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Single Case

Pneumatosis Cystoides Intestinalis Secondary to Sunitinib Treatment for Gastrointestinal Stromal Tumor

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Keywords

Pneumatosis cystoides intestinalis · Sunitinib · Gastrointestinal stromal tumor · Liver metastasis

Abstract

A 67-year-old man with liver and retroperitoneal metastases from a gastrointestinal stromal tumor arising in the jejunum had been administered oral sunitinib for 2 months. He presented to our department with right-sided lower abdominal pain. His general condition was good, with no high-grade fever, and the other vital signs were also stable. Contrast-enhanced computed tomography was promptly performed, and pneumatosis cystoides intestinalis (PCI) was detected in a wide area around the ileocecal lesion. There were no signs of acute abdomen requiring emergency surgery due to conditions such as intestinal perforation, ischemia, or obstruction. Sunitinib was discontinued and the patient was placed on nil orally with intravenous infusion. PCI resolved promptly and the patient was discharged on the 21st day after admission. PCI is a rare side effect of sunitinib with only 8 cases reported previously, which can complicate with acute abdomen or gastrointestinal perforation, in some cases. Thus, the early identification of sunitinib as the cause of PCI is important. Although PCI is a rare adverse effect of sunitinib, clinicians must be aware of it to promptly provide the correct diagnosis and treatment.

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Background

Progress in research on the mechanisms of tumorigenesis has led to development of new drugs for malignant neoplasms. Molecular-targeting agents are a new category of drugs that have been widely adopted for clinical use. Because of the unique actions of molecular-targeting agents, clinicians treating cancer should be aware of unexpected adverse effects that may be caused by these drugs. Sunitinib malate (Sutent®; Pfizer, New York, NY, USA) is one of the molecular-targeting agents and is a tyrosine kinase inhibitor [1] used for the treatment of advanced gastrointestinal stromal tumor (GIST) and renal cell cancer. Pneumatosis cystoides intestinalis (PCI) is a rare adverse effect of sunitinib [2] and is characterized by the presence of gas in the submucosa or subserosa of the intestinal wall [3]. PCI also has other etiologies, including ischemia, inflammation, systemic disease, pulmonary disease, trauma/iatrogenic, other medications, and idiopathic [4]. Treatment of PCI is related to the underlying etiology and ranges from observation to surgical intervention.

We report a rare case of PCI caused by sunitinib therapy for GIST, which was successfully managed by conservative treatment without surgical intervention.

Case Presentation

A 67-year-old man was receiving treatment for recurrent GIST at our department. The patient had first undergone jejunal resection with peritoneal drainage for perforation of a jejunal tumor when he was 57 years old. The resected tumor was an irregular white mass lesion that measured 9.0 × 3.5 cm and showed perforation. Pathological examination revealed interlacing bundles of spindle-shaped tumor cells with round nuclei (Fig. 1a). On immunostaining, the tumor cells were positive for c-KIT (Fig. 1b) and DOG-1 (Fig. 1c) and were focally positive for CD34 (Fig. 1d) and S-100 protein, but αSMA was negative. The MIB-1 labeling index was low at 10%. Based on these findings, the tumor was diagnosed as GIST arising in the jejunum. After the first operation, he underwent laparotomy twice more for resection of recurrent GIST and was placed on oral imatinib. After 5 years of imatinib treatment, liver metastasis (Fig. 2a) and retroperitoneal metastasis (Fig. 2b) were detected by contrast-enhanced computed tomography (CT). At that time, there was no sign of PCI on the CT scans (Fig. 2c). Imatinib was discontinued and oral administration of sunitinib was started with a regimen of 50 mg daily for 4 weeks followed by 2 weeks off therapy. After 2 months of sunitinib administration, the patient presented to our department with pain in the lower right abdomen. His general condition was good, with no fever, and the other vital signs were also stable. The abdomen was soft and flat, although localized tenderness without rebound was detected in the lower right quadrant. The patient's medical history included hypertension and diabetes. Hematology tests were within the normal range (WBC was 4,990/μL, Hb was 13.9 × 10⁴/μL, and Plt was 13.9 × 10⁴/μL), but CRP was elevated to 5.18 mg/dL. There was no evidence of kidney or liver dysfunction. Contrast-enhanced CT was performed, showing that the metastasis in the liver was unchanged and the retroperitoneal tumor was diminishing. However, CT scans also revealed PCI in a broad area around the ileocecal region (Fig. 3a). There was no free gas and no ascites. Administration of sunitinib was discontinued, and the patient was admitted to our department for observation. A proton pump inhibitor and a calcium channel blocker were continued

