# Case Report of Pneumatosis Intestinalis Secondary to Sunitinib Treatment for Refractory Gastrointestinal Stromal Tumor

ANTHONY JARKOWSKI III[1], RYAN HARE[1], VALERIE FRANCESCUTTI[2], NEAL WILKINSON[2] and NIKHIL KHUSHALANI[3]

*Departments of [1]Pharmacy, [2]Surgery and [3]Medicine, Roswell Park Cancer Institute, Buffalo, NY 14263, U.S.A.*

**Abstract.** *Pneumatosis intestinalis (PI) occurs when interluminal air enters the bowel wall of the gastrointestinal tract via a mucosal defect. The condition is caused by numerous disease states, direct trauma, and various drugs. When PI is secondary to drug therapy, discontinuation of the offending agent results in the resolution of PI. We report on the case of a 73-year-old male with a history of refractory gastrointestinal stromal tumor experiencing PI while on sunitinib treatment. PI was noted via computed tomography (CT) scans 68 days after starting sunitinib therapy and showed near complete resolution on a follow up CT performed one month after discontinuing sunitinib. Given that a CT scan performed five months prior to the initiation of sunitinib did not show PI, lack of abdominal symptoms in our patient, and resolution of PI after discontinuing sunitinib, the cause of PI in our patient was likely due to sunitinib treatment.*

Pneumatosis intestinalis (PI) occurs when gas enters the submucosal, subserosal tissue, and less frequently in the muscularis propria of the gastrointestinal wall (1). The diagnosis of PI is currently made by way of computed tomographic (CT) scans. PI has been described in patients treated with the vascular endothelial growth factor inhibitor (VEGF-A) bevacizumab (Avastin®; Genentech Inc, San Francisco, CA, USA) (2), and has more recently been documented as a probable adverse effect of the multi-targeted tyrosine kinase inhibitors (TKIs) sorafenib (Nexavar®; Bayer Pharmaceutical Corporation, West Haven, CT, USA) and sunitinib (Sutent®; Pfizer, New York, NY, USA) (3, 4).

*Correspondence to:* Anthony Jarkowski III, Pharm.D., BCOP, Clinical Pharmacy Specialist, Department of Pharmacy, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA, Clinical Pharmacy Specialist, Department of Pharmacy, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, U.S.A. Tel: 1 7168454089, Fax: 1 7168454095, e-mail: Anthony.Jarkowski@roswellpark.org

*Key Words:* Sunitinib, pneumatosis intestinalis, gastrointestinal stromal tumor.

PI is associated with a variety of other medical conditions and disease states including inflammation/autoimmunity, infectious processes, collagen-vascular etiologies (1, 5), chronic obstructive pulmonary disease/emphysema, asthma, acquired immune deficiency syndrome , cystic fibrosis, and lupus enteritis (1, 5). Acute life-threatening causes of PI include mesenteric ischemia, intestinal obstruction, toxic megacolon, and secondary to bowel preparation treatments (5, 6). The commonality among all etiologies is compromised mucosal integrity, with or without an increase in intraluminal pressure against the gastrointestinal wall (1, 5). Both compromised integrity and increased intraluminal pressure are thought to increase the likelihood of bowel gas penetrating within the submucosal or subserosal tissue of the gastrointestinal tract (5).

Although PI is often asymptomatic, common acute symptoms of the condition include abdominal cramping, pain, and diarrhea (1, 5). Common chronic symptoms of PI include weight loss, constipation, and bloody stools (1, 5). Early signs of the condition are nonspecific, and may be mistaken for signs of tumor progression or adverse effects from drug therapy. Therefore, it is important for clinicians to be aware that PI is a rare but possible adverse effect associated with VEGF inhibitors (3, 4). If the cause of PI is considered secondary to drug therapy, the condition will usually resolve upon discontinuation of the offending agent, without the necessity for subsequent surgical interventions (5).

