Unusual Upper Gastrointestinal Bleeding due to Late Metastasis from Renal Cell Carcinoma: A Case Report

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A case of recurrent massive upper gastrointestinal bleeding originating from metastatic renal cell carcinoma is reported. A 63-year-old woman underwent right nephrectomy 9 years previously and experienced no recurrence during follow-up. A gradually enlarging ulcerative tumor over the bulb of the duodenum and four subsequent episodes of massive bleeding from this tumor occurred between June 2001 and March 2002. The patient underwent surgery in April 2002 for intractable bleeding from the tumor. Renal cell carcinoma metastasis to the duodenum was confirmed from the surgical specimen. Upper gastrointestinal bleeding due to malignancy is very rare and the duodenum is the least frequently involved site. Furthermore, a solitary late renal cell carcinoma metastasis 9 years after a nephrectomy is extremely uncommon. This case suggests that life-long follow-up of renal cell carcinoma patients is necessary, owing to unpredictable behavior and the possibility of long disease-free intervals. In nephrectomized patients suffering from gastrointestinal bleeding, complete evaluation, especially endoscopic examination, is indicated. The possibility of late recurrent renal cell carcinoma metastasis to the gastrointestinal tract should be kept in mind, although it is rare. If the patient is fit for surgery, metastatectomy is the first choice of treatment.

Key Words: duodenal metastasis, renal cell carcinoma, upper gastrointestinal bleeding
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Common metastatic sites for renal cell carcinoma (RCC) are the lungs, bone, liver, adrenal glands, and brain. Uncommon sites include the thyroid gland, gallbladder, pancreas, and orbit [1]. The gastrointestinal tract is an unusual location for solitary late recurrence of RCC [2,3]. Among solitary late metastases, duodenal metastases from RCC are uncommon and have been reported only in sporadic cases [4–7]. In addition, massive gastrointestinal tract bleeding originating from metastases is also encountered rarely, accounting for only 0.06% of all cases of metastatic tumors in a large pan-endoscopic series [8].

Late solitary recurrence of RCC presenting with recurrent upper gastrointestinal tract bleeding is therefore very rare [9]. Although patients surviving disease-free for 8 years following nephrectomy can be considered cured [9], there have been reports of late recurrence developing 10 to 30 years after nephrectomy [2]. In this paper, we report a 63-year-old woman who underwent right nephrectomy for RCC and presented with late duodenal metastasis manifesting as recurrent massive upper gastrointestinal bleeding 9 years later.

Case Presentation

A 54-year-old woman underwent right radical nephrectomy for RCC at our hospital in 1992. The classification was clear-

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cell cancer, T2N0M0, stage II. No involved lymph nodes or distant metastases were detected at that time and adjuvant therapy was not administered after the operation. The patient remained in good health during 9 years of follow-up.

In June 2001, at the age of 63, she suffered from an episode of massive melena and marked anemia. A duodenal ulcer over the bulbar area was initially detected by endoscopy, and blood transfusion and anti-peptic ulcer therapy was administered. Unfortunately, the patient suffered from several episodes of massive upper gastrointestinal bleeding and severe anemia. A gradually growing protruding ulcerative mass over the posterior wall of the duodenal bulb was found at repeat endoscopy (Figure 1). Endoscopic biopsy specimens taken between August 2001 and March 2002 revealed an inflammatory polyp and necrotizing inflammation with some dysplastic cells only. No intestinal obstruction, perforation, or intussusception had been induced by the tumor. Because of recurrent massive bleeding and a gradually enlarging duodenal tumor, the patient was referred to the surgical department of our hospital in March 2002. On admission, no palpable abdominal mass or regional lymphadenopathy was detected. The patient's hemoglobin was 5.9 g/dL and her hematocrit was 18.6%, as revealed by a complete blood count. Serum levels of the tumor markers CA19-9 and carcinoembryonic antigen (CEA) were 18.9 U/mL and 0.82 ng/mL, respectively.

