was performed.

Macroscopically, the huge tumor involved the duodenum and was 9.5 × 7.0 × 4.0 cm in size with a blood clot stuck to the surface, containing multiple hemorrhage foci and necrosis in the tumor. Histological examination demonstrated a clear cell carcinoma, which was compatible with a recurrence of RCC (Fig. 3A) with focal hemorrhaging and severe nuclear pleomorphism (Fig. 3B).

Although uncontrollable diabetes mellitus and paralytic ileus brought about difficulties during postoperative management, dietary intake gradually recovered. Finally, on November 2, he suddenly complained of severe lower abdominal pain and died the next morning, the forty-second postoperative day. An autopsy was not performed but the supposed cause of sudden death was intra-abdominal bleeding or panperitonitis due to rupture of the small intestine.

CASE 2

An 82-year-old woman underwent a right nephrectomy for RCC at the age of 69 and adjuvant immunotherapy was continued for 5 years consisting of interferon-α and 5-fluorouracil. She had been doing well without clinical symptoms, but in March 1992, she visited another hospital with a complaint of melena. Systemic examination revealed a large recurrent tumor at the right renal fossa invading the hepatic flexure of the colon with multiple metastases of the pancreas. Until January 1999, arterial embolizations of the right colic artery and other feeders were repeated six times to control intestinal bleeding (Fig. 4). Despite this, continuous bleeding required increasing blood transfusions and she was referred to our hospital on January 21. On admission, her general status was...
good. Dynamic computed tomography showed a large mass arising from the right renal bed invading the psoas muscle and the ascending colon (Fig. 5). An operation was performed on February 8.

Peritoneal dissemination or liver metastasis was not seen, and the tumor was palpable as a large mass located at the right renal fossa, fixed to the retroperitoneum and invading the right psoas muscle and the hepatic flexure of the colon. Resection of the tumor and a right hemicolectomy were performed.

Macroscopically, the tumor was 7.0 × 6.0 × 3.5 cm in size, invading the ascending colon with several ulcerations (Fig. 6A). The histopathology was consistent with a metastatic clear cell carcinoma of renal origin (Fig. 6B), invading the submucosal layer of the colon and partially developing ulcerations. The retroperitoneal surgical margin was macroscopically negative, but positive microscopically. The postoperative course was uneventful and she remains in a good condition. She was followed as an outpatient at her local hospital.

**IMMUNOHISTOCHEMICAL FINDINGS FOR KI-67 ANTIGEN**

Because Ki-67 antigen labeling has been reported to be a significant predictor of outcome in RCCs (4,5), we performed immunohistochemical evaluation for Ki-67 labeling index (Ki-67 L.I.) in our cases with rabbit anti-human Ki-67 antigen (dilution 1:50, Dako, Denmark) (Fig. 7). In case 1, immunostaining could be performed in the tumor tissues obtained at the time of his first (primary renal tumor), third (metastatic lung tumor) and last (locally recurrent tumor) operations: Ki-67 L.I. was 5.6, 10.4 and 67.9, respectively. In case 2, we could only perform in locally recurrent tumor and its Ki-67 L.I. was 20.4.

**DISCUSSION**

RCCs are known to have a tendency to develop hematogenous metastases to the lung, brain, liver, bone and occasionally the pancreas (6,7). On the other hand, local recurrence within the renal fossa, which can result from incomplete resection of the primary tumor, persistence of tumors in the regional lymph nodes or occult metastasis to the ipsilateral adrenal gland, have been reported with poor prognoses (6). The rate of local recurrence of RCC was reported to be 2.7–17.0% (3,6,8) after
nephrectomy for RCC. The interval to local recurrence was 2–84 months (average 31 months) (1) and 5–71 months (median 16.5 months) (2). In the present study, the diagnoses of local recurrence were made 5 and 13 years after the primary nephrectomies. Case 1 developed other distant metastases before the fossa recurrence; on the other hand, case 2 had been well without any symptoms for 13 years, implicating the possibly slow-growing biological character of the tumor. The patients without tumor recurrence at 5 years after the first diagnosis of RCC had a recurrence rate of 21% during the following 5 years (9). Therefore, long and careful follow-up is indicated for patients who have undergone nephrectomy for RCC. Periodic postoperative evaluation, including abdominal ultrasonography, computed tomography or magnetic resonance imaging, is recommended for earlier diagnosis of local recurrence (3,10).