Sunitinib is a multitargeted TKI approved by the Food and Drug Administration (FDA) for the treatment of metastatic renal cell carcinoma (RCC), and as second line therapy in gastrointestinal stromal tumors (GIST) after failure or discontinuation of imatinib mesylate (Gleevec©) (7, 8). Biochemical and cellular assays reveal that sunitinib inhibits VEGF receptor 1 and 2, fetal liver tyrosine kinase receptor, KIT (stem-cell factor receptor), and platelet-derived growth factor (PDGF) (8, 9). The efficacy of sunitinib is thought to be primarily due to its inhibition of the cell surface receptors for VEGF or PDGF, reducing angiogenesis to tumor cells (9,

10). Reduced vascularity to the gastrointestinal tract by multitargeted TKIs (including sunitinib) may compromise the integrity of the tissue, increasing the opportunity for free bowel air to penetrate the walls of the gastrointestinal tract (3).

At the time of writing, there is a paucity of data on PI secondary to VEGF-targeted therapy. We present a case of PI that is a probable adverse effect to second-line sunitinib therapy for GIST (11).

## Case Report

A 73-year-old Caucasian male with a history of renal transplantation presented for an abdominal ultrasound after findings of an abdominal bruit. At that time, a large intra-abdominal tumor was identified, and later confirmed using a CT scan. CT-guided biopsy of the lesion was performed, which revealed the tumor to be CD34 and CD117 positive, and cytokeratin 7 negative, consistent with GIST. The patient was subsequently started on 400 mg imatinib mesylate by mouth once daily. For approximately 2 years, the patient tolerated the imatinib mesylate treatment fairly well, but due to dysgeusia and depression, the patient requested that the treatment be stopped. One year following this, there was increasing omental disease noted on CT. The patient was started on venlafaxine for depression, and restarted on 100 mg imatinib mesylate daily, with eventual dose escalation to 400 mg. The patient developed profound depression and continued to have dysgeusia secondary to the imatinib mesylate treatment. As a result, imatinib mesylate therapy was discontinued, and continuous daily therapy with 37.5 mg sunitinib was started.

Unfortunately, the patient did not tolerate sunitinib therapy well. In the first cycle, the patient reported increased nausea, dyspepsia, and abdominal bloating and pain. Hypertension was also noted as the patient's blood pressure readings elevated from baseline since the start of sunitinib therapy. The patient denied headaches, vision changes, chest pain, and shortness of breath. However, the patient's appetite had been well maintained since the discontinuation of imatinib and start of sunitinib treatment.

A CT of the chest, abdomen, and pelvis 68 days after the start of sunitinib therapy revealed extensive PI of the right and transverse colon (Figure 1 a and b), with no evidence of free intraperitoneal air. There was extensive air in the retroperitoneum, suggesting a retroperitoneal perforation. In addition, there was evidence of disease progression, with an increase in omental disease compared to prior imaging. Given the lack of abdominal symptoms, PI was suspected to be secondary to sunitinib treatment rather than the alternate causes listed above with standard disease progression. Clinically, the patient was in no distress, with vital signs and blood work in the normal range, nor did he exhibit peritonitis on physical examination. A surgical consultation recommended non-operative management given the patient was hemodynamicaly stable and symptom-free. Considering the clinical scenario and high suspicion that the PI was related to sunitinib, this medication was discontinued. One month after discontinuing sunitinib, a follow up CT scan revealed near complete resolution of the PI (Figure 2 a and b). At the subsequent clinic visit, the patient described a decrease in abdominal bloating after discontinuation of sunitinib. The patient was subsequently started on nilotinib (Tasigna®; Novartis, East Hanover, NJ, USA) one month after discontinuing sunitinib. Importantly, nilotinib does not significantly inhibit VEGF, therefore therapy with nilotinib was deemed appropriate and safe for this patient (12). While the patient was receiving nilotinib, there was no reoccurrence of PI. The patient, however, developed progressive disease and succumbed to his disease 54 days after the initiation of nilotinib treatment.

