Pneumatosis Intestinalis and Bowel Perforation Associated With Molecular Targeted Therapy: An Emerging Problem and the Role of Radiologists in Its Management

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OBJECTIVE. The purpose of this article is to study the imaging features, management, and outcome of pneumatosis intestinalis and bowel perforation associated with molecular targeted therapy.

MATERIALS AND METHODS. In this retrospective study, 48 patients with cancer who developed pneumatosis or intestinal perforation were found by searching a radiology database. Of these patients, 24 patients (13 women and 11 men; mean age, 61 years; range, 39–83 years) receiving molecular targeted therapy without any confounding factors for pneumatosis or perforation were selected. Initial and follow-up CT scans were evaluated by two radiologists; medical records were reviewed to note clinical features, management, and outcome.

RESULTS. Seventeen (70.8%) patients were asymptomatic. Colorectal cancer (n = 10) and renal cell carcinoma (n = 5) were the most common malignancies; bevacizumab (n = 14) and sunitinib (n = 6) were the most common associated drugs. Imaging findings included intestinal perforation (20 sites in 18 patients), pneumatosis (n = 10), ascites (n = 8), pneumoperitoneum (n = 7), fistula formation (n = 7), and fluid collections (six collections in five patients). Fifteen (62.5%) patients were treated conservatively, seven (29.2%) underwent surgery, and two (8.3%) underwent percutaneous drainage. Molecular targeted therapy was discontinued in 22 of 24 patients; findings resolved in 19 patients, remained stable in one, and worsened in one. One patient died after surgery. In both instances where the drug was continued, the abnormality worsened. Findings recurred in three of four patients in whom the drug was restarted after initial resolution.

CONCLUSION. Radiologists should be aware of intestinal complications associated with molecular targeted therapy, including pneumatosis, bowel perforation, and fistula formation. Most patients can be treated conservatively after discontinuation of molecular targeted therapy. Continuing or restarting molecular targeted therapy can cause worsening or recurrent pneumatosis or perforation.

Keywords: bowel complication, perforation, cancer, fistula, intestinal pneumatosis, molecular targeted therapy

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Understanding of the numerous intracellular signaling pathways in tumorigenesis has opened the door for a new class of molecular targeted agents. Because of its relatively selective action, potential for long-term activity, and better toxicity profile, molecular targeted therapy has transformed cancer treatment and is now routinely used, either alone or in combination with other drugs, to treat many common neoplasms, including renal cell carcinoma (RCC), colorectal cancer, lung cancer, melanoma, and gastrointestinal stromal tumor (GIST) [1–5]. As molecular targeted therapy usage becomes commonplace, unexpected associated adverse effects are being noted [6]. Radiologists must identify molecular targeted therapy–related adverse events in a timely manner, to optimize clinical management and decrease morbidity.

Bowel toxicity, especially pneumatosis intestinalis and bowel perforation, has been reported in association with molecular targeted therapy agents, including bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), and sunitinib malate and sorafenib, which are tyrosine kinase inhibitors targeting various receptors, including VEGF and platelet-derived growth factor [7–10]. Isolated case reports document these findings, which are also mentioned as a part of clinical studies evaluating new drug regimens [10–14]. Large series on pneumatosis and bowel perforation are lacking, and management of these adverse events, whether conservative or surgical, is unclear. Most important, although

the association between molecular targeted therapy and bowel complications is known, the imaging literature on the subject is very limited, and there is a need for increased awareness among radiologists about bowel complications of molecular targeted therapy.

This study retrospectively evaluates the imaging features, management, and outcome of pneumatosis intestinalis and bowel perforation associated with molecular targeted therapy.

Materials and Methods

Subjects

In this institutional review board–approved HIPAA-compliant retrospective study performed at a tertiary cancer institute, a radiology database search from January 2006 through October 2011 revealed 48 patients with cancer whose radiology reports mentioned pneumatosis intestinalis (or variations, including pneumatosis, intestinal pneumatosis, pneumatosis cystoides intestinalis, or intramural gas), pneumoperitoneum (or extraluminal air, free air, or gas bubbles), or bowel perforation (intestinal perforation or rupture). Thirty-nine patients were receiving molecular targeted therapy at the time of pneumatosis or intestinal perforation. Patients were excluded from this cohort if imaging studies were not available or if review of the medical record revealed concurrent risk factors for pneumatosis, perforation, or fistula formation—specifically, steroid treatment, radiation treatment within 1 year, surgery within 3 months, diverticulitis, inflammatory bowel disease, nonsteroidal antiinflammatory drug use, primary or secondary tumor causing a fistula (e.g., colorectal carcinoma), recent endoscopy, mesenteric ischemia, or peptic ulcer disease. On the basis of these criteria, 15 patients were excluded (imaging studies were not available, $n = 1$; long-term steroid treatment for conditions such as chronic obstructive pulmonary disease, $n = 4$; radiation treatment within 1 year, $n = 3$; surgery within 3 months, $n = 1$; diverticulitis, $n = 1$; primary or secondary tumor directly invading bowel, $n = 4$; and mesenteric artery occlusion, $n = 1$). Other risk factors, including inflammatory bowel disease, nonsteroidal antiinflammatory drug use, intact primary tumor (especially in case of colorectal cancer), recent endoscopy, and history of peptic ulcer, were looked for, but none of the remaining patients had these risk factors. Imaging studies of the remaining 29 patients were reviewed. Five patients were excluded because changes were secondary to tumor invading the bowel ($n = 4$) or were associated with mesenteric artery occlusion causing ischemic bowel changes in a patient with history of atrial fibrillation ($n = 1$). The remaining 24 patients (13 women and 11 men; mean age, 61 years; range, 39–83 years) receiving molecular targeted therapy who had pneumatosis or bowel perforation in the absence of other confounding factors were included. Pneumatosis or perforation was diagnosed on CT in all cases.

