Pneumatosis Intestinalis After Cetuximab-containing Chemotherapy for Colorectal Cancer

Shinkyo Yoon1, Yong Sang Hong1, Seong Ho Park2, Jae Lyun Lee1 and Tae Won Kim1,*

1Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine and 2Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

*For reprints and all correspondence: Tae Won Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 86 Asanbyeongwon-gil, Poongnap-dong, Songpa-gu, Seoul 138-736, Republic of Korea. E-mail: twkimmd@amc.seoul.kr

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Cetuximab, a chimeric monoclonal antibody to epidermal growth factor receptor, is an effective chemotherapeutic agent for patients with metastatic colorectal cancer. Whereas several specific adverse reactions to cetuximab such as skin rash and nail toxicity have been reported, there have been few reports of pneumatosis intestinalis related to cetuximab-containing chemotherapy. We describe here three patients with colorectal cancer who developed pneumatosis intestinalis during treatment with cetuximab-containing chemotherapy, which developed after 7, 19 and 47 weeks of cetuximab treatment, and discovered on routine follow-up computed tomographic scans for response evaluations. None of these patients complained of abdominal pain, showed signs of peritoneal irritation on physical examination or had elevated serum concentrations of acute inflammatory markers. Following cessation of cetuximab and conservative medical treatment, all three patients showed complete resolution of pneumatosis intestinalis on abdominal pelvic computed tomographic scans.

Key words: pneumatosis intestinalis – cetuximab – colon cancer

INTRODUCTION

Pneumatosis intestinalis (PI) is defined as subserosal or sub-mucosal gas-filled cysts in the gastrointestinal tract, usually documented by computed tomography (CT) or simple radiography (1). The clinical course of PI, which ranges from uneventful recovery to death, is dependent on the underlying etiology. Incidental detection of PI in asymptomatic patients has increased, especially in cancer patients, due to the use of routine CT scanning to evaluate patient response to treatment.

Cetuximab is a chimeric IgG1 monoclonal antibody that binds to epidermal growth factor receptor (EGFR) with high specificity and affinity, thus inhibiting the ligand-induced phosphorylation of EGFR. Cetuximab has been shown effective in patients with metastatic colorectal cancer, either previously untreated or refractory to irinotecan, but only in patients having tumors containing wild-type KRAS (2–4).

We describe here three metastatic colorectal patients with cetuximab-induced PI detected incidentally during routine CT scans; all patients had an uneventful recovery after conservative medical treatment.

PATIENTS

Patient 1

A 55-year-old woman with rectal cancer underwent anterior pelvic resection, followed by 5 months of adjuvant concurrent chemoradiotherapy with 5-fluorouracil (5-FU) plus leucovorin (LV). Seventeen months after surgery, she developed a lung metastasis and received palliative first-line chemotherapy with irinotecan and S-1. The tumor progressed, however, after 6 months. Since KRAS sequencing of a tumor...
biopsy sample showed wild-type, she was started on second-line chemotherapy with cetuximab 500 mg/m² and irinotecan 180 mg/m² every 2 weeks. After six cycles of cetuximab and irinotecan, an abdominal pelvic CT scan showed diffuse intramural air throughout her entire colon, most notably in the ascending and proximal transverse colon, with mild extension of air along the pericolic lymphovascular bundles (Fig. 1). There was no evidence of colonic ischemia/necrosis, colonic/pericolic inflammatory change or colonic perforation. She had complained only of Grade 1 diarrhea. The patient appeared afebrile with stable vital signs, and physical examination showed no signs of peritoneal irritation. Laboratory findings showed no abnormalities. Following discontinuation of chemotherapy, she was closely observed in the outpatient clinic. An abdominal pelvic CT performed 3 weeks later showed that air density in the bowel wall had disappeared. Moreover, the patient did not complain of any other symptoms during the 3 weeks. As cetuximab was suspected to be the cause of PI, she was restarted on irinotecan monotherapy. PI did not recur (Table 1).

PATIENT 2

A 52-year-old man diagnosed with sigmoid colon cancer and multiple liver metastases and, with no history of previous bowel surgery or bowel obstruction, was started on neoadjuvant chemotherapy, consisting of cetuximab 500 mg/m² plus FOLFOX [oxaliplatin 85 mg/m², LV 200 mg/m² and 5-FU (400 mg/m² bolus on days 1 and 2400 mg/m² continuous infusion)] for 46 h every 2 weeks. An abdominal pelvic CT scan performed after eight cycles of cetuximab plus FOLFOX showed extensive air collection in the colonic wall and in the suberosal/pericolic areas from the cecum to the proximal colon (Fig. 2). A small amount of intramural air was also noted in the terminal ileum. There was no evidence, however, of colonic ischemia/necrosis, colonic/pericolic inflammatory change or colonic perforation. The patient did not have any abdominal pain, febrile sense or abdominal tenderness to palpation. His laboratory findings were within normal ranges. Chemotherapy was stopped and conservative treatment, including prophylactic antibiotics, was started. A follow-up CT scan performed 6 weeks later showed complete resolution of colonic and pericolic air. After complete recovery, he was restarted on chemotherapy with 5-FU, LV and irinotecan (FOLFIRI) without recurrence of PI (Table 1).