and diabetic drugs (dipeptidyl peptidase-4 inhibitor, sulfonylurea, voglibose) were discontinued. He was placed on nil orally with intravenous infusion for 5 days. Diabetic drugs were restarted at the point of re-starting oral intake. The abdominal symptoms resolved, and PCI showed improvement when plain CT was performed on the 6th day after admission (Fig. 3b). There was no recurrence of abdominal symptoms, and plain CT on the 19th day after admission demonstrated complete resolution of PCI (Fig. 3c). Laboratory tests showed normalization of CRP. The patient was discharged on the 21st day after admission. Administration of sunitinib was not restarted. The patient subsequently underwent his 4th abdominal operation, which was partial hepatectomy and resection of the retroperitoneal tumor. No signs of PCI were detected during surgery, as expected from the preoperative examinations, including CT.

Discussion

PCI is a rare adverse effect of sunitinib that is characterized by multiple gas-filled cysts within the submucosa or subserosa of the intestinal wall [5]. The etiology of PCI can be classified into four categories [6]: (A) changes of the intestinal wall, such as inflammatory bowel disease and mesenteric ischemia; (B) bowel distention, such as gastric and or intestinal dilatation due to spontaneous, traumatic, and iatrogenic causes; (C) peritonitis caused by diverticulitis, abdominal wall gangrene, or pylephlebitis; and (D) miscellaneous etiologies, such as transplantation, pneumatosis intestinalis, corticosteroid therapy, and chronic pulmonary disease.

Sunitinib (Sutent®; Pfizer, New York, NY, USA) is a tyrosine kinase inhibitor that has been approved by the Food and Drug Administration for advanced GIST and renal cell cancer. It targets various receptors, including vascular endothelial growth factor (VEGF) receptors, platelet-derived growth factor (PDGF) receptors, and c-KIT [1]. In patients with refractory GIST treated by sunitinib, the median time to tumor progression improved to 27.3 weeks compared with 6 weeks for patients receiving placebo ($p < 0.0001$) [7]. Gastrointestinal adverse effects of sunitinib are not uncommon, with diarrhea being most frequent [7]. However, PCI is rarely reported as an adverse effect of sunitinib. Our search of the English and Japanese literature only identified 8 cases of PCI during sunitinib administration (Table 1) [2, 8–12]. The precise mechanism of PCI related to sunitinib therapy is unknown. Bevacizumab (another VEGF inhibitor) reduces the capillary density in the intestinal wall, leading to decreased mucosal regenerative capacity that may contribute to development of intestinal micro-perforations [13]. A report about PCI related to sunitinib by Flaig et al. [2] mentioned the pathological findings of the resected right colon, suggesting that ischemic colitis with chronic inflammation led to the occurrence of PCI.

PCI is usually diagnosed by CT, as in the present case. The other imaging examination that may be useful for diagnosis of PCI is a plain X-ray film of the abdomen. Treatment of PCI depends on its etiology and ranges from conservative management to surgery. Conservative management includes simple observation, hyperbaric oxygen therapy, parenteral nutrition, and administration of antibiotics. Surgery is needed when PCI is complicated by perforation, for the management of primary conditions like intestinal ischemia or obstruction, or when conservative therapy fails. Exclusion of conditions that need surgical treatment is important