Review of Imaging

The first CT scan showing pneumatosis or perforation and follow-up scans were evaluated in consensus by two fellowship-trained radiologists with 8 and 13 years of experience. The following information was noted: the reason for CT (routine follow-up or restaging study in an asymptomatic patient or study performed to evaluate an abdominal symptom), study date, imaging findings (including pneumatosis, mesenteric or portal venous gas, intestinal perforation and pneumoperitoneum, and evidence of fistula formation), and site of bowel involvement. If perforation involved normal bowel wall, the tumor deposit or surgical anastomosis (anastomotic dehiscence) was noted. If fistula formation was present, the fistula location and involved structures were noted. The diagnostic criteria for fistula included, depending on the location, the presence of extraenteric tract; enhancing granulation tissue; internal air or fluid, or both, within any fistulous tract or within another structure tumor or bladder juxtaposed to the bowel loop; and thickening or stranding involving the involved portion of the bowel loop. The presence of bowel-wall thickening, stranding, fluid collection or abscess formation, ascites, hemoperitoneum, and bowel obstruction was noted. The presence or absence of metastatic disease and whether there was treatment response, stable disease, or progression at the time of diagnosis of pneumatosis or perforation was also noted. Patients were followed until death or until the present time. Any available follow-up studies were evaluated to see whether findings resolved or recurred, with or without molecular targeted therapy. If findings recurred, the extent of findings was compared with the original episode according to subjective assessment by the two reviewers in consensus.

Clinical Correlation

Electronic medical records were reviewed to record the malignancy type, type and duration of molecular targeted therapy, presence or absence of clinical symptoms before the scan, whether the drug was discontinued after diagnosis of the complication, treatment offered, and outcome. Imaging findings were correlated with operative findings in surgically treated patients. In patients who had undergone radiation treatment ($n = 7$), the interval since radiation was noted (median, 46 months; range, 14–86 months). If molecular targeted therapy was restarted, the time of reinstitution of molecular targeted therapy and whether pneumatosis or perforation recurred were also noted.

Results

Colorectal cancer ($n = 10$) and RCC ($n = 5$) were the most common malignancies. Bevacizumab ($n = 14$) and sunitinib ($n = 6$) were the most common drugs associated with pneumatosis or perforation. Other drugs included sorafenib, cetuximab, erlotinib, and ipilimumab in one patient each. All the patients with colorectal cancer were taking combination therapy: six received bevacizumab along with folinic acid (leucovorin), fluorouracil, and oxaliplatin, and four received bevacizumab with folinic acid, fluorouracil, and irinotecan. One patient with ovarian cancer was receiving bevacizumab along with carboplatin and paclitaxel. All other patients were taking single-agent molecular targeted therapy. Table 1 presents molecular targeted therapy and imaging findings.

None of the patients had a history of pneumatosis or perforation. The median duration of molecular targeted therapy before pneumatosis or perforation was detected was 3 months (range, 1–13 months). Six (25%) patients presented after just 1 month of treatment. Of 24 patients, 17 (70.8%) were asymptomatic, with the findings detected incidentally on routine restaging studies. In four of 17 asymptomatic patients (23.5%), a history of mild abdominal pain was elicited only in retrospect, after the CT diagnosis was made. Among symptomatic patients, abdominal or pelvic pain was the most common symptom (5/24 [20.8%]). Patients who were receiving molecular targeted therapy longer than 4 months were more frequently symptomatic; however, this difference did not meet statistical significance (5/9 [55.6%] symptomatic while taking molecular targeted therapy > 4 months vs 2/15 [13.3%] symptomatic among those taking molecular targeted therapy for ≤ 4 months; $p = 0.06$, Fisher exact test).

