

# Chemotherapy–Induced Colitis

Carlos H. Barcenas and Nuhad K. Ibrahim  
*University of Texas MD Anderson Cancer Center, Houston,  
 USA*

## 1. Introduction

Colitis is a very complex disease entity with several etiologic and pathogenesis characteristics. It may have acute or chronic forms that may be with significant morbidity and negative effect on the quality of life of the patient. While the most common and recognizable forms are those of infectious etiologies, however, other forms include ulcerative, Crohn's, immunologic, vascular, pseudo membranous, lymphocytic and collagenous types, to name some. Many different classes of pharmaceutical agents, including non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, statins, triptans, anti-viral agents, hormone replacement therapies, antidepressants, and antibiotics, are known to induce colitis.<sup>1-4</sup> Colitis is also a well documented side effect of chemotherapy. Chemotherapy-induced colitis may manifest in different clinical settings and have serious sequelae that may impact patient care and outcomes.

Over the past few decades, several novel cytotoxic agents have been found to cause significant gastrointestinal toxicity. The presentation and pathological characteristics of the colitis induced by these novel agents do not necessarily adhere to the traditional description of neutropenic enterocolitis. These newer forms of colitis include taxane-induced colitis<sup>5-10</sup> and anti-cytotoxic T-lymphocyte antigen-4 antibody immune-breakthrough enterocolitis.<sup>11-14</sup>

Description of colitis induced by other commonly used cytotoxic agents include reports of cases caused by vinorelbine,<sup>15</sup> capecitabine,<sup>16</sup> interferon,<sup>17</sup> bevacizumab,<sup>18,19</sup> rituximab,<sup>20</sup> dasatinib,<sup>21</sup> and topotecan.<sup>22-24</sup> Given the increasingly frequent use of chemotherapeutic agents capable of causing colitis, clinicians and oncologists should be knowledgeable of this complex condition and its various pathogeneses, risk factors, and prognoses to enhance patient care.

In this chapter we will review the clinical characteristics of the well-known and traditional neutropenic colitis; in addition, we will discuss the more recently described colitis induced by taxanes and by anti-CTLA-4 antibody.

## 2. Neutropenic enterocolitis

Neutropenic colitis is a well recognized entity, however, encountered among cancer patients undergoing chemotherapy treatment. It was the first form of chemotherapy-induced colitis

to be described in literature and is a well-known clinical syndrome. Mortality among patients with neutropenic enterocolitis, mainly due to sepsis and bowel perforation, has been reported at rates exceeding 50%.<sup>25, 26</sup> Early recognition of this condition may lead to lower mortality rates, but no prospective studies have explored this topic.

Neutropenic enterocolitis has been known by several names, including typhlitis (from the Greek *typhlon*),<sup>27</sup> neutropenic colitis, necrotizing enterocolitis, ileocecal syndrome, and cecitis.<sup>25, 28</sup> In 1962, neutropenic enterocolitis was described as “necrotizing enteropathy” in autopsy pathology findings of 65 leukemia patients and 7 lymphoma patients.<sup>29, 30</sup>

In 1970, Wagner et al<sup>27</sup> described the clinical characteristics and radiographic findings in a group of pediatric patients with advanced neutropenic enterocolitis identified using postmortem findings, and concluded that specific radiographic findings could suggest the diagnosis of typhlitis. Katz et al performed an updated postmortem review of 33 pediatric patients in 1990, and concluded that improved awareness of the signs and symptom of typhlitis, and the setting in which it occurs, may allow for early effective intervention.<sup>31</sup> Sloas et al<sup>32</sup> retrospectively identified 24 pediatric patients with neutropenic enterocolitis treated at a single institution over 30 years and found that the condition occurred more frequently in patients with acute leukemias, and also had the following conclusions: a) computed tomography (CT) scans and ultrasonography (US) were more sensitive for diagnosis than the plain radiography; b) the increase in the incidence of typhlitis may have been due to the wider availability of this imaging technology and to the increase in the intensity of the chemotherapeutic regimens; c) most patients responded to aggressive medical management, in contrast to prior case reports.

