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SHORT REPORT

Colonic pneumatosis and intestinal perforations with sunitinib treatment for renal cell carcinoma

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Case histories

Patient 1 A woman with renal cell carcinoma (RCC) presented with sudden right sided flank pain and anuria. Two years earlier she was diagnosed with RCC clear cell type and had a left-sided nephrectomy performed at that time. Her initial staging evaluation revealed multiple pulmonary nodules consistent with metastatic disease and she was started on sorafenib therapy. She remained on this therapy for 9 months, but was then found to have progressive disease and high-dose interleukin-2 (IL2) was initiated. The patient developed bilateral pulmonary edema during her initial course of IL2 which was believed to be secondary to IL2-induced capillary leak and required endotracheal intubation. Accordingly, IL2 was abandoned without completing a full course and treatment with sunitinib (50 mg daily for 4 weeks followed by a 2 week break) was pursued.

Thirteen months after starting sunitinib, the patient described approximately 12 h of acute right-sided flank pain with no urine output over that time period. Her past history included a tiny calculus in the right kidney. She denied vomiting, diarrhea or recent change in her bowel movements. Laboratory analysis revealed a lactate of 3.5 mmol/l (normal range 0.5–2.2 mmol/l). A computed tomography (CT) exam of the abdomen and pelvis was ordered, showing colonic pneumatosis on the right and pneumoretroperitoneum (Fig. 1a–d). The patient proceeded to surgery, with placement of a ureteral stent and a right-sided hemi-colectomy. Cystoscopy and an intraoperative retrograde ureteropyelogram did not demonstrate an obstructive stone and the anuria was attributed to gastrointestinal perforation (GIP). Pathologic examination of the right colon showed extensive pneumatosis cystoides intestinalis (Fig. 1e) and focal areas of ulceration of the mucosa with transmural acute and chronic inflammation and giant cell reaction (Fig. 1f); microthrombi were observed in the vessels of the lamina propria. Three regional lymph nodes

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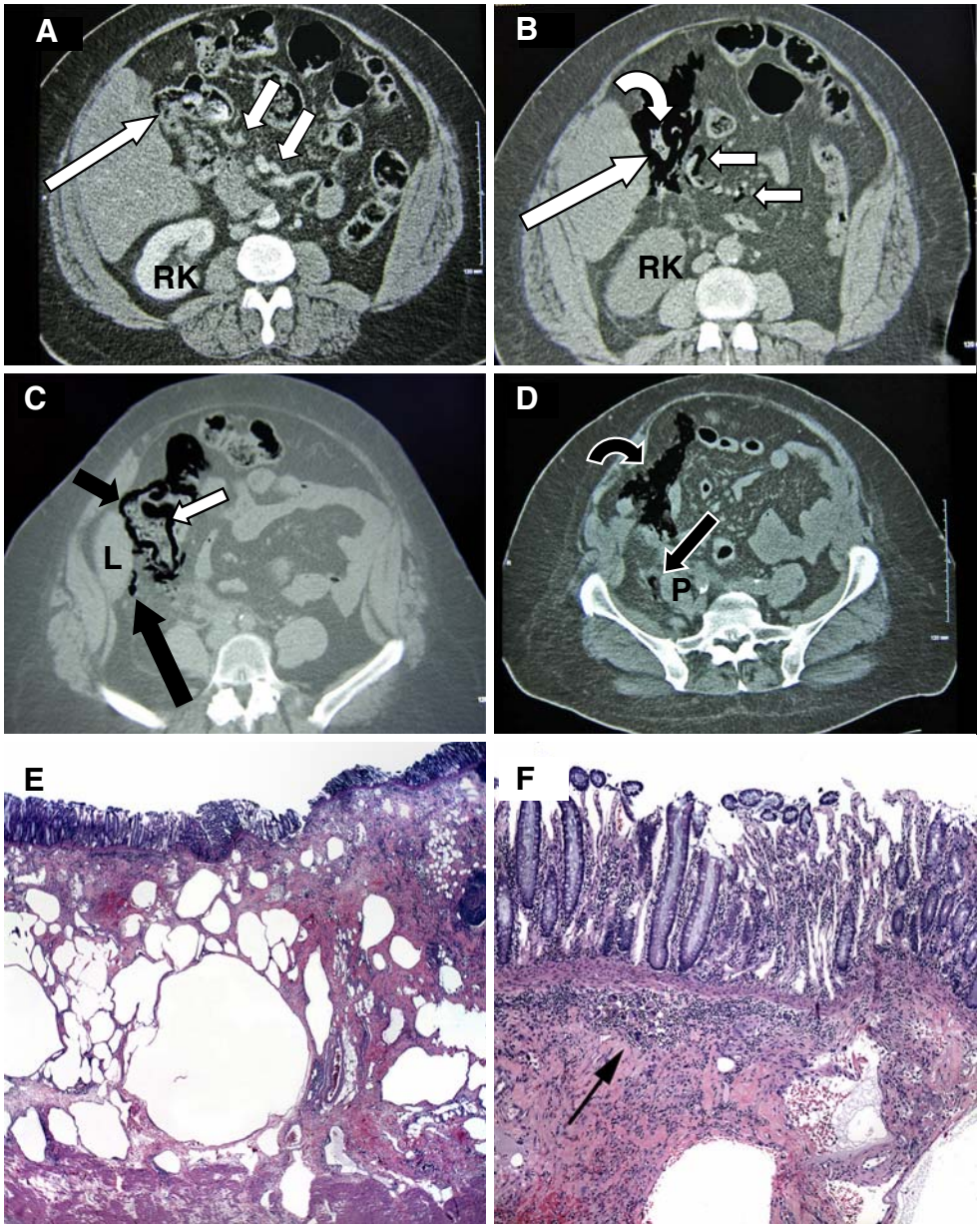