Abdominal magnetic resonance imaging (MRI) showed a lobulated tumor (2.6 × 2.8 cm) in the second portion of the duodenum. There were no enlarged lymph nodes and no intra-abdominal metastases were found in the liver, pancreas, opposite kidney, or adrenal gland. To treat the intractable recurrent duodenal bleeding caused by this tumor, and due to the suspicion of malignancy, the patient underwent laparotomy in April 2002. A grayish white tumor with an ulcerative surface and measuring 1.4 × 1.5 × 3 cm was found 1 cm distal to the pyloroduodenal junction.

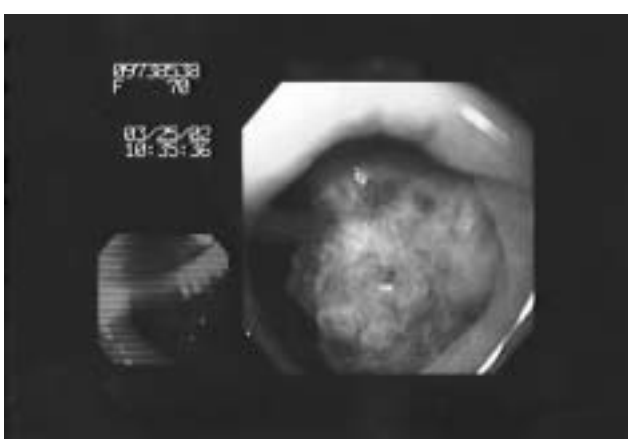

Figure 1. *The ulcer became a protruding mass with partial obstruction of the duodenal bulb, as revealed by repeated endoscopy in March 2002.*

Malignancy was confirmed by pathologic examination of frozen sections of ulcer biopsy. Radical subtotal gastrectomy was subsequently performed because Vater's ampulla and the pancreas were not affected. The cancer cells had infiltrated and entirely replaced the muscle layer. From comparison with specimens obtained from her right nephrectomy 9 years earlier, it was concluded that this tumor was RCC metastasis to the duodenum (Figure 2). Six regional lymph nodes showed chronic lymphadenitis but there was no apparent metastasis or invasion of other intra-abdominal organs.

The postoperative course was uneventful, except for mild episodes of paralytic ileus, and the patient was discharged 27 days after surgery. There was no evidence of recurrence at 10 months.

Discussion

Duodenal metastasis from RCC is very rare [4]. Only 7.1% of gastrointestinal metastases are from RCC, and only 4% of RCC metastasizes to the small intestine [10]. In postmortem and endoscopic series, gastrointestinal tract metastases occur in 0.06% to 4% of patients with malignant disease, and gastrointestinal bleeding secondary to metastases is also infrequent [8,10–12]. The most common gastrointestinal tract metastases originate from breast cancer (8.2–33%), melanoma (10–26%), lung cancer (14%), and squamous cell carcinoma of the esophagus [8]. The small intestine is involved in just 2% of all gastrointestinal tract metastases [10]. Furthermore, the incidence of apparently solitary metastases is only 1% to 3% among all metastases, with the duodenum being the least frequent site [6]. According to recent literature, there have been only 17 cases of duodenal metastases due to RCC reported as of 2001 [4]. However, in most of these cases, the primary and metastatic tumors were found at the same time. Therefore, late metastasis of RCC presenting as a solitary duodenal tumor with recurrent upper gastrointestinal bleeding [2], as in this case, is very unusual.