Tumor stage at diagnosis and histological grade have been considered as the most important prognostic predictors in patients with RCC (11,12). However, subsets of patients within a specified stage and grade may have considerable differences in survival time. Histological grading is assessed subjectively and lacking in reproducibility (13). In our cases, case 1 was stage IV and case 2 was stage II at the time of diagnosis, the 5-year cancer specific survival rates of which are reported as 3.9–20% (11,14) and 76.1–88% (11,14,15), respectively. Recent studies have discussed whether cell proliferation markers, such as Ki-67 L.I. (4,5,16), proliferating cell nuclear antigen (PCNA) (4,5,17) and silver-stained nucleolar organizer regions (AgNOR) (4,5) could be a prognostic parameter in RCC and survival analysis showed that the elevation of Ki-67 L.I. was a significant predictor of poor prognosis (4,5,16,18). We then performed immunohistochemical evaluation for Ki-67 L.I. in the recurrent tumor of case 2 was 20.4, it seemed lower in the primary tumor. However, we could not determine what is different in the clinical course between general course (poor prognosis and rapid recurrence) and unusual course (good prognosis or late recurrence) of RCC, according to these two experiences. Immunotherapy and chemotherapy were administered initially, but they seemed to have little effect. Because good PS has been reported as the most favorable prognostic factor of stage IV RCC (15,19), we consider that a sufficiently good general condition to tolerate the repeated operations was the most important reason why case 1 survived for 5 years and 9 months after initial treatment.

Although immunotherapy, chemotherapy, radiotherapy and surgical resection have been performed as management for recurrence of RCCs (8,20,21), only aggressive surgery provided favorable results. Several reports justify excision of metastases of renal cell carcinoma with reasonable 5-year survival rates (7,22,23) in selected patients, but without evidence by prospective randomized trial. Esrig et al. (1) performed surgical resection on 11 patients with local recurrence of RCC and reported four cases with a long disease-free survival time, recommending aggressive surgical management. Tanguay et al. (2) retrospectively analyzed 16 surgically resected locally recurrent RCCs and reported that incomplete resection or positive surgical margins are associated with a high risk of local or distant failure and combined treatment with immunotherapy and surgery may offer greater benefit than surgery alone.

Gastrointestinal tract metastases are a rare cause of massive gastrointestinal bleeding. The small intestine is involved by metastatic tumors in 2% of autopsies and renal cell carcinoma metastases account for 7.1% of these lesions (24). Graham (25) reported that only 4% of renal cell carcinomas metastasized to the small intestine. Hemostasis of gastrointestinal bleeding occurring due to metastasis or invasion of malignant tumor is hard to manage endoscopically. Arterial embolization of tumor-supplying arteries was reported to control gastrointestinal bleeding effectively (26–28), but there are no long-term follow-up data. In our case 1, the recurrent tumor massively invaded the fourth portion of the duodenum, around which the tumor could develop multiple feeders from any direction and failed in spite of the embolization of the lumbar artery, which was one of the supplying arteries. In case 2, intestinal bleeding was well controlled by repeated arterial embolization for 10 months after diagnosis of the fossa recurrence. However, embolotherapy is only a palliative, while the tumor develops other collateral vessels and has potential for re-bleeding.

Patients with RCCs often remain in good condition, in spite of massive tumor growth or multiple metastases, but when gastrointestinal bleeding occurs due to a recurrent tumor, the life quality of the patient is severely distressed. In those cases, if the intestinal bleeding can be controlled, it is possible to improve their general condition and a surgical approach should be considered. In case 1, poor condition on his last admission brought about an unfortunate outcome during postoperative hospitalization. Although in both cases distant metastases were
determined in other organs, they caused no clinical symptoms. Therefore, we believed that home care was possible after resection of the tumor. The second patient is now in good condition 9 months after her last operation and is being followed up as an outpatient at her local hospital, although multiple pancreas metastases remain.

In conclusion, arterial embolization should be selected as the first management for massive gastrointestinal bleeding owing to recurrent RCCs, but in some cases, where it may not provide or maintain an effective result, surgical resection should be performed before losing the chance. Additionally, cooperation between the urologist, the interventional radiologist and the general surgeon provides the greatest chance of achieving a favorable quality of survival.

References