Fig. 1 (Patient 1) **a** CT scan, with oral and IV contrast, 1 month before presentation with pneumatosis. Axial image, shows normal collapsed hepatic flexure (*long arrow*) containing intraluminal feces admixed with gas and contrast. No pneumatosis is demonstrated and there is no gas tracking along the mesenteric vasculature (*short arrows*). Note right kidney (*RK*). **b** Noncontrast CT shows gas in the wall of the hepatic flexure (*long arrow*) surrounding intraluminal material (*curved arrow*). Gas also tracks along the superior mesenteric artery and vein branches (*short arrows*). Note right kidney (*RK*) and absence of the left kidney following nephrectomy. **c** At an axial level that includes the liver tip (*L*), high-contrast electronic windowing better demonstrates gas in the wall of the hepatic flexure (*short black arrow*) surrounding semisolid intraluminal feces (*white arrow*). Note gas (*long arrow*) dissecting along Gerota's fascia, indicating small volume pneumoretroperitoneum. **d** Axial CT shows gas in the ileocolic mesentery (*curved arrow*), and small volume pneumoretroperitoneum (*arrow*) along the right psoas (*P*) muscle. **e** Low power microscopic image (×2 objective) showing colonic submucosa and muscularis propria with extensive pneumatosis cystoides intestinalis. **f** Medium power microscopic image (×10 objective) showing colonic mucosa with focal areas of necrosis underlined by submucosa with acute and chronic inflammation and focal giant cell reaction (*arrow*)

were negative for malignancy and the surgical resection margins showed viable tissue. The gross and microscopic findings were consistent with ischemic colitis. The examined segment of terminal ileum and the appendix did not show evidence of ischemia. The finding of chronic inflammation and giant cell reaction in the colonic submucosa suggested that the ischemic process was not of sudden onset. The observed ischemic damage appears to have had a more insidious origin as compared with other cases of acute ischemia such as those produced by regional

vasculopathies (i.e. atherosclerosis) with or without arterial hypotension. The patient had no history of previous bowel surgery, gross disease involvement of the colon, vascular disease or atherosclerosis.

Patient 2 A woman with RCC presented for routine CT scan follow-up during sunitinib treatment. Three years earlier she had been diagnosed with clear cell RCC and treated with a right-sided nephrectomy. She was without evidence of disease until one year after nephrectomy, when she developed pulmonary metastases and was treated with high-dose IL2. This was given for two cycles, with no radiographic response and overall poor tolerability. Despite vasopressor administration and aggressive intravenous hydration, the patient experienced significant hypotension and confusion with the IL2 treatment. The patient was then treated with sunitinib, with a dose reduction from 50 mg to 37.5 mg daily for 4 weeks out of a 6 week cycle due to fatigue and somatitis. She enjoyed a near complete response but continued to experience significant adverse events (progressive fatigue, neutropenia, nausea, and hypothyroidism) and was subsequently given a drug holiday after 9 months of sunitinib therapy.