Neutropenic enterocolitis has also been reported in adult patients.<sup>33, 34</sup> The increase in number of reported adult cases was likely due to increased physician awareness and to increase in the use of more aggressive chemotherapy. Some authors suggested that surgical outcomes may be better in adults compared to pediatric patients.<sup>33, 34</sup> Otherwise the clinical presentation, radiographic findings and prognosis has been reported as similar in both adults and in pediatric cases.

Besides being primarily associated with acute leukemia, neutropenic enterocolitis has also been reported in patients with aplastic anemia, multiple myeloma, myelodysplastic syndromes, AIDS, cyclic neutropenia, and neutropenia induced by chemotherapy for solid tumors or stem cell transplants.<sup>25, 31, 35-39</sup>

A recent single-institution retrospective review of pediatric patients with neutropenic enterocolitis who had previously received intensive chemotherapy regimens revealed that cytarabine was associated with greater mortality compared to other chemotherapeutic agents.<sup>40</sup> Cytarabine is considered a prototype drug for the development of chemotherapy-induced neutropenic colitis as it is the most common agent associated with episodes of neutropenic enterocolitis reported in various studies.<sup>26, 41</sup>

## 2.1 Epidemiology

The true incidence of neutropenic enterocolitis is unknown. Based on autopsy reports, its incidence among children with leukemia has been reported as high as 46%.<sup>26,31</sup> After a

systematic review of the literature that included 21 studies, Gorschluter et al<sup>41</sup> calculated the pooled incidence rate of neutropenic enterocolitis among adult patients hospitalized for hematological malignancies, high-dose chemotherapy for solid tumors, or aplastic anemia to be 5.3% (95% confidence interval, 4.7%–5.9%), which was similar to the pooled incidence rate of a subgroup of patients with acute leukemias who were treated with myelosuppressive chemotherapy (5.6%; 95% confidence interval, 4.6%–6.9%).

Initial publications of neutropenic enterocolitis cases reported associated mortality rates of 40–50%.<sup>41</sup> A more recent publication reported a mortality rate of 37.5%.<sup>42</sup> However, one publication reported a mortality rate of 11.7% among pediatric patients.<sup>40</sup> Earlier recognition of this condition and improvement in its management may have lowered the mortality rates associated with neutropenic enterocolitis over the years; however, large series on this subject are lacking.

## 2.2 Pathogenesis

The pathogenesis of neutropenic enterocolitis remains unclear but may involve several factors including mucosal injury by direct chemotherapy toxicity or leukemic infiltration; severe neutropenia; and/or a weakened host defense to intestinal microorganisms.<sup>25,36</sup> Leukemic infiltrates may rarely be implicated, however.<sup>31</sup> Neutropenia and infection are essential causative factors. Bacteria may invade the bowel wall—a process that neutropenia may facilitate—and bacterial endotoxins may infiltrate the bowel, resulting in bacteremia, sepsis, necrosis, and hemorrhage. Anatomically, neutropenic enterocolitis almost always affects the cecum, possibly because of the cecal dispensability and its low blood supply, but can extend to the ascending, transverse, descending, and/or sigmoid colon, as well as the terminal ileum.<sup>31</sup> Pathology specimens may show mucosal edema, mucosal loss, intramural edema, bowel wall thickening (BWT), ulcerations, focal hemorrhage, and/or transmural necrosis. Surgical specimens may contain multiple microorganisms, including gram-negative rods, gram-positive cocci, anaerobes, enterococci, *Candida*, and/or cytomegalovirus.<sup>25, 31, 32</sup> Polymicrobial infection is possible.

Several cytotoxic therapies have been associated with neutropenic enterocolitis. In the earliest case reports of neutropenic enterocolitis, the condition was associated with cytotoxic agents used to treat leukemias and lymphomas, such as cytarabine, vincristine, doxorubicin, methotrexate, cyclophosphamide, etoposide, and prednisone.<sup>25,26,31,32</sup> Later studies implicated other agents used to treat solid tumors, such as vinorelbine, taxanes, carboplatin, cisplatin, gemcitabine and fluorouracil.<sup>25,38,43-48</sup> Avigan et al<sup>49</sup> reported neutropenic enterocolitis in 2 patients who underwent autologous stem cell transplant for solid tumors.