to avoid unnecessary surgery. In the present case, there was no indication for surgery because there were no signs of intestinal perforation, ischemia, or obstruction. It has been suggested that the WBC is significantly correlated with ischemia complicating PCI [4]. The WBC was within the normal range in the present patient. Because more severe conditions such as perforation may be associated with PCI [10], prompt identification of sunitinib as the cause is important and clinicians must be aware of this rare adverse effect. When PCI is induced by a medication, discontinuation of the relevant drug should be considered [2, 9, 11, 12]. Although sunitinib was effective for recurrent GIST in the present case, it was discontinued because of the risk of severe complications such as intestinal perforation [10]. After discontinuation of sunitinib, PCI recovered promptly in the present case and there was no recurrence. According to one case report, sunitinib was reintroduced after resolution of PCI and there was no recurrence [8]. We decided not to restart sunitinib in the present patient, considering the risk of recurrent PCI and its complications, as in other reports [9, 11, 12].

In conclusion, we experienced a rare case of PCI related to sunitinib that was promptly diagnosed after the onset of abdominal symptoms. PCI resolved completely after discontinuation of sunitinib. Early diagnosis of PCI related to sunitinib is important, so clinicians should be aware of this rare adverse effect.

Statement of Ethics

Consent for publication has been obtained from the patient.

Disclosure Statement

The authors declare no conflicts of interest.

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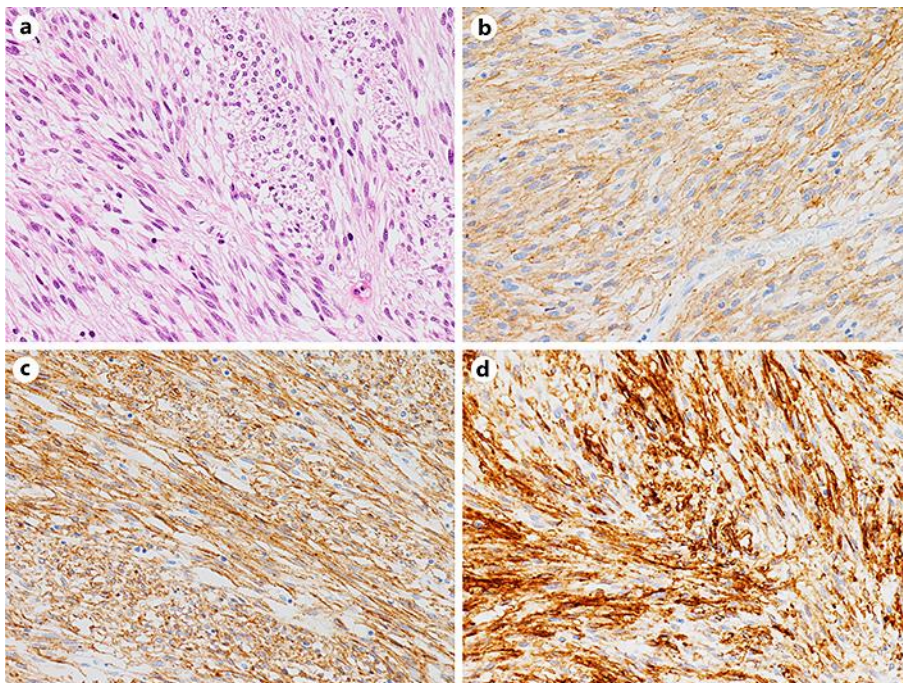


Fig. 1. Pathological examination of the GIST arising in the jejunum. **a** The tumor is mainly composed of spindle-shaped cells (HE stain, original magnification $\times 400$). **b** Immunostaining for c-KIT was positive in tumor cells (HE stain, original magnification $\times 400$). **c** Immunostaining for DOG-1 was positive in tumor cells (HE stain, original magnification $\times 400$). **d** Immunostaining for CD34 protein was weakly positive in tumor cells (HE stain, original magnification $\times 400$).



Fig. 2. CT before administration of sunitinib. **a** Liver metastasis (arrow). **b** Retroperitoneal metastasis (arrow). **c** There is no evidence of PCI.