At the time of this presentation, she had been taking sunitinib at a dose of 37.5 mg for 5 months, after a 6 month break. In addition to the mild diarrhea typical of her previous cycles of sunitinib therapy, the patient additionally described intermittent "cramping" abdominal pain, of mild to moderate intensity, over the last 7 days of treatment. She denied black or bloody stools but described a significant decrease in her appetite. On exam, the vital signs were stable and her abdomen was soft, without guarding or rebound tenderness. Laboratory evaluation revealed a lactate elevation to 4.8 mmol/l. The CT documented pneumatosis of the right colon with perforation into the adjacent mesentery, but without frank pneumoperitoneum (Fig. 2). The sunitinib was held and the patient was admitted to the hospital and observed carefully for any clinical deterioration, without pursuing surgical intervention. A follow-up CT 3 weeks later demonstrated resolution of the colonic pneumatosis. The patient did not have a history of previous gastrointestinal surgery, significant vascular disease or radiographic evidence of gross large bowel involvement of the cancer.

Discussion

Sunitinib is an oral multi-kinase receptor inhibitor with Food and Drug Administration approval for the treatment of advanced RCC and gastrointestinal stromal tumors. When studied in the first-line setting, sunitinib significantly improved the progression free survival, from 5 to 11 months, when compared to interferon in RCC [1]. Sunitinib targets several kinases, including the vascular endothelial growth factor (VEGF) receptors, which are believed to be important to its efficacy in RCC. Bevacizumab, a monoclonal antibody, also targets the VEGF pathway by binding and neutralizing VEGF. The use of bevacizumab in colorectal cancer (CRC) has clearly been associated with GIP. A recent review of the literature noted a GIP incidence of 0–3.3% in CRC patients treated with bevacizumab and chemotherapy, with a prospective phase III trial reporting an incidence of 1.5% [2]. In a preliminary report of bevacizumab treatment in a large community-based study of 1968 CRC patients, the incidence of GIP was 1.7% with a median time of 2.1 months from the start of bevacizumab [3]. An increased risk of GIP was noted in those with an intact versus resected primary tumor, suggesting a role for colonic tumor necrosis in some cases of perforation. A study of bevacizumab in advanced ovarian cancer describes GIP in 5 of 44 patients (11%) with one patient death attributable to GIP [4]. All patients with GIP in this study had known colonic tumor involvement. GIP with bevacizumab has also been linked to non-abdominal cancers, although GIP appears to be much less common in this setting. There is one reported case in non-small cell lung cancer, but this was also associated with a tumor at the site of perforation [5]. Judging from this data, tumor involvement of the gastrointestinal tract appears related to many of

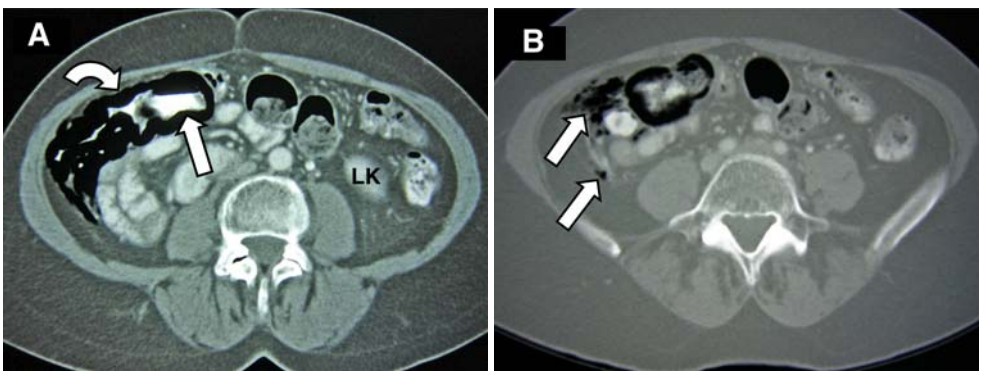

Fig. 2 (Patient 2). **a** Axial CT shows severe pneumatosis (*curved arrow*) in the wall of the mobile, transversely oriented cecum. Note oral contrast (*arrow*) in the bowel lumen. *LK* inferior pole of the left kidney. **b** High-contrast axial CT scan shows gas (*arrows*) in the ileocolic mesentery

the cases of GIP observed with bevacizumab. Notably, neither of our patients had evidence of metastatic disease to the colon, suggesting a different mechanism than intestinal tumor necrosis and regression as a cause of perforation in these cases.

