

Diagnostic contribution of C-reactive protein kinetics for gastric metastasis from renal cell carcinoma

Hiroshi Fukushima · Manabu Tatokoro · Kazutaka Saito · Yasuhisa Fujii ·
Mizuaki Sakura · Noboru Numao · Fumitaka Koga · Hitoshi Masuda ·
Hiroyuki Yamada · Kazunori Kihara

Received: 24 September 2011 / Accepted: 11 January 2012 / Published online: 10 March 2012
© The Japan Society of Clinical Oncology 2012

Abstract C-reactive protein (CRP) has been reported as a useful biomarker for renal cell carcinoma (RCC). Here, we report a case in which CRP kinetics of a continuous increase in CRP levels led to the detection of RCC metastasis to the stomach, a rare metastatic site. A 58-year-old man diagnosed with metastatic RCC underwent cytoreductive nephrectomy. Four months after the surgery, his CRP level started to increase continuously. Thus, we suspected disease progression. Extensive studies, including thoracoabdominal computed tomography and bone scan, however, detected neither local recurrences nor metastatic lesions. A further increase in CRP levels and gradual progression of anemia prompted us to investigate the digestive tract. Gastric endoscopy finally revealed gastric metastasis. After partial gastrectomy, his CRP level immediately decreased to a normal level. The patient is currently alive with no evidence of disease progression and his CRP level remains within the normal range, 44 months after his metastatic RCC diagnosis. The continuous increase in CRP levels reflected the development of gastric metastasis. The decrease in CRP levels after partial gastrectomy was indicative of a good response to treatment. This case demonstrates that CRP kinetics may be helpful in predicting disease progression as well as response to therapeutic intervention.

Keywords C-reactive protein · Renal cell carcinoma · Gastric metastasis · Biomarker

Introduction

The identification and development of biomarkers provide a means of predicting disease progression as well as survival in patients with cancer [1]. We previously reported that C-reactive protein (CRP) may be a useful biomarker in patients with renal cell carcinoma (RCC) [2]. Furthermore, CRP kinetics, which involves the dynamic change of CRP levels, has been demonstrated to have the potential to assess the efficacy of therapeutic intervention and to predict survival [2]. Here, we report a case that shows the practical applicability of CRP kinetics. A continuous increase in CRP levels gave us an opportunity to detect RCC metastasis to the stomach, a rare metastatic site.

Case report

A 58-year-old diabetic man was referred to our hospital, complaining of pain in his upper left arm. X-ray imaging revealed a fracture with considerable bone destruction in the left humerus and a bone scan revealed increased radionuclide uptake in the same area. Pathological findings from the percutaneous biopsy specimen were clear cell carcinoma. Abdominal computed tomography (CT) revealed a well-enhanced mass with a size of 7.1 cm on the upper pole of the right kidney, which led to the diagnosis of RCC with left humerus metastasis (T2aN0M1) according to the 2009 TNM classification. The patient's baseline CRP level was 2 mg/l. Radiotherapy (50 Gy at 2 Gy/fraction) combined with zoledronic acid was used to treat the

H. Fukushima · M. Tatokoro · K. Saito (✉) · Y. Fujii ·
M. Sakura · N. Numao · F. Koga · H. Masuda · K. Kihara
Department of Urology, Tokyo Medical and Dental University,
1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
e-mail: kz-saito.uro@tmd.ac.jp

H. Yamada
Department of Esophagogastric Surgery, Tokyo Medical and
Dental University, Tokyo, Japan

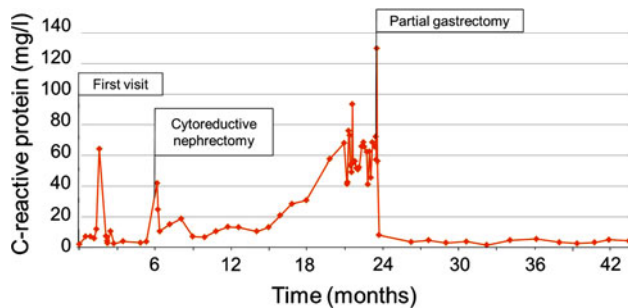


Fig. 1 CRP kinetics in the current case. Four months after cytoreductive nephrectomy, the CRP level started increasing continuously from 6.7 to 76 mg/l at 15 months after the surgery. Shortly thereafter, the CRP level further increased to 93 mg/l. The CRP level immediately decreased to 3.5 mg/l after partial gastrectomy. The CRP level has remained below 5 mg/l since then

humeral metastasis [3] and interferon- α -based cytokine therapy [4] was concurrently started in a presurgical setting. The osteolytic lesion in the left humerus exhibited calcification after a month of treatment, indicating partial response (PR) according to the World Health Organization criteria [5]. Six months after the initiation of systemic therapy, cytoreductive nephrectomy was performed. Pathological examination revealed clear cell carcinoma with a Fuhrman nuclear grade of 3. Cytokine therapy was resumed after the surgery.