## 2.3 Clinical presentation

The onset of neutropenic enterocolitis symptoms usually occurs 10–14 days after the initiation of chemotherapy, when the neutropenia is at its nadir and the patient becomes febrile.<sup>25</sup> Neutropenic enterocolitis should be suspected in any patient with profound neutropenia (absolute neutrophil count <500 neutrophils/ $\mu$ l), fever, and right lower quadrant abdominal pain. Nausea, vomiting, abdominal distention, and watery or bloody diarrhea may also be present.<sup>26,31,50,51</sup> An acute surgical abdomen with peritoneal signs and septic shock may suggest bowel perforation.

## 2.4 Diagnosis

Currently, there is no consensus on standardized diagnostic criteria for neutropenic enterocolitis. A recently published diagnostic criteria for neutropenic enterocolitis was proposed by Gorschluter et al<sup>41</sup>:

- Presence of fever (axillary temperature  $>38.0^{\circ}\text{C}$  or rectal temperature  $>38.5^{\circ}\text{C}$ )
- Abdominal pain (self reported as grade 3 or more using a visual analogous pain score ranging from 1 to 10)
- US or CT demonstration of BWT of  $>4$  mm (transverse scan) over  $>30$  mm (longitudinal scan) in any segment

Pathologic examination of the cecum or affected area would be considered the gold standard but is not practical as colonoscopy and colonic biopsy are generally contraindicated because of the increased risk of bowel perforation, intraabdominal infection, and (especially in thrombocytopenic patients) bleeding.

Imaging studies are recommended to support the clinical diagnosis. Abdominal CT scan (without oral contrast) tends to be preferred over plain abdominal films because CT scan seems to have a lower false-negative rate of diagnosis and is better able to differentiate neutropenic enterocolitis from acute appendicitis or appendiceal abscess.<sup>32</sup> However, CT scan cannot be performed easily in severely ill patients. Therefore, ultrasonography may complement CT or replace it as the diagnostic modality of choice in select patients. In one prospective study, US revealed BWT of  $>4$  mm in all 4 patients with neutropenic colitis and in 1 patient with mucositis, leading the authors to conclude that BWT of  $>4$  mm is a good discriminator to make a clinical diagnosis of neutropenic enterocolitis.<sup>52</sup>

Radiological findings suggestive of neutropenic enterocolitis include BWT, a dilated and fluid-filled cecum, diffuse cecal wall thickening, an inflammatory mass in the right-lower quadrant, pericecal fluid, and inflammatory changes in the pericecal soft tissues.<sup>25,32</sup> Plain films may be normal or show nonspecific findings and occasionally reveal a fluid-filled, distended cecum with dilated adjacent small bowel loops, thumb printing, or localized pneumatosis intestinalis.<sup>26</sup> Barium enemas are usually contraindicated, as they could lead to bowel perforation.

Using an US-measured BWT of  $>5$  mm as the cutoff point for diagnosis, Cartoni et al<sup>53</sup> demonstrated that patients with a positive US had a significantly longer mean duration of symptoms (7.9 days vs. 3.8 days) and a higher mortality rate (29% vs. 0%) than patients with a negative US. Furthermore, among patients with a positive US, the mortality rate among patients with a BWT of  $>10$  mm (60%) was significantly higher than the mortality rate among patients with a BWT of  $\leq 10$  mm (4.2%).

However, BWT may not be specific for neutropenic enterocolitis alone. For example, a retrospective review of abdominal CT findings in 76 neutropenic patients revealed that BWT was most common in patients with *C. difficile* colitis, whereas the primary finding in patients with neutropenic enterocolitis and bowel ischemia was pneumatosis.<sup>54</sup> The specific use of BWT to diagnose neutropenic enterocolitis is thus a matter of debate, and a prospective validation study is needed.