Imaging findings included intestinal perforation (total of 20 sites of perforation in 18 patients) (Fig. 1), pneumatosis ($n = 10$) (Fig. 2), ascites ($n = 8$), pneumoperitoneum ($n = 7$) (Figs. 2 and 3), fistula formation ($n = 7$) (Fig. 4), and fluid collections (six collections in five patients). Other findings included associated bowel wall thickening ($n = 4$), surrounding stranding ($n = 3$), and proximal bowel obstruction ($n = 4$; partial in three patients and complete in one patient). No patients had bowel obstruction distal to the site of pneumatosis

TABLE 1: Primary Malignancy, Molecular Targeted Treatment, and Important Imaging Features for 24 Patients

Patient No.	Cancer	Molecular Targeted Therapy	Duration of Therapy (mos)	Symptoms	Finding	Location
1	Colorectal	Bevacizumab	6	Pelvic pain	Perforation	Rectum
2	Colorectal	Bevacizumab	9	Hematuria and pneumaturia	Perforation and colovesical and colourethral fistula	Rectum
3	Colorectal	Bevacizumab	1	None	Perforation	Rectum
4	Colorectal	Bevacizumab	4	None	Pneumatosis and perforation	Small bowel
5	Colorectal	Bevacizumab	1	None	Perforation and tumor-bowel fistula	Small bowel
6	Colorectal	Bevacizumab	8	None	Perforation	Rectum
7	Colorectal	Bevacizumab	2	None	Perforation	Rectum
8	Colorectal	Bevacizumab	3	None	Pneumatosis	Small bowel
9	Colorectal	Bevacizumab	10	Abdominal pain	Pneumatosis	Transverse colon
10	Colorectal	Bevacizumab	2	None	Pneumatosis	Cecum and ascending colon
11	RCC	Bevacizumab	6	None	Perforation and tumor-bowel fistula	Duodenum
12	RCC	Sunitinib	3	None	Pneumatosis and perforation	Small bowel
13	RCC	Sunitinib	8	Abdominal pain and distention	Perforation and enterocutaneous fistula	Small bowel
14	RCC	Sunitinib	2	None	Perforation and tumor-bowel fistula	Stomach
15	RCC	Sunitinib	1	Abdominal pain and distention	Pneumatosis, perforation (two sites), and tumor-bowel fistula	Stomach, small bowel, cecum, and ascending colon
16	Lung	Bevacizumab	6	None	Pneumatosis	Stomach and small bowel
17	Lung	Erlotinib	4	None	Pneumatosis	Cecum and ascending colon
18	Ovary	Bevacizumab	1	None	Perforation	Small bowel
19	Ovary	Bevacizumab	1	None	Perforation	Transverse colon
20	Pancreas (endocrine tumor)	Sunitinib	13	Abdominal pain	Perforation	Small bowel
21	Tongue	Cetuximab	1	None	Pneumatosis	Transverse colon
22	GIST	Sorafenib	7	None	Pneumatosis and perforation	Small bowel
23	Leiomyosarcoma	Sunitinib	2	None	Perforation and tumor-bowel fistula	Small bowel
24	Melanoma	Ipilimumab	3	Diarrhea	Perforation (two sites)	Descending and sigmoid colon

Note—GIST = gastrointestinal stromal tumor, RCC = renal cell carcinoma.

or perforation. The ileum was most commonly involved, (n = 8), followed by jejunum (n = 5), rectum (n = 5), stomach (n = 3), cecum and ascending colon (n = 3), transverse colon (n = 3), duodenum (n = 1), and descending and sigmoid colon (n = 1).

Among 18 patients with perforation (at a total of 20 sites), perforation occurred at the tumor in eight patients (Fig. 4), at the normal bowel wall in six patients, and at the site of surgical anastomosis (anastomotic dehiscence, although not in the immediate postoperative period) in five patients (Fig. 1). Two patients had two sites of perforation: one had perforation involving normal bowel wall and at the tumor, and another had two perforations involving normal bowel wall. Of 10 patients with pneumatosis, seven had pneumatosis involving normal bowel wall, two involved normal bowel wall and tumor deposits, and one patient had pneumatosis adjacent to the surgical anastomosis. Mesenteric venous gas was seen in four of 10 patients with pneumatosis; portal venous gas was not seen. Of those who developed fistulae, five patients had tumor-bowel fistula (Fig. 4), one patient developed colovesical and colourethral fistula, and one patient developed enterocutaneous fistula. Of 18 patients with intestinal perforation, pneumoperitoneum was seen in seven (38.9%). Of the remaining 11 patients, five had fistula formation, four had localized collections adjacent to the perforation site, one had an enterocutaneous fistula and peritoneal and abdominal wall collections, and one patient had microperforation, with minimal air adjacent to the perforation site. Of five patients who had collections, four were related to anastomotic dehiscence.