The natural history and behavior of RCC remains unpredictable and poorly understood, in spite of intensive study. RCC may remain stable for long periods without growing and metastasizing, and metastases may develop many years after removal of the primary tumors [13–15]. This may be due to the long tumor doubling time, which

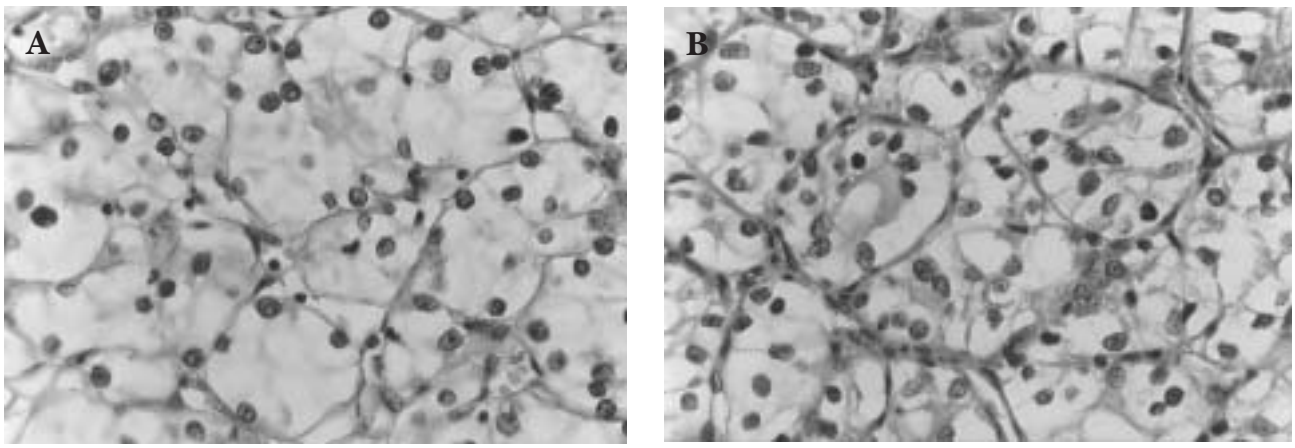

Figure 2. *(A) Previous nephrectomy specimen, characterized by sheets of clear cells with distinct borders interspersed with numerous thin-walled blood vessels (hematoxylin & eosin, original magnification, × 400). (B) The duodenum is infiltrated by tumor cells with clear cytoplasm and distinct cell borders. These tumor cells have the same characteristics as the primary renal cell carcinoma in (A) (hematoxylin & eosin, original magnification, × 400).*

accounts for the delayed appearance of metastases and also permits longer survival of the host [16]. Although patients who have disease-free survival for 8 years following nephrectomy can be considered cured [9], as was the present case, late recurrence is seen in 5% to 11% of patients who survive 10 years from the date of nephrectomy [14,15].

The possible mechanisms of duodenal involvement of RCC may be via direct invasion by the tumor or through lymphatic, transcelomic, or hematogenous spread [6,17]. Microscopic examination of the resected specimen revealed that the cancer cells had invaded the serosa and muscular layer of the duodenum, although its mucosa was not remarkable. Six regional lymph nodes revealed chronic lymphadenitis only. In the presented case, metastasis was via hematogenous spread or direct invasion.

The major complications of duodenal metastases from RCC are obstruction, intussusception, and bleeding [4–6, 12,17]. Metastatectomy can improve survival in patients with a solitary metastatic lesion and should be performed if patients are fit for surgery [2,3,6,13]. Metastatectomy can result in a 5-year survival rate of 31% to 35%, which compares favorably with the known 5-year survival of 13% to 17% in nephrectomized patients with metastatic disease [6,18]. Maldazys and deKernion concluded that a longer disease-free interval was associated with longer average survival, particularly when the interval exceeded 24 months [16]. There is no role for chemotherapy or radiotherapy in metastatic RCC [1,7], but the immunotherapeutic approach with interleukin-2 has achieved preliminary durable partial or even complete remission of advanced RCC [1]. However, this requires further evaluation and longer follow-up. Clear-cell RCC is the most common type, accounting for about 70% of RCC, and most studies have pointed out that there is a slightly better prognosis with clear-cell RCC than with granular or mixed RCC. Sarcomatoid RCC has the worst survival rate [19].