Four months after the surgery, the patient's CRP level started increasing continuously (6.7–76 mg/l at 15 months after the surgery) (Fig. 1) and we suspected systemic progression of disease. Extensive studies, including thoracoabdominal CT and bone scan, however, detected neither local recurrences nor metastatic lesions. A further increase in CRP levels to 93 mg/l and gradual progression of asymptomatic anemia prompted us to investigate the digestive tract. A fecal occult blood test was positive. Thus, the patient underwent gastric endoscopy, which detected a pedunculated mass of 6 cm in the cardia of the stomach (Fig. 2a). The biopsy specimen was reported as clear cell carcinoma, which was compatible with RCC metastasis. There was no evidence of progression of the left humerus metastasis. Consequently, partial gastrectomy was performed. Pathological findings of the gastric tumor were clear cell carcinoma, like those of the original tumor (Fig. 2b). The CRP level immediately decreased to 3.5 mg/l after the surgery (Fig. 1). The patient has remained well with no evidence of disease progression and his CRP levels remain below 5 mg/l, 44 months after the diagnosis of metastatic RCC.

Discussion

RCC can metastasize to virtually any visceral organ of the body, including the stomach, although the incidence of

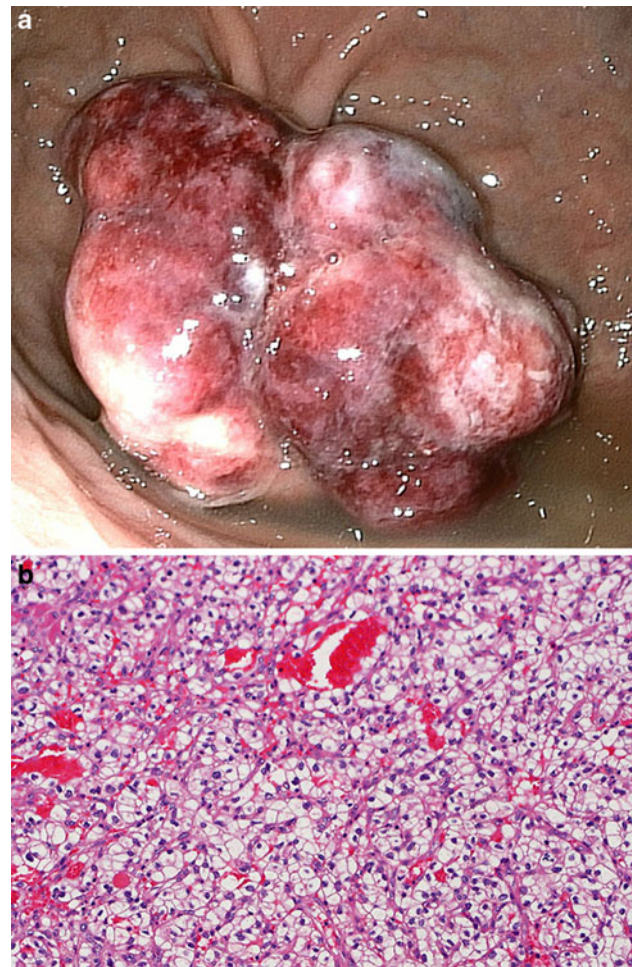


Fig. 2 a Endoscopic appearance of the gastric tumor. b Microscopic appearance of the gastric tumor (H&E, $\times 200$). The final pathology was consistent with clear cell carcinoma

such metastasis is relatively rare [6]. In an autopsy study, gastric metastasis was observed only in 7 of 113 cases with RCC. Also, the site of primary lesion was kidney only in 7 of 347 cases with metastatic gastric cancer [7].