## 2.5 Treatment

There is no standardized treatment guideline for neutropenic enterocolitis because of a lack of prospective randomized trials. Treatment decisions for patients with neutropenic enterocolitis are therefore based on descriptive or retrospective studies and clinical experts' opinions. A conservative treatment approach consisting of a combination of blood products support, broad-spectrum antibiotics, and bowel rest achieved by intravenous fluids and total parenteral nutrition has been recommended for patients who present without complications such as peritonitis, perforation, or massive bleeding.<sup>55,56</sup> Antibiotic coverage for *C. difficile* infection should be added if this infection has not been ruled out.<sup>32</sup> Antifungal treatment should also be considered, as per the guidelines for the management of neutropenic fever. Granulocyte colony-stimulating factor (G-CSF) may also be used to accelerate recovery from neutropenia.<sup>25,26,47,57</sup> Although case report series have reported the benefit of granulocyte transfusions,<sup>58</sup> such therapy is not recommended by consensus. Anticholinergic, anti-diarrheal, and opioid agents should be avoided because they may worsen ileus.

In 1979, Varki et al<sup>59</sup> reported a case of severe neutropenic enterocolitis in which early clinical recognition and surgical intervention resulted in survival advantage. Surgical intervention is recommended for patients with refractory gastrointestinal bleeding (after correcting cytopenias or coagulopathy), peritonitis, bowel perforation and patients who continue to deteriorate despite medical management.<sup>25,26</sup> The standard surgical approach is a 2-stage right hemicolectomy,<sup>25</sup> as neutropenia may impede primary bowel anastomoses.<sup>60</sup>

Because the likelihood of developing a second episode of neutropenic enterocolitis during a subsequent cycle of chemotherapy is notable, patients should be allowed to completely recover from an episode of neutropenic enterocolitis before subsequent chemotherapy is administered.<sup>25</sup>

## 3. Taxane-induced (ischemic) Colitis

Taxane-induced colitis is a recognized and a distinguished entity of the classically recognized neutropenic colitis or typhlitis. As its name suggest, patients with neutropenic colitis are neutropenic and commonly febrile, occurring at about 2 weeks of the administration of chemotherapy; on the otherhand, taxane- induced colitis occurs at a shorter interval, and is not necessarily associated with neutropenia or fever. Lower abdominal pain with or without diarrhea or blood per rectum should alert the physician to its occurrence.

In 2000, our group reported 6 patients with docetaxel-associated ischemic colitis.<sup>5</sup> Because of the early onset of symptoms, these patients did not fit the classic picture of neutropenic enterocolitis; besides, not all these patients were neutropenic or febrile, the cardinal features of neutropenic enterocolitis. Three patients had received docetaxel in combination with vinorelbine in a phase I trial. The other 3 patients were identified during a scheduled review of toxic effects in subjects enrolled in clinical trials receiving docetaxel: one of the patients received docetaxel as single agent, another patient received it in combination with pamidronate and the last one received it in combination with cyclophosphamide. Other studies have also noted as well the association of taxane-induced colitis with docetaxel with or without its combination with vinorelbine, another antitubulin agent.<sup>6</sup> There have been

several case reports of patients who developed ischemic colitis and had a normal or high white blood cell counts after receiving paclitaxel<sup>7, 8</sup> or nab-paclitaxel (Dr. Nuhad Ibrahim, personal communication).

Of the 1,350 breast cancer patients who received taxane-based chemotherapy at MD Anderson Cancer Center between 1997 and 1999, 14 were diagnosed with colitis.<sup>9</sup> Of the 520 patients who received docetaxel, 10 patients (1.9%) developed colitis, and of the 830 patients who received paclitaxel, 4 patients (0.5%) developed colitis. The clinical data of these 14 patients were used to describe the characteristics of taxane-induced colitis. Colitis recurred in 2 patients who were re-challenged with the same taxane and at the same dose-schedule. CT scan findings typically showed diffuse or localized thickening of the colonic wall and revealed pneumoperitoneum in 1 patient. Colonoscopy confirmed ischemic colitis in 2 patients. Blood cultures were positive for coagulase-negative *Staphylococcus* in 3 (20%) of the colitis events, in addition to *Stenotrophomonas maltophilia* in 1 of these events. All patients had negative *C. difficile* titers. All patients who developed colitis received supportive care with intravenous fluids and broad-spectrum antibiotics. One patient died of septic shock. Two patients underwent hemicolectomy, the pathology of which revealed bowel perforation secondary to transmural necrosis.