Nevertheless, in moribund patients with multiple retroperitoneal nodes and duodenal infiltration by multiple secondaries, curative resection may be impossible and proximal diversion and palliative surgery, which is not harmful for critically ill patients, could offer the only effective treatment [7]. On the other hand, metastatic RCC is a hypervascular tumor [4,17]. In patients suffering from massive and active gastrointestinal bleeding owing to duodenal metastases from RCC, emergency arteriography and embolization of the gastroduodenal artery is an alternative life-saving treatment [17]. Lynch-Nyhan et al reported successful embolization via the gastroduodenal artery in two cases of massive gastrointestinal bleeding due to duodenal metastases of RCC [17].

Endoscopy has long been a standard diagnostic tool for upper gastrointestinal bleeding. It is also important in evaluating metastatic lesions and obtaining biopsies, especially when radiographic findings in the gastrointestinal tract are normal [8,20]. However, in hematogenous metastasis to the gastrointestinal tract, the tumor cells fail to traverse the capillary network and implant themselves in the submucosa [8,21]. Owing to the submucosal growth, endoscopic biopsies are often inadequate [21]. It is also difficult to diagnose primary or metastatic RCC in small biopsies because of the

wide variety of histologic appearances [22], which may explain why there was no histologic confirmation and clinical diagnosis until surgical exploration in the present case. The natural history of duodenal ulcer is to heal, and there is no association between carcinoma and duodenal ulcer [23,24]. It is difficult to differentiate malignant and benign ulcers at initial endoscopy [24]. However, the possibility of malignancy of the duodenal ulcer should be considered if the ulcer does not heal after 8 weeks of medical treatment or if there are polypoid masses or submucosal tumor masses with elevation and ulceration at the apex or multiple nodules of varying sizes with tip ulceration on repeated endoscopic examination [23]. An immunomarker specific for RCC is not currently available [22] and there is no universal agreement on the frequency or type of studies required in the follow-up of patients with RCC [25].

In summary, life-long follow-up is indicated in patients with RCC. In nephrectomized patients suffering from gastrointestinal bleeding, complete endoscopic evaluation is necessary. Our case emphasizes the necessity of repeated endoscopic examination and histologic evaluation in suspected cancer patients. The possibility of upper gastrointestinal bleeding due to late recurrence of RCC should be kept in mind, even though it is rare. If patients are fit for surgery, there should be no hesitation about performing surgical exploration and metastatectomy.