Of the 22 of 24 (91.7%) patients who had known metastatic disease when they developed pneumatosis or perforation, 20 (90.9%) patients either had stable disease (n = 11) or response (n = 9) to molecular targeted therapy. Two (9.1%) patients showed disease progression when developing bowel complications. Fifteen (62.5%) patients were treated conservatively, seven (29.2%) underwent surgery, and two (8.3%) underwent imaging-guided percutaneous drainage. Of 18 patients with perforation, 11 (61.1%) were treated conservatively and seven were treated (38.9%) surgically, three of whom had concurrent fistulae. Of seven patients with fistulae, three (42.8%)

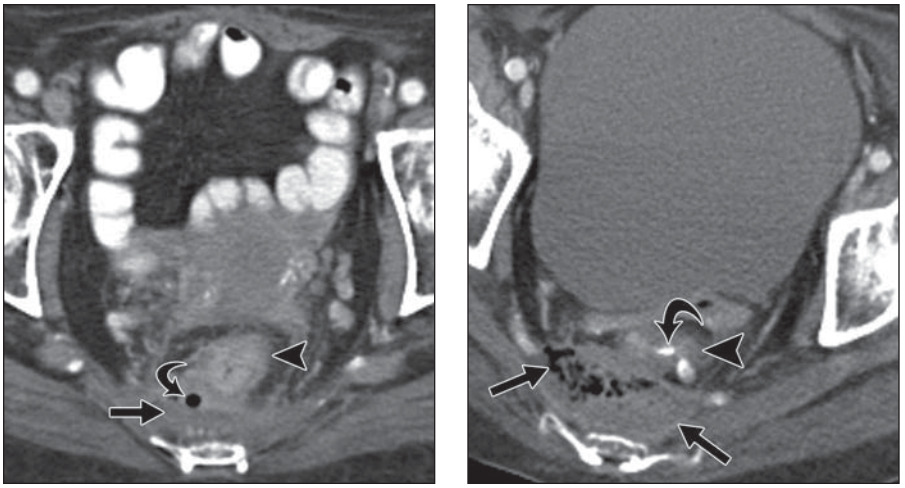

Fig. 1—83-year-old woman with rectal cancer, receiving bevacizumab and folinic acid, fluorouracil, and irinotecan treatment for 8 months, who presented with pelvic pain.
A, Contrast-enhanced CT in axial plane through pelvis shows small presacral collection (*straight arrow*) and focus of air (*curved arrow*) outside colon (*arrowhead*) adjacent to surgical anastomosis (not seen). Treatment was continued.
B, Follow-up CT shows increased size of air-containing presacral collection (*straight arrows*). Also seen are decompressed colon (*arrowhead*) and surgical anastomosis (*curved arrow*).

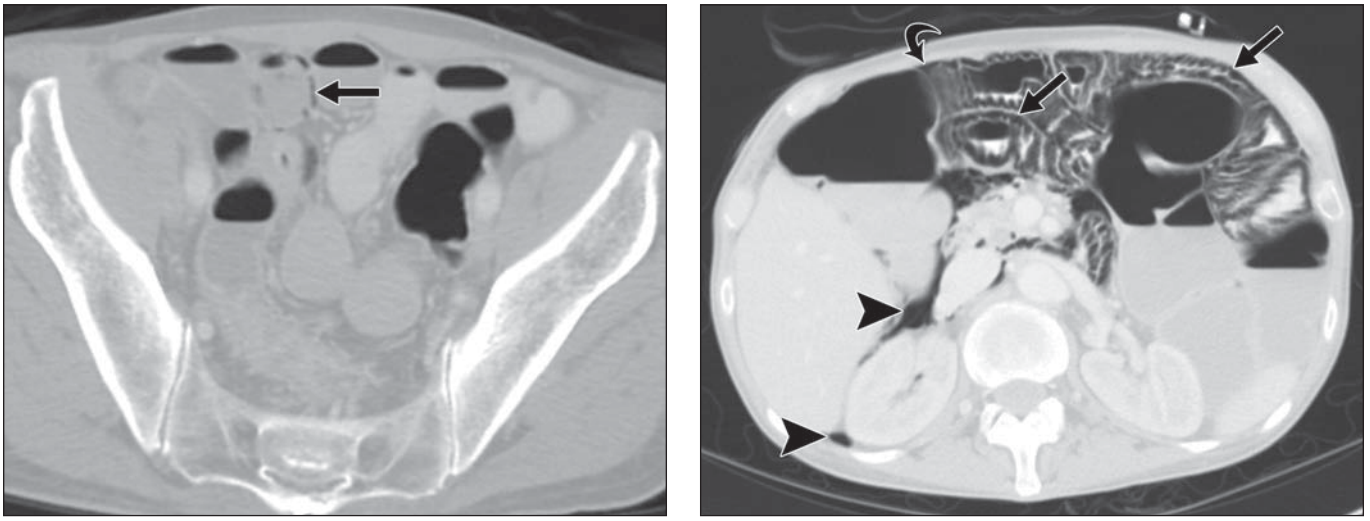

Fig. 2—53-year-old asymptomatic man with lung cancer taking bevacizumab for 6 months.
A, Lung window from routine restaging CT in axial plane shows subtle pneumatosis intestinalis (*arrow*) involving small bowel. Bevacizumab therapy was stopped, and pneumatosis resolved on follow-up CT (not shown). Bevacizumab therapy was restarted.
B, Second follow-up CT after 1 month shows extensive pneumatosis (*straight arrows*), perforation showing small pneumoperitoneum (*curved arrow*), and retroperitoneal air (*arrowheads*).

underwent surgery, two (28.6%) underwent percutaneous drainage, and two (28.6%) were treated conservatively. The fistula could be identified on surgery in only one patient; in the other two patients, the exact location of the fistula could not be identified because of the presence of tumor and inflammatory changes. Colovesical and colourethral fistulae in one patient were identified on cystoscopy. Enterocutaneous fistula in one patient was confirmed on the basis of the presence of drainage. All patients with pneumatosis (10/10 [100%]) were treated conservatively.