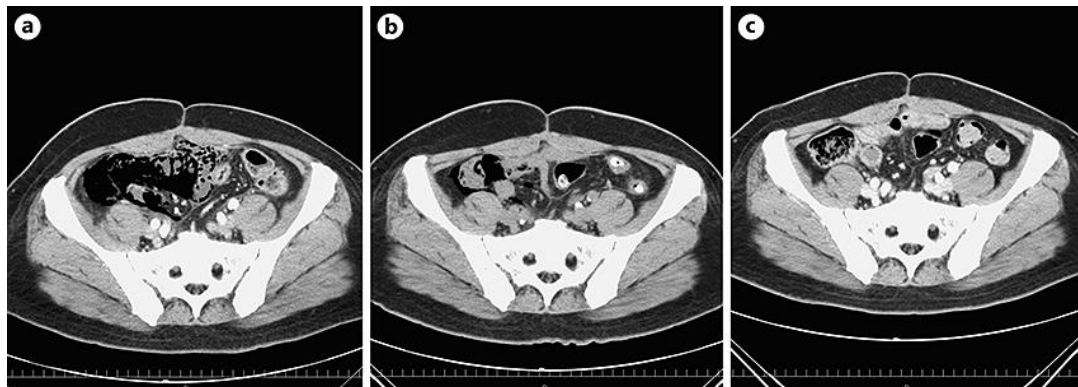


Fig. 3. CT performed at the time of PCI diagnosis and on follow-up. **a** CT performed for the detection of the cause of right lower abdominal pain. PCI is seen in a wide area around the ileocecal region. There is no free gas or ascites. **b** CT on the 6th day after discontinuation of sunitinib. PCI is reduced. **c** CT on the 19th day after discontinuation of sunitinib. PCI has completely disappeared.

Table 1. Previously reported PCI due to sunitinib

Ref.	Sex	Age, years	Primary tumor	Metastatic sites	Prior therapy	Dose, mg/day	Sunitinib duration	Medical history	Symptoms	Location	Perforation	Treatment	Sunitinib continuation
2	F	NA	RCC	lung	nephrectomy, sorafenib, high-dose IL-2	50	13 months	calculus in kidney	abdominal pain, no urine output	right colon	no	right-sided hemi-colectomy	NA
2	F	NA	RCC	lung	nephrectomy, high-dose IL-2	37.5	5 months	NA	abdominal pain, diarrhea, decrease in appetite	right colon	no	conservative treatment	NA
8	M	68	RCC	lymph nodes, bone	nephrectomy, irradiation, temserolimus	37.5	27 months	pulmonary embolism	cauda equina syndrome	small bowel	no	surgical exploration	re-introduced
9	M	73	GIST	NA	imatinib	37.5	68 days	renal transplantation, depression	abdominal pain, abdominal bloating	right and transverse colon	no	conservative treatment	discontinued
10	NA	NA	RCC	NA	NA	NA	3 months	NA	none	small bowel	yes	NA	NA
10	NA	NA	RCC	NA	NA	NA	1 months	NA	abdominal pain, abdominal distention	stomach, small bowel, cecum, ascending colon	yes	NA	NA
11	M	78	RCC	lung, sub-epidermal	nephrectomy, VATS	25	NA	diabetes, polymyalgia rheumatica, hypertension	none	right and transverse colon	no	conservative treatment	discontinued
12	F	68	PNET	liver	octreotide analogue, everolims	25	NA	NA	diarrhea, fatigue, dyspepsia, abdominal discomfort	distal ileum and colon	no	conservative treatment	discontinued
pres-ent case	M	67	GIST	liver, retro-peritoneum	jejunal resection, tumor resection, imatinib	37.5	2 months	diabetes, hypertension	abdominal pain	distal ileum and right colon	no	conservative treatment	discontinued

IL-2, interleukin-2; NA, data not available; PNET, pancreatic neuroendocrine tumor; RCC, renal cell cancer; Ref., reference.