### 3.1 Pathogenesis

The mechanism of taxane-induced colitis is unknown. Bowel necrosis or perforation may be a direct effect of the drug's rendering microtubule bundles nonfunctional, resulting in transient mitotic arrest. Paclitaxel is also known to have antiangiogenic activity and can induce apoptosis, which could account for the necrosis observed in biopsy samples of affected bowel; however, this has not been validated.<sup>9, 10</sup>

### 3.2 Clinical presentation and diagnosis

The diagnosis of taxane-induced colitis is based on the presence of acute, usually supra pubic abdominal pain with or without neutropenia, fever, diarrhea, or hematochezia. While blood cultures may or not be positive, *C. difficile* titers are always negative. Taxane-induced colitis tends to occur early in the course of the chemotherapy, with a reported median onset of 6 days after the start of a taxane administered every 3 weeks. Colitis onset occurs within 72 hours when the taxane is given weekly, however (Not published data, DR Nuhad Ibrahim).

The radiographic findings of taxane-induced colitis are not specific. CT scan of abdomen and pelvis may reveal involvement of any segment of the bowel or pan colitis as well as BWT, peritoneal stranding, and/or ascites.<sup>10</sup> The cecum may not be involved, as is almost always the case in patients with neutropenic enterocolitis. Histological analysis of a biopsied sample typically reveals ischemic features. Colonoscopy is not recommended because of the risk of bowel perforation.

### 3.3 Treatment

Aggressive supportive care with intravenous fluids, broad-spectrum antibiotics, and close surgical monitoring until the symptoms have resolved is recommended. Because taxane-

induced colitis seems to be dose-related, the taxane dose should be reduced or discontinued to prevent a recurrence.

#### **4. Anti-cytotoxic T-lymphocyte antigen-4 antibody–induced enterocolitis**

One novel method of treating cancer is using monoclonal antibodies to target molecules that enhance antitumor immunity. One such molecule, cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a T-cell receptor whose primary role is to down regulate T-cell activation, which results in immune-tolerance to self-antigens and prevents damage to normal host tissue.<sup>61</sup> Preclinical data have shown that CTLA-4 antibodies induce antitumor activity. Anti-CTLA-4 therapy indirectly targets tumor cells by activating the immune system against the tumor.<sup>62</sup> Two human monoclonal antibodies against CTLA-4 have been developed: ipilimumab, which was recently approved by the U.S. Food and Drug Administration for the treatment of metastatic melanoma, and tremelimumab.<sup>63</sup>

##### **4.1 Pathogenesis**

Clinical trials of anti-CTLA-4 therapy have revealed a relationship between tumor response and immune-related adverse events, suggesting that the anti-CTLA-4 antibody's mechanism of antitumor action may also affect the normal tissue and explain why this therapy is associated with a spectrum of side effects, including enterocolitis.<sup>12,13</sup> Several mechanisms by which the CTLA-4 blockade exerts its antitumor activity have been proposed: anti-CTLA-4 agents may block CD4<sup>+</sup> and CD25<sup>+</sup> regulatory T cells, which normally suppress the function and proliferation of tumor-specific CD4<sup>+</sup> and CD8<sup>+</sup> effector T cells and natural killer cells; or the CTLA-4 blockade may enable the proliferation and enhance the function of effector CD4<sup>+</sup> and CD8<sup>+</sup> cells, thereby inducing antibody responses; or anti-CTLA-4 antibodies may also cause direct cytotoxicity by directly binding to tumor cells that constitutively express CTLA-4.<sup>14, 62</sup>

The reported safety profiles of CTLA-4 blockade in melanoma patients and in patients with other cancers such as lung, prostate, and renal cancer are similar, which suggests the therapy has class-specific toxicity. The immune-related adverse events in patients receiving anti-CTLA-4 therapy are thought to be the result of nonspecific or cross-reactive tissue damage caused by activated T cells.<sup>13</sup>

Others have suggested that intestinal micro flora and bacterial antigens may be contributing factors to the enterocolitis seen in patients with graft-versus-host disease.<sup>64</sup> This type of enterocolitis may have a similar pathogenesis to the enterocolitis associated with anti-CTLA-4 antibodies. Future clinical research should evaluate the role of prophylactic antibiotics in this entity.