In 22 of 24 (91.7%) patients, molecular targeted therapy was withheld after the development of bowel complications. Molecular targeted therapy was continued in two of 24 (8.3%) patients. Follow-up CT was performed after a median of 1 month (range, 2 days to 3 months). Of 22 patients for whom molecular targeted therapy was discontinued, the findings resolved on follow-up CT in 19 patients (Fig. 3), remained stable in one patient, and worsened in one patient; one patient (who presented with abdominal pain and had evidence of colonic perforation on CT) died on day 6 after surgery secondary to surgical complications. In both the patients for whom molecular targeted therapy was continued (bevacizumab in combination treatment for both), the abnormality (tumor-bowel fistula in one patient and presacral collection secondary to anastomotic dehiscence in the other) (Fig. 1) worsened on follow-up CT. For these two patients, molecular targeted therapy was discontinued after the first follow-up CT in one patient, after which the tumor-bowel fistula improved. In the patient in whom molecular targeted therapy was continued, presacral collection worsened on the second follow-up CT, which was the last imaging examination the patient received. Eleven patients were receiving bevacizumab in combination therapy. In nine of these patients, only bevacizumab was held and the other drugs (fluorouracil and oxaliplatin in five patients; folinic acid, fluorouracil, and irinotecan in three patients; and carboplatin and paclitaxel in one patient)

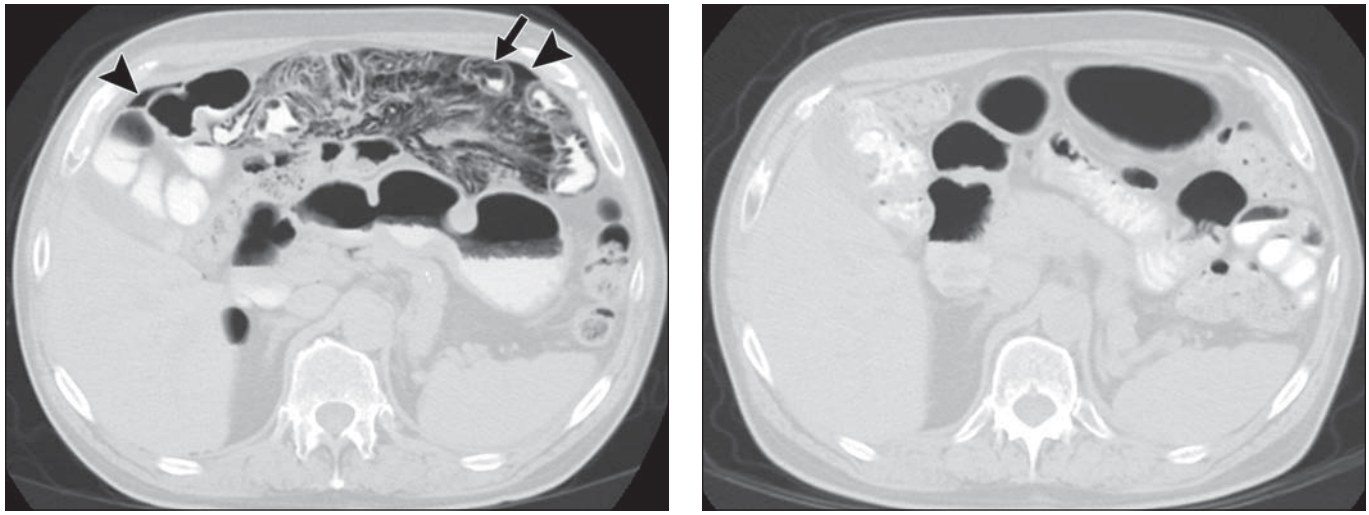

Fig. 3—68-year-old asymptomatic man with renal cell carcinoma taking sunitinib for 3 months.
A, Lung window from routine restaging CT in axial plane shows extensive pneumatosis (*arrow*) involving small bowel and small pneumoperitoneum (*arrowheads*). Sunitinib was discontinued.
B, Findings resolved on follow-up CT obtained after 2 months.