References

1. Figlin R. Renal cell carcinoma: management of advanced disease. *J Urol* 1999;161:381–7.
2. Freedman AI, Tomaszewski JE, Van Arsdalen KN. Solitary late recurrence of renal cell carcinoma presenting as duodenal ulcer. *Urology* 1992;39:461–3.
3. Takatera H, Maeda O, Oka T, et al. Solitary late recurrence of renal cell carcinoma. *J Urol* 1986;136:799–800.
4. Hashimoto M, Miura Y, Matsuda M, Watanabe G. Concomitant duodenal and pancreatic metastases from renal cell carcinoma: report of a case. *Surg Today* 2001;31:180–3.
5. Haynes IG, Wolverson RL, O'Brien JM. Small bowel intussusception due to metastatic renal carcinoma. *Br J Urol* 1986; 58:460.
6. Toh SK, Hale JE. Late presentation of a solitary metastasis of renal cell carcinoma as an obstructive duodenal mass. *Postgrad Med J* 1996;72:178–9.
7. Nabi G, Gandhi G, Dogra PN. Diagnosis and management of duodenal obstruction due to renal cell carcinoma. *Trop Gastroenterol* 2001;22:47–9.
8. Hsu CC, Chen JJ, Changchien CS. Endoscopic features of metastatic tumors in the upper gastrointestinal tract. *Endoscopy* 1996;28:249–53.
9. Hansen JB, Thybo E. Long-term survival after nephrectomy for adenocarcinoma renis. *Scand J Urol Nephrol* 1972;6: 47–50.
10. Willis RA. Secondary tumors of the intestine. In: Willis RA. *The Spread of Tumors in the Human Body*, 3rd edition. London: Butterworth & Co, 1973:209–13.
11. Telerman A, Gerard B, Van den Heule B, Bleiberg H.Gastrointestinal metastases from extra-abdominal tumors. *Endoscopy* 1985;17:99–101.
12. Short TP, Thomas E, Joshi PN, et al. Occult gastrointestinal bleeding in renal cell carcinoma: value of endoscopic evaluation. *Am J Gastroenterol* 1993;88:300–2.
13. deKernion JB, Ramming KP, Smith RB. The natural history of metastatic renal cell carcinoma: a computer analysis. *J Urol* 1978;120:148–52.
14. McNichols DW, Segura JW, DeWeerd JH. Renal cell carcinoma: long-term survival and late recurrence. *J Urol* 1981;126:17–23.
15. Nakano E, Fujioka H, Matsuda M, et al. Late recurrence of renal cell carcinoma after nephrectomy. *Eur Urol* 1984;10:347–9.
16. Maldazys JD, deKernion JB. Prognostic factors in metastatic renal carcinoma. *J Urol* 1986;136:376–9.
17. Lynch-Nyhan A, Fishman EK, Kadir S. Diagnosis and management of massive gastrointestinal bleeding owing to duodenal metastasis from renal cell carcinoma. *J Urol* 1987; 138:611–3.
18. Tolia BM, Whitmore WF Jr. Solitary metastasis from renal cell carcinoma. *J Urol* 1975;114:836–8.
19. Tomera KM, Farrow GM, Liber MM. Sarcomatoid renal carcinoma. *J Urol* 1983;130:657–9.
20. Morini S, Bassi O, Colavolpe V. Malignant melanoma metastatic to the stomach: endoscopic diagnosis and findings. *Endoscopy* 1980;12:86–9.
21. Holderman WH, Jacques JM, Blackstone MO, Brasitus TA. Prostate cancer metastatic to the stomach. Clinical aspects and endoscopic diagnosis. *J Clin Gastroenterol* 1992;14:251–4.
22. McGregor DK, Khurana KK, Cao C, et al. Diagnostic primary and metastatic renal cell carcinoma: the use of the monoclonal antibody 'Renal Cell Carcinoma Marker'. *Am J Surg Pathol* 2001;25:1485–92.
23. Konar A, Das AS, De PK, et al. Natural history of severe duodenal ulcer disease. *Indian J Gastroenterol* 1998;17:48–50.
24. Rotterdam H. Carcinoma of the duodenum. In: Rotterdam H, Enterline HT, eds. *Pathology of the Stomach and Duodenum*, 1st edition. New York: Springer, 1989;205–12.
25. Dreicer R, Williams RD. Renal parenchymal neoplasms. In: Tanagho EA, McAninch JW, eds. *Smith's General Urology*, 15th edition. New York: McGraw-Hill, 2000;378–98.

腎細胞癌十二指腸轉移併出血一病例報告

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惡性腫瘤轉移至消化道的病例，在臨床上並不常見，機率僅約 0.06–4%，因此轉移而導致消化道出血者又更為罕見，其中又以十二指腸受侵犯的機率為最低。本文報告一相當罕見的病例，病患在住院九年前因右側腎臟腎細胞而接受根治性右側腎臟切除術，而在九年後，因大量上消化道出血而住院，經內視鏡檢查發現有十二指腸腫瘤併出血，因此接受次全胃切除術；經病理切片證實為九年前之腎細胞癌的晚期復發。由於腎細胞癌在切除後的變化較難預測且可能在較長的時間後才會復發。因此，對腎細胞癌術後之患者必須長時間加以追蹤。由本病例可以得知即使患者在腎臟切除後許久才發生消化道出血，腎細胞癌併消化道轉移的可能性亦必須加以考慮及詳加檢查。若患者狀況允許，則手術切除轉移處為首選之治療方式。

關鍵詞：腎細胞癌；十二指腸轉移；消化道出血

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