## Discussion

Sunitinib is a multikinase TKI with approval by the FDA for metastatic RCC and second-line therapy for GIST after imatinib (7). In a single-arm study, sunitinib demonstrated efficacy in the treatment of GIST refractory to imatinib treatment (12). Median time-to-tumor progression in patients with refractory GIST was 27.3 weeks compared to 6 weeks in patients who received placebo ($p<0.0001$) (12). Common adverse effects seen in the FDA trials for approval of sunitinib for advanced RCC and GIST were altered taste, mucositis, skin abnormalities, and diarrhea (12). Reductions in left-ventricular ejection fraction and hypertension were also noted (12). Other side effects attributed to sunitinib include hair depigmentation, asthenia, dyspnea, neutropenia, hand-foot syndrome, edema, hypothyroidism, anorexia, nausea and vomiting, anemia and thrombocytopenia (8,10).

Our patient demonstrated some side-effects consistent with those commonly seen in clinical trials, including hypertension, diarrhea, and altered taste (8, 10, 13). However, our patient experienced PI that was probably due to sunitinib treatment (Naranjo Probability Score=5) (11). PI was not a documented side-effect in phase I, II, or III clinical trials for sunitinib, and was not documented to be associated with sunitinib treatment until recent case reports (3-4). Consistent with previous case reports of patients experiencing PI secondary to sunitinib treatment, the PI in our case was classified as a probable adverse effect of sunitinib therapy (Naranjo Probability Score=5) (3, 4, 11). Inconsistent with previous case reports was the duration of exposure to sunitinib therapy before PI appeared. Coriat *et al*. documented a case report of a patient presenting with PI probably due to sunitinib therapy after at least four months of treatment (3). Flaig *et al*. also documented two patients presenting with PI (4). For the first patient, PI was

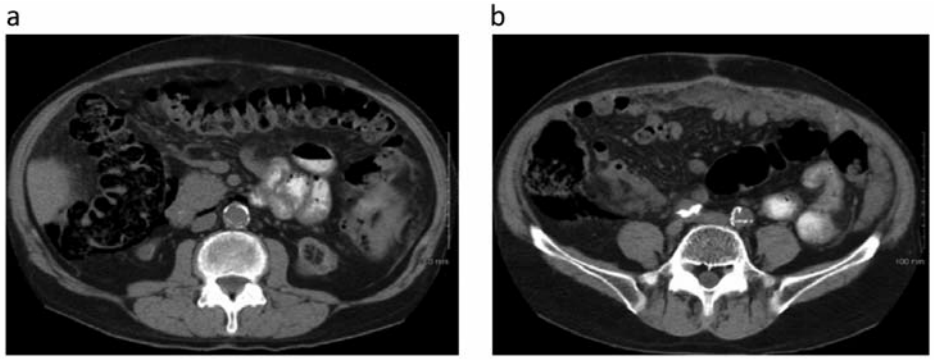


Figure 1. *CT scans of the abdomen showing extensive pneumatosis intestinalis of the of the right and transverse colon.*