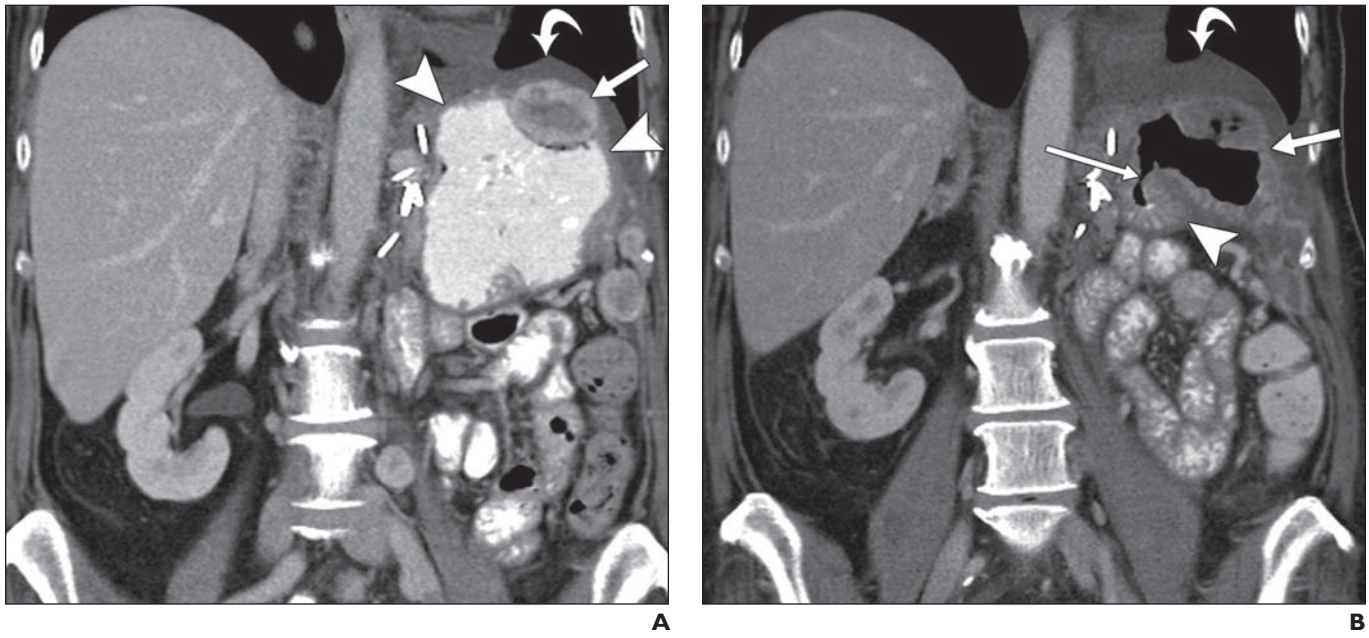

Fig. 4—67-year-old man with renal cell carcinoma.
A, Pretreatment CT in coronal plane shows peripherally enhancing mass (*straight arrow*) abutting fundic region of contrast–filled stomach (*arrowheads*). Small left pleural effusion (*curved arrow*) is noted. Multiple surgical clips are seen on left side from prior nephrectomy.
B, CT after 2 months of treatment with sunitinib shows communication (*long thin arrow*) between decompressed stomach (*arrowhead*) and mass (*short thick arrow*), which now contains large central air-filled cavitary region (tumor-bowel fistula). Left pleural effusion (*curved arrow*) is again noted.

were continued. Findings resolved in all of these patients without recurrence.

Thirteen (54.1%) patients have died at present. The median duration of follow-up was 6 months (range, 0–48 months). In four patients, the molecular targeted therapy was restarted (bevacizumab in three and sunitinib in one patient; the same drug was restarted in all four patients, with the same dosing in three patients and reduced dose in one patient) after a median period of 1 month (range, 1–2 months), once the initial findings were resolved. In three patients, more-severe findings were seen on follow-up CT: pneumatosis, perforation, and pneumoperitoneum in two patients (Fig. 2) and recurrent tumor-bowel fistula in one patient. The fourth patient had no evidence of pneumatosis or perforation at 5 months of follow-up. Findings did not recur in any patients in whom molecular targeted therapy was not restarted.

Discussion

Pneumatosis intestinalis is characterized by subserosal or submucosal air within the bowel wall. It can represent an incidentally detected harmless finding or signal a more serious underlying condition such as bowel ischemia. Its clinical relevance can be difficult to determine. Intestinal perforation is traditionally regarded as a serious complication requiring prompt surgical treatment. Although it is important to consider other causes and risk factors for pneumatosis and perforation, radiologists should be aware that pneumatosis and intestinal perforation can manifest as drug toxicity. It is important to note that 70.8% of patients in this study were asymptomatic. This underscores the important role of radiologists in detection of this complication. Although there are several case reports of pneumatosis or perforation associated with molecular targeted therapy, and also rare sporadic reports related to conventional chemotherapy [9–17], to our knowledge, this is the first large series in radiology literature reporting pneumatosis and intestinal perforation associated with molecular targeted therapy, along with its management and outcome.