CT is generally recommended as a routine radiological screening test for the follow-up of patients with RCC [8]. However, routine CT screening may fail to detect some rare visceral metastasis such as gastric metastasis [9]. This may cause delay in the diagnosis within the operable state. Indeed, for gastric metastasis, few cases were asymptomatic at the time of diagnosis [6]. In the current case, due to a continuous increase in CRP levels, a thorough investigation to find a new metastatic lesion was undertaken, resulting in the early diagnosis of gastric metastasis. Longitudinal monitoring of CRP levels may help identify this relatively rare metastatic lesion in the asymptomatic phase. Thus, CRP kinetics may be effective in detecting disease progression early in the follow-up of RCC patients.

Pretreatment CRP level has been proposed as a prognosticator in patients with RCC [2]. Furthermore, retrospective analyses revealed that CRP kinetics conveys additional prognostic information as a dynamic marker [2]. Metastatic RCC patients with CRP normalization induced by multimodal therapies have better prognoses than those without CRP normalization [10]. In the current case, CRP normalization was durably achieved after metastasectomy and thus, long-term survival can be expected. Indeed, the patient has remained healthy with no evidence of disease progression and the CRP level remains below 5 mg/l, 20 months after partial gastrectomy.

Thus far, CRP kinetics has never been prospectively studied in patients with RCC. As such, there has not been any supporting evidence demonstrating that CRP kinetics reflects disease progression. In our previous report, approximately half of the patients with metastatic RCC exhibited elevated CRP levels upon presentation of metastasis [10]. The current case suggested that CRP kinetics contributes to the detection of gastric metastasis. Taken together, these findings indicate that CRP kinetics may be useful in predicting disease progression and evaluating the efficacy of therapeutic intervention.

In the current case, partial gastrectomy was performed because there was no evidence of bone metastasis progression. Although it was reported that long-term survival following metastasectomy is only observed among patients who have had complete removal of all metastatic lesions [11], we believe that the current patient can be expected to gain therapeutic benefit from metastasectomy because the other metastatic lesion, a left humerus metastasis, had remained well controlled. Indeed, the CRP level decreased immediately after the surgery and has been durably maintained at a low level since [10].

In conclusion, the current case demonstrates the practical applicability of CRP as a clinically useful biomarker for patients with RCC. CRP kinetics, which involves the longitudinal monitoring of CRP levels, may be helpful to survey disease activity such as the development of new

metastatic lesions as well as the response to therapeutic intervention. A continuous increase in CRP levels in RCC patients is suggestive of possible recurrent disease.

Acknowledgments No financial support was required.

Conflict of interest No author has any conflict of interest.

References

1. Crispin PL, Boorjian SA, Christine ML et al (2008) Predicting disease progression after nephrectomy for localized renal cell carcinoma: the utility of prognostic models and molecular biomarkers. *Cancer* 113:450–460
2. Saito K, Kihara K (2010) Role of C-reactive protein as a biomarker for renal cell carcinoma. *Expert Rev Anticancer Ther* 10:1979–1989
3. Kijima T, Fujii Y, Suyama T et al (2008) Radiotherapy to bone metastases from renal cell carcinoma with or without zoledronate. *BJU Int* 103:620–624
4. Tatokoro M, Fujii Y, Kawakami S et al (2011) Phase-II trial of combination treatment of interferon-alpha, cimetidine, cyclooxygenase-2 inhibitor and renin-angiotensin-system inhibitor (I-CCA therapy) for advanced renal cell carcinoma. *Cancer Sci* 102:137–143
5. World Health Organization (1979) WHO handbook for reporting results of cancer treatment. WHO, Geneva
6. Pollheimer MJ, Hinterleitner TA, Pollheimer VS et al (2008) Renal cell carcinoma metastatic to the stomach: single-centre experience and literature review. *BJU Int* 102:315–319
7. Oda I, Kondo H, Yamao T et al (2001) Metastatic tumors to the stomach: analysis of 54 patients diagnosed at endoscopy and 347 autopsy cases. *Endoscopy* 33:507–510
8. Skolarikos A, Alivizatos G, Laguna P et al (2007) A review on follow-up strategies for renal cell carcinoma after nephrectomy. *Eur Urol* 51:1490–1501
9. Small JH, Aitchison F, Carroll NR (1996) Computed tomography of the gastro-duodenal region. *Eur J Radiol* 22:95–103
10. Saito K, Tatokoro M, Fujii Y et al (2009) Impact of C-reactive protein kinetics on survival of patients with metastatic renal cell carcinoma. *Eur Urol* 55:1145–1153
11. Pavlovich C, Russo P, Burt ME et al (1998) Resection of metastatic renal cell carcinoma. *J Clin Oncol* 16:2261–2266