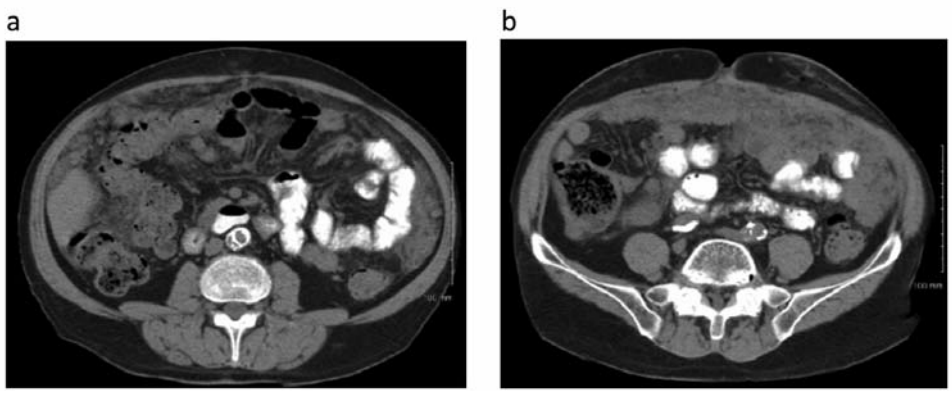


Figure 2. *CT scans of the abdomen showing resolution of pneumatosis intestinalis of the right and transverse colon.*

recognized after 13 months of sunitinib therapy (4). The second patient received nine months of treatment, a six-month drug holiday, and five more months of sunitinib therapy before PI was identified (4). Our patient, however, only received sunitinib therapy for a little over two months before discontinuation of therapy due the findings of PI on CT. A previous CT scan performed five months prior showed no evidence of PI, suggesting the addition of sunitinib as the causation of the PI.

To our knowledge, this is the first documented case of PI in a patient treated with sunitinib therapy for refractory GIST (3, 4). Previous case reports document PI in patients receiving sunitinib therapy for metastatic RCC. The inhibition of VEGF by sunitinib therapy is believed to be vital to its antitumor and antiangiogenic properties (8, 9). Bevacizumab, another monoclonal antibody used in the treatment of colorectal cancer, also targets and inhibits VEGF (13). However, unlike sunitinib, bevacizumab has been well-documented to cause GI perforations (4, 13). A prospective phase III trial revealed a 1.5% incidence of GI perforations in patients treated with bevacizumab. Likewise, Coriat *et al*. documented a case report of PI as a probable side effect of sorafenib, another VEGF inhibitor used in the treatment of RCC and hepatocellular carcinoma (3). Although our case report cannot add insight upon the likelihood of sorafenib or bevacizumab causing PI in patients, our findings are consistent with previous reports suggesting sunitinib as being a causative agent for PI (3-4). Coriat *et al*. proposed the possibility that the reduction of vascularity due to the inhibition of VEGF in healthy tissue might result in ischemic effects on healthy cells of the GI tract, compromising the integrity of the tissue, and thus supporting the induction of PI (3, 14).

## Conclusion

To our knowledge, this is the first documented case report of PI with sunitinib for the treatment of refractory GIST. Unlike previous reports, our patient developed PI relatively quickly after starting sunitinib. Similar to previous reports, our patient's symptoms of PI improved upon discontinuation of sunitinib therapy. However, resolution of PI based upon imaging *via* a CT scan was seen after sunitinib discontinuation. Early signs of PI are non-specific, and

therefore the clinician must be aware that the condition, although rare, is a probable but rare side-effect of sunitinib therapy and is usually self-limiting upon anti-VEGF discontinuation. The induction of PI is likely a class effect of the VEGF inhibitors, considering the hypoxic effects of the drug class (3, 14) With increasing use of anti-VEGF strategies, especially in combination with chemotherapy, another cause of damage to the GI mucosa, the incidence of drug-induced PI may increase.

The management of drug-induced PI varies depending on the severity. In some instances, PI can be life-threatening and necessitates urgent surgical intervention (15). In other cases, PI will resolve upon discontinuation of the offending agent alone. A management algorithm has been provided by Wayne *et al*. to help identify patients who would likely require surgical intervention, and patients who would likely benefit from discontinuation of the offending agent only (15). The algorithm uses patient-specific factors, including stability and presenting history, a scoring system for vascular disease severity, radiological and laboratory findings, and whether or not the patient had recent iatrogenic GI trauma, to help place patients into subgroups with the corresponding preferred treatment modalities (15). In a study by Wayne *et al*., 88 patients with PI were treated using this algorithm. Results of the study showed 100% specificity, 89% sensitivity, and a positive predictive value of 100% (15). This algorithm may provide guidance for the treatment of PI and may prevent unnecessary surgery in cases of benign PI, and afford timely surgical interventions in patients with acute and life-threatening cases of PI (15).