Bevacizumab is a monoclonal antibody to VEGF and is commonly used for treatment of colorectal cancer, non–small cell lung cancer, and RCC [6]. Multityrosine kinase inhibitors such as imatinib (GIST), sunitinib (GIST, RCC, and pancreatic endocrine tumor), sorafenib (RCC, hepatocellular carcinoma, and GIST), and erlotinib (non–small cell lung cancer and pancreatic cancer) are also commonly clinically used [6]. Cetuximab (monoclonal antibody against epidermal growth factor receptor) is used to treat colorectal and head and neck cancers), and ipilimumab (a monoclonal antibody that works by activating the immune system) is used against melanoma [6, 18–20]. Bevacizumab is known to cause intestinal perforation or fistulae in 1.5–4% of patients [12, 21–23]. Up to 4% of patients treated with sorafenib have developed intestinal perforation [24]. The incidence of perforation and pneumatosis with other molecular targeted therapies is not known. The exact mechanism of molecular targeted therapy–associated bowel perforation is unknown. Several mechanisms have been proposed, including class-specific anti-VEGF effects compromising bowel wall integrity, intestinal wall disruption due to necrosis of the serosal tumor deposits, impaired healing of pathologic or surgical bowel injury, and ischemia related to mesenteric thrombosis (in case of bevacizumab) [25].

A prior report described pneumatosis after long-term (> 4 months) treatment with molecular targeted therapy [10]. However, in our study, the median duration of molecular targeted therapy before pneumatosis or perforation was 3 months (range, 1–13 months), with 25% of patients presenting after just 1 month of treatment. There are reports of tumor response with molecular targeted therapy as early as after 1–2 months of treatment [26, 27]. Therefore, it is not surprising that the toxicity may also be seen early in the course of molecular targeted therapy. Most (70.8%) patients who developed pneumatosis or perforation were asymptomatic, with findings detected on routine restaging studies. It is important to look for these complications on every follow-up CT in patients receiving molecular targeted therapy.

Pneumatosis often involved normal bowel (normal bowel wall was involved, with or without sites of tumor deposits, in 90% of patients). Although perforation may involve normal bowel, most perforations occurred at either the tumor or surgical anastomosis. This may be related to the class-specific action of antiangiogenic drugs to decrease tumor vascularity, possibly compromising bowel integrity [6]. Twenty of 22 (90.9%) patients with metastatic disease were either stable or improving while taking molecular targeted therapy. Traditionally, pneumoperitoneum is associated with perforation. However, in our study, only 38.9% (7/18) of patients with perforation developed pneumoperitoneum. The remaining patients had fistula formation or localized fluid collections adjacent to the perforation.

Mesenteric venous gas was seen in 40% of patients with pneumatosis. Portal venous gas was not seen. The traditional belief that pneumatosis heralds a poor outcome has been questioned [28]. However, Lassandro et al. [29] found that portal vein gas in patients with pneumatosis indicates a poor prognosis. Our findings are consistent with these reports in that none of our patients had portal venous gas, and most recovered with conservative treatment. Wiesner et al. [28] postulated that pneumatosis may be due to partial ischemic bowel wall damage. This idea seems plausible given the class-specific antiangiogenic property of these molecular targeted therapies, which may lead to intestinal vascular compromise without frank ischemia. This may also explain why most patients recovered with drug cessation.

All patients with pneumatosis were treated conservatively, and in all of them the findings resolved once molecular targeted therapy was discontinued. Surgery was avoided even in most patients with perforation. Badgwell et al. [22] have shown that selected cases of intestinal perforation in the setting of molecular targeted therapy can be managed conservatively. However, it is important to identify fistula formation, because most of these patients require some intervention, and any decision to follow with conservative management needs to be taken after careful consideration of the clinical context.

Molecular targeted therapy was withheld for most (22/24 [91.7%]) patients, and the findings resolved in most (86.4%) of the patients and worsened in only one (4.5%) patient. Findings worsened in both the patients for whom molecular targeted therapy was continued, and recurred in three of four patients for whom molecular targeted therapy was restarted after initial resolution. Findings did not recur once molecular targeted therapy was discontinued. Also, findings resolved in all of the patients receiving combination chemotherapy where only bevacizumab was held and conventional chemotherapy was continued. It has been recommended that bevacizumab be stopped permanently after perforation, whereas sunitinib can be restarted once the patient stabilizes [6]. However, in our study, one patient developed recurrent tumor-bowel fistula after sunitinib was restarted. Therefore, restarting molecular targeted therapy should be viewed cautiously.

This study has several limitations, including its retrospective nature. We did our best to exclude patients with confounding factors causing pneumatosis; however, it is impossible to conclude that the findings in these patients were definitely caused by molecular targeted therapy. Relationships among various factors, such as malignancy type, specific drugs, presence of symptoms, various findings, and clinical outcomes, could not be assessed because of the relatively small numbers of individual cancer types and specific drugs; larger studies are required to establish any relationships and to confirm our findings.

Pneumatosis perforation and fistula formation are established adverse effects of molecular targeted therapy. Radiologists should specifically look for these complications, even in asymptomatic patients and early after starting molecular targeted therapy. Timely event detection is imperative to optimal management. Most patients with molecular targeted therapy–associated intestinal complications can be treated conservatively after discontinuation

of molecular targeted therapy; continuation of treatment or restarting molecular targeted therapy can cause worsening or recurrent pneumatosis or perforation.