Studies have found an association between enterocolitis and objective tumor regression in melanoma patients and renal cell carcinoma patients, suggesting that enterocolitis could be a surrogate marker of drug efficacy.<sup>11</sup>

##### **4.2 Clinical presentation**

The most common grade 3 or 4 adverse events reported in clinical trials of anti-CTLA-4 therapy are enterocolitis, dermatitis, hepatitis, hypophysitis, and uveitis. The most frequent

gastrointestinal adverse event in patients with anti-CTLA-4 antibody-induced immune-breakthrough enterocolitis is diarrhea.

Beck et al<sup>11</sup> found that of 198 patients with metastatic melanoma or renal cell carcinoma that were treated with ipilimumab, 41 patients (21%) had been diagnosed with enterocolitis. The hallmark symptom was diarrhea, which occurred in 40 patients (98%) and whose occurrence ranged from 3 soft stools per day to 20 watery stools daily. Other presenting symptoms included abdominal pain (20%), nausea/vomiting (15%), fever (12%), anal pain (10%), rectal bleeding (2%), and constipation (2%). The median time from the last dose of ipilimumab to the onset of symptoms was 11 days (range, 0–59 days), and there was no predictable pattern of symptomology.

Other studies have reported that diarrhea occurs in up to 44% of patients treated with ipilimumab, with grade 2 or worse diarrhea occurring in about 35% of patients and grade 3 or 4 diarrhea occurring in around 18% of patients.<sup>14</sup> One study reported a median time to diarrhea onset of 14 days (range, 5–36 days).<sup>13</sup> Generally, patients have watery or loose diarrhea that occurs 4–8 times a day without blood, fever, nausea, vomiting, or weight loss. Some patients may have abdominal pain.

### 4.3 Diagnosis

This clinical entity should be suspected in patients receiving a CTLA-4 antibody who develop diarrhea, and in whom other causes of diarrhea have been ruled out. Infectious diarrhea, such as that caused by parasites or *C. difficile*, should be excluded. Beck et al<sup>11</sup> considered patients to have enterocolitis if they had biopsy findings showing enterocolitis or had sudden-onset diarrhea with no alternative etiology, which lessened or resolved with steroids. Macroscopic findings include erythema, edema, friability, and erosions.<sup>13</sup> Histopathological analysis typically reveals neutrophilic inflammation (46% of patients), lymphocytic inflammation (15% of patients), or a combination of neutrophilic and lymphocytic inflammation (38% of patients).<sup>11</sup>

### 4.4 Treatment

The management of anti-CTLA-4 antibody-induced immune-breakthrough enterocolitis is based on the severity of the diarrhea. Guidelines and treatment algorithms have been published.<sup>12,14</sup> Patients who develop grade 1 diarrhea should receive symptomatic treatment and supportive care. In patients with grade 2 diarrhea, stool studies and colonoscopy can be used to determine whether enterocolitis is present; once the condition is confirmed, treatment is initiated with oral budesonide or prednisone tapering over a minimum of 4 weeks. Patients with grade 3 or 4 diarrhea should be given high-dose steroids such as intravenous methylprednisolone (2 mg/kg) once or twice a day with a minimum taper of 4 weeks. Patients whose enterocolitis is steroid-refractory should be given infliximab.<sup>65</sup> Patients on long-term immunosuppressive therapy should be given prophylactic antimicrobials. Patients receiving anti-CTLA-4 antibody should be educated about immune-related adverse events, which can occur at any time during therapy and require timely treatment.<sup>13</sup>