PATIENT 3

A 72-year-old man with rectal cancer and liver metastasis received pre-operative chemoradiotherapy with 5-FU/LV followed by a palliative low anterior resection. Post-operatively, he was started on FOLFIRI, but, 8 months later, a lung metastasis was noted on routine follow-up chest CT. He was started on a biweekly schedule of cetuximab (500 mg/m²) and irinotecan (180 mg/m²). A follow-up CT scan after 24 cycles of chemotherapy revealed diffuse intramural air in the cecum through the proximal transverse colon with a small amount of air in the pericolic area (Fig. 3). There was no evidence, however, of colonic ischemia/necrosis, inflammation or perforation. The patient did not complain of abdominal pain, diarrhea or feelings of fever or chilling. Examination showed no evidence of tenderness, guarding or rebound tenderness to palpation. His vital signs were stable. Chemotherapy was halted, and the patient was closely observed. A follow-up abdominal CT scan 2 weeks later showed almost complete resolution of intramural colonic air and pericolic air. He was subsequently restarted on irinotecan alone, with no evidence of PI recurrence (Table 1).

RESULTS

We have described here three patients who experienced PI that was likely due to cetuximab-containing chemotherapy. All three patients were asymptomatic and recovered after cessation of cetuximab with conservative treatment.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender/age (years)</th>
<th>Primary tumor</th>
<th>Metastasis site</th>
<th>Prior therapy</th>
<th>Concomitant chemotherapy</th>
<th>Time under cetuximab treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55/F</td>
<td>Rectal cancer</td>
<td>Liver</td>
<td>Anterior pelvic resection</td>
<td>Irinotecan</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>52/M</td>
<td>Sigmoid colon cancer</td>
<td>Liver</td>
<td>No surgery</td>
<td>FOLFOX</td>
<td>135</td>
</tr>
<tr>
<td>3</td>
<td>72/M</td>
<td>Rectal cancer</td>
<td>Liver</td>
<td>Low anterior resection</td>
<td>Irinotecan</td>
<td>331</td>
</tr>
</tbody>
</table>

Figure 1. Computed tomography in Patient 1, showing pneumatosis intestinalis of the ascending and proximal transverse colon.
The pathogenesis of PI remains poorly understood, but it may be due to loss of mucosal integrity, increased intraluminal pressure and/or increased intraluminal gas production caused by bacterial overgrowth (5). Various predisposing factors have been reported associated with PI, including trauma, inflammatory and autoimmune disease, infections, and pulmonary and drug-induced diseases. Our patients had no known risk factors other than administration of chemotherapy.

We treated 485 colorectal cancer patients with cetuximab-containing chemotherapy during presentation of three PI cases. PI is a rare complication of chemotherapy and may be caused by agents such as 5-FU, cytarabine, docetaxel, irinotecan and etoposide. It may also be caused by molecularly targeted agents, which have become standards of care in many types of cancer. For example, PI has been associated with antiangiogenic agents, including bevacizumab or sunitinib (6, 7). Prior to this report, to the best of our knowledge, only one patient had been described as having PI after treatment with the EGFR inhibitor cetuximab; that patient was also treated with oxaliplatin, tegafur–uracil and LV (8). Two of our patients were treated with both irinotecan and cetuximab. Although PI in these patients may have been due to irinotecan, this was unlikely, inasmuch as retreatment of one patient with irinotecan alone did not induce a recurrence of PI. We have not yet identified any possible mechanism for cetuximab-induced PI.

Of note, all three patients were asymptomatic, with PI found incidentally during routine CT scanning for response evaluation. This finding suggests the need for careful clinical follow-up and a high level of suspicion of PI. Three distinct clinical PI subgroups have been described—mechanical disease, acute mesenteric ischemia and benign idiopathic—based on history, physical examination and laboratory and radiologic findings (9). Patients with benign PI tend to be asymptomatic and have fewer peritoneal signs than those with mechanical or ischemic PI. Moreover, the mortality rate was lower in the benign (5.2%) than in the mechanical (10.7%) and ischemic (56.5%) groups, although the laparotomy rate was lower in the benign group. In other words, PI especially that due to benign idiopathic causes can be successfully managed by conservative treatment. None of our three patients showed evidence of bowel ischemia or perforation. Moreover, following the cessation of chemotherapy and conservative treatment, PI in all three resolved without sequelae.

Interestingly all three of our patients received cetuximab biweekly. The currently approved cetuximab dosing regimen for patients with metastatic colorectal cancer consists of an initial dose of 400 mg/m², followed by 250 mg/m² weekly. However, weekly administration is not convenient for chemotherapy regimens, with biweekly administration of 500 mg/m² cetuximab being a more convenient alternative (10, 11). It is important to determine whether this dose and schedule is associated with the development of PI.

In conclusion, we describe here three patients with metastatic colorectal cancer who developed PI while on cetuximab-containing chemotherapy. A conservative, non-surgical treatment may be effective in patients without perforation or peritonitis.

**Conflict of interest statement**

None declared.

**References**