References

1. Maira F, Catania A, Candido S, et al. Molecular targeted therapy in melanoma: a way to reverse resistance to conventional drugs. *Curr Drug Deliv* 2012; 9:17–29
2. Metzger-Filho O, Moulin C, Awada A. Molecular targeted therapy in prevalent tumors: learning from the past and future perspectives. *Curr Clin Pharmacol* 2010; 5:166–177
3. Reichardt P, Reichardt A, Pink D. Molecular targeted therapy of gastrointestinal stromal tumors. *Curr Cancer Drug Targets* 2011; 11:688–697
4. Hudes GR, Carducci MA, Choueiri TK, et al. NCCN Task Force report: optimizing treatment of advanced renal cell carcinoma with molecular targeted therapy. *J Natl Compr Canc Netw* 2011; 9(suppl 1):S1–S29
5. Widakowich C, de Castro G Jr, de Azambuja E, Dinh P, Awada A. Review: side effects of approved molecular targeted therapies in solid cancers. *Oncologist* 2007; 12:1443–1455
6. Rutkowski P, Ruka W. Emergency surgery in the era of molecular treatment of solid tumours. *Lancet Oncol* 2009; 10:157–163
7. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004; 64:7099–7109
8. Atkins M, Jones CA, Kirkpatrick P. Sunitinib maleate. *Nat Rev Drug Discov* 2006; 5:279–280
9. Asmis TR, Chung KY, Teitcher JB, Kelsen DP, Shah MA. Pneumatosis intestinalis: a variant of bevacizumab related perforation possibly associated with chemotherapy related GI toxicity. *Invest New Drugs* 2008; 26:95–96
10. Coriat R, Ropert S, Mir O, et al. Pneumatosis intestinalis associated with treatment of cancer patients with the vascular growth factor receptor tyrosine kinase inhibitors sorafenib and sunitinib. *Invest New Drugs* 2011; 29:1090–1093
11. Hurwitz H, Kabbinavar F. Bevacizumab combined with standard fluoropyrimidine-based chemotherapy regimens to treat colorectal cancer. *Oncology* 2005; 69(suppl 3):17–24
12. Burger RA. Experience with bevacizumab in the management of epithelial ovarian cancer. *J Clin Oncol* 2007; 25:2902–2908
13. Messersmith WA, Jimeno A, Jacene H, et al. Phase I trial of oxaliplatin, infusional 5-fluorouracil, and leucovorin (FOLFOX4) with erlotinib and bevacizumab in colorectal cancer. *Clin Colorectal Cancer* 2010; 9:297–304
14. Candelaria M, Bourlon-Cuellar R, Zubieta JLG-L, Noel-Ettiene LM, Sánchez-Sánchez JM. Gastrointestinal pneumatosis after docetaxel chemotherapy. *J Clin Gastroenterol* 2002; 34:444–445
15. Mimatsu K, Oida T, Kawasaki A, et al. Pneumatosis cystoides intestinalis after fluorouracil chemotherapy for rectal cancer. *World J Gastroenterol* 2008; 14:3273–3275
16. Zander T, Briner V, Buck F, Winterhalder R. Gastric pneumatosis following polychemotherapy. *Eur J Intern Med* 2007; 18:251–252
17. Kung D, Ruan DT, Chan RK, Ericsson ML, Saund MS. Pneumatosis intestinalis and portal venous gas without bowel ischemia in a patient treated with irinotecan and cisplatin. *Dig Dis Sci* 2008; 53:217–219
18. Parikh PM, Bhattacharyya GS, Vora A. Cetuximab in head and neck cancer. *Indian J Cancer* 2011; 48:145–147
19. Azzopardi N, Lecomte T, Ternant D, et al. Cetuximab pharmacokinetics influences progression-free survival of metastatic colorectal cancer patients. *Clin Cancer Res* 2011; 17:6329–6337
20. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363:711–723
21. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350:2335–2342
22. Badgwell BD, Camp ER, Feig B, et al. Management of bevacizumab-associated bowel perforation: a case series and review of the literature. *Ann Oncol* 2008; 19:577–582
23. Saif MW, Elfiky A, Salem RR. Gastrointestinal perforation due to bevacizumab in colorectal cancer. *Ann Surg Oncol* 2007; 14:1860–1869
24. Wiebe L, Kasza KE, Maki RG, et al. Activity of sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): a phase II trial of the University of Chicago Phase II Consortium. *J Clin Oncol* 2008; 26(May 20 suppl: abstr 10502)
25. Han ES, Monk BJ. What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? *Gynecol Oncol* 2007; 105:3–6
26. Ananthnarayan S, Bahng J, Roring J, et al. Time course of imaging changes of GBM during extended bevacizumab treatment. *J Neurooncol* 2008; 88:339–347
27. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; 368:1329–1338
28. Wiesner W, Mortelé KJ, Glickman JN, Ji H, Ros PR. Pneumatosis intestinalis and portomesenteric venous gas in intestinal ischemia: correlation of CT findings with severity of ischemia and clinical outcome. *AJR* 2001; 177:1319–1323
29. Lassandro F, Scaglione M, Rossi G, Grassi R, Romano L. Portomesenteric vein gas: diagnostic and prognostic value. *Emerg Radiol* 2002; 9:96–99