## References


1 Koreishi A, Lauwers G and Misdraji J: Pneumatosis intestinalis: A challenging biopsy diagnosis. Am J Surg Pathol *31*: 1469-1475, 2007.

2 Shih T and Lindley C: Bevacizumab: An angiogenesis inhibitor for the treatment of solid malignancies. Clinical Ther *28*: 1779-1802, 2006.

3 Coriat R, Ropert S, Mir O, Billemont B, Chaussade S, Massault P,Blanchet B, Vignaux O and Goldwasser F: Pneumatosis intestinalis associated with treatment of cancer patients with the vascular growth factor receptor tyrosine kinase inhibitors sorafenib and sunitinib. Investi New Drugs pp. 1-4, 2010.

4 Flaig T, Kim F, La Rosa F, Breaker K, Schoen J and Russ P: Colonic pneumatosis and intestinal perforations with sunitinib treatment for renal cell carcinoma. Invest New Drugs *27*: 83-87, 2009.

5 St. Peter SD, Abbas MA and Kelly KA: The spectrum of pneumatosis intestinalis. Arch Surgery *138*: 68-75, 2003.

6 Ho L, Paulson E and Thompson W: Pneumatosis intestinalis in the adult: benign to life-threatening causes. Am J of Roentgenol *188*: 1604-1613, 2007.

7 Rock E, Goodman V, Jiang J, Mahjoob K, Verbois S, Morse D, Dagher R and Justice R: Food and Drug Administration drug approval summary: Sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma. Oncologist *12*: 107-113, 2007.

8 Faivre S, Delbaldo C, Vera K, Robert C, Lozahic S, Lassau N, Bello C, Deprimo S, Brega N, Massimini G, Armand JP, Scigalla P and Raymond E: Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncology *24*: 25-35, 2006.

9 Mendel DB, Douglas Laird A, Xin X, Louie SG, Christensen JG, Li G, Schrek RE, Abrams TJ, Ngai TJ, Lee LB, Murray LJ, Carver J, Chan E, Moss KG, Haznedar JO, Sukbuntherng J, Blake RA, Sun L, Tang C, Miller T, Shirazian S, McMahon G and Cherrington JM: *In vivo* antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: Determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res *9*: 327-337, 2003.

10 Chouhan JD, Zamarripa DE, Lai PH, Oramasionwu CU and Grabinski JL: Sunitinib (Sutent(registered trademark)): A novel agent for the treatment of metastatic renal cell carcinoma. J Oncology Pharm Pract *13*: 5-16, 2007.

11 Naranjo CA, Busto U and Sellers EM: A method for estimating the probability of adverse drug reactions. Clin Pharmacol and Ther *30*: 239-245, 1981.

12 Goodman VL, Rock EP, Dagher R, Ramchandani RP, Abraham S, Gobburu JVS, Booth BP, Verbois SL, Morse DE, Liang CY, Chidambaram N, Jiang JX, Tang S, Mahjoob K, Justice R and Pazdur R: Approval summary: Sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. Clin Cancer Res *13*: 1367-1373, 2007.

13 Saif MW, Elfiky A and Salem RR: Gastrointestinal perforation due to bevacizumab in colorectal cancer. Ann Surgi Oncol *14*: 1860-1869, 2007.

14 Jain RK: Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy. Nat Med *7*: 987-989, 2001.

15 Wayne E, Ough M, Wu A, Liao J, Andresen KJ, Kuehn D and Wilkinson N: Management algorithm for pneumatosis intestinalis and portal venous gas: treatment and outcome of 88 consecutive cases. J Gastrointest Surg *14*: 437-448, 2010.


*Received June 29, 2011*
*Revised August 2, 2011*
*Accepted August 3, 2011*