Unlike bevacizumab, the incidence of GIP with sunitinib is not clearly defined. In the initial sunitinib phase I trial, one patient with a gastrointestinal stromal tumor (GIST) and peritoneal metastases died from peritonitis at the dose of 75 mg daily, consistent with GIP [6]. However, no cases of GIP were described in a prospective study of GIST in which 207 patients were treated with sunitinib [7]. In the pivotal study establishing sunitinib for the treatment of RCC, 375 patients received sunitinib with no reports of GIP [1]. Additionally, the preliminary report of the Sunitinib Expanded Access Program at the 2007 ASCO annual meeting did not specifically comment on GIP in 2341 treated RCC patients, although additional details may be found in the anticipated manuscript [8]. An overview of gastrointestinal perforation with anti-vascular agents is provided in Table 1 [9–14]. Both patients described here received high-dose IL2 prior to sunitinib, unlike the treatment naïve patients in the pivotal study, in which no GIP was described. A possible role for prior treatment with IL2 treatment in these cases of GIP associated with sunitinib cannot be dismissed.

We believe these to be the first reported cases of colonic pneumatosis and GIP in RCC patients treated with sunitinib. Pneumatosis intestinalis, the presence of gas in the intestinal sub-mucosa or sub-serosa, may be observed in many clinical settings including obstructive pulmonary disease, systemic sclerosis, ischemic bowel disease and in association with drug therapy, including glucocorticoids and cytosine arabinoside [15]. Based on the findings in the first case, the cause of colonic pneumatosis was likely bowel ischemia as noted on pathologic review. The findings of chronic inflammation and giant cell reaction in the colonic submucosa in this case suggest that the ischemic process was not of sudden onset. The observed microthrombi in the lamina propria represent a plausible inciting event leading to colonic pneumatosis and GIP. Of note, both of these patients had been treated with sunitinib for an extended period of time (13 and 14 months respectively). Anti-VEGF therapy is known to decrease intestinal capillary density and an associated decrease in mucosal regenerative capacity has been suggested as a factor in bevacizumab-associated GIP [16]. A recent case report describes pneumatosis intestinalis associated with bevacizumab in a patient with a pancreatic neuroendocrine tumor who was found to have a small amount of pneumoperitoneum and extensive bowel pneumatosis on CT imaging [16]. While oftentimes a benign radiographic finding, pneumatosis intestinalis was associat-

Table 1 Summary of gastrointestinal perforations with anti-vascular therapies

Cancer type	Therapy	Number of treated patients	Percentage GIP reported	Reference
Colorectal cancer	Bevacizumab with irinotecan, fluorouracil and leucovorin	393	1.5%	Hurwitz et al. [9]
Colorectal cancer	Bevacizumab plus "standard chemotherapy"	1968	1.7%	Sugrue et al. [3]
Colorectal cancer	Bevacizumab with oxaliplatin	694	0.6%	Saltz et al. [10]
Ovarian cancer	Bevacizumab and cyclophosphamide	70	5.7%	Garcia et al. [11]
Ovarian cancer	Bevacizumab	62	NR	Berger et al. [12]
Ovarian cancer	Bevacizumab	44	11.4%	Cannistra et al. [4]
Breast cancer	Bevacizumab and paclitaxel	365	0.5%	Miller et al. [13]
Non-small cell lung cancer	Bevacizumab, carboplatin and paclitaxel	427	NR	Sandler et al. [14]
Phase 1 (multiple)	Sunitinib	28	3.5% (one patient)[a]	Faivre et al. [6]
Gastrointestinal stromal tumor	Sunitinib	202	NR	Demetri et al. [7]
Renal cell carcinoma	Sunitinib	375	NR	Motzer et al. [1]

GIP Gastrointestinal perforation, *NR* None reported

[a] One patient with known peritoneal metastasis at the 75 mg dose developed "peritonitis" and included here as a likely GIP

ed with GIP in both of our cases, suggesting the need for careful clinical follow-up and consideration of drug therapy modification with this finding during sunitinib use in RCC. A high level of clinical suspicion may be required to quickly identify GIP in this context, especially since sunitinib treatment is commonly associated with diarrhea and other gastrointestinal symptoms [1].

In conclusion, we report two cases of GIP and colonic pneumatosis in RCC during sunitinib treatment. While GIP has been observed with other anti-VEGF therapies such as bevacizumab, similar cases have not been reported with sunitinib in RCC. Several features were observed in both cases which may aid in the clinical identification of this event including colonic pneumatosis with right sided colonic involvement, lactate elevation and previous high-dose IL2 exposure.

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