	<b>Neutropenic Enterocolitis</b>	<b>Ischemic Colitis</b>	<b>Anti-CTLA4 Antibody Enterocolitis</b>
Incidence, %	5.3 <sup>a</sup>	1.03 <sup>b</sup>	21, <sup>c</sup> 44 <sup>d</sup>
Chemotherapy	Various	Taxanes	Ipilimumab Tremelimumab
Symptoms	Neutropenia, fever, and RLQ abdominal pain	Lower (suprapubic) abdominal pain with or without diarrhea or hematochezia and the absence of <i>C. difficile</i> . Fever and neutropenia are not sufficient but not necessary features.	Diarrhea (watery or loose, without blood) occurring 4–8 times a day without fever, nausea, vomiting, or weight loss. Some patients have abdominal pain.
Median time to symptom onset, days (range)	12 (10–14) <sup>e</sup>	6 (3–8)	11 (0–59)
Diagnosis	Clinical presentation and radiologic finding.	Clinical presentation and radiologic findings. Ischemic colitis is the hallmark pathologic finding.	Clinical presentation. Histopathology evaluation may reveal neutrophilic and/or lymphocytic inflammation.
Radiologic findings	Cecal involvement is necessary and/or sufficient; additional colonic segments, pan-colonic, or distal ileum may be involved. US or CT may reveal bowel wall thickening > 4 mm (transverse scan) over more than 30 mm (longitudinal scan) in any.	Not specific. Any segment of the bowel may be involved; disease may be pan-colonic. Cecal involvement may be sufficient but not necessary. CT scan may reveal bowel wall thickening, peritoneal stranding, or ascites	Not specific

Treatment	Conservative management includes bowel rest, IV fluids, antibiotics, and G-CSF. Surgical intervention is reserved for patients with peritonitis, bowel perforation, or massive bleeding.	Supportive care with IV fluids, antibiotics, and close surgical monitoring.	Symptomatic treatment, steroids, or infliximab, depending on the severity of the symptom
-----------	--	---	--

CTLA 4, cytotoxic T-lymphocyte antigen 4; RLQ, right lower quadrant; CT, computed tomography; US, ultrasonography; IV, intravenous; G-CSF, granulocyte-colony stimulating factor.

<sup>a</sup> Gorschluter M, Mey U, Strehl J, et al, Eur J Haematol 2005

<sup>b</sup> Li Z, Ibrahim NK, Wathen JK, et al, Cancer 2004

<sup>c</sup> Beck KE, Blansfield JA, Tran KQ, et al, J Clin Oncol 2006

<sup>d</sup> Kaehler KC, Piel S, Livingstone E, et al, Semin Oncol 2010

<sup>e</sup> Davila ML, Curr Opin Gastroenterol 2006

Table 1. Comparison of characteristics of three types of chemotherapy-induced colitis

## 5. Conclusion

Chemotherapy-induced colitis is a significant complication of multiple chemotherapeutic agents. Its occurrence adds not only to the morbidity of the patient, but also may impact the treatment choices of the patient's cancer management. Early recognition may help the patient avoid grave consequences including death related to its severity. It is therefore essential that it is recognized in its different forms and the various drugs it may be associated with. It remains an uncommon event, however, but early appraisal of the presenting symptom complex in the context of chemotherapy administration is prudent.

## 6. References

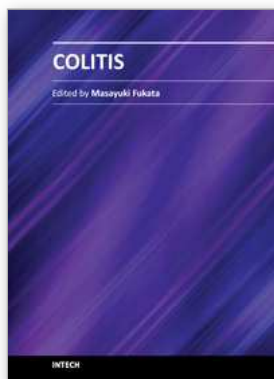
- [1] Cappell MS: Colonic toxicity of administered drugs and chemicals. Am J Gastroenterol 99:1175-90, 2004
- [2] Schwartz DC, Smith DJ: Colonic ischemia associated with naratriptan use. J Clin Gastroenterol 38:790-2, 2004
- [3] Westgeest HM, Akol H, Schreuder TC: Pure naratriptan-induced ischemic colitis: a case report. Turk J Gastroenterol 21:42-4, 2010
- [4] Zervoudis S, Grammatopoulos T, Iatrakis G, et al: Ischemic colitis in postmenopausal women taking hormone replacement therapy. Gynecol Endocrinol 24:257-60, 2008
- [5] Ibrahim NK, Sahin AA, Dubrow RA, et al: Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. Lancet 355:281-3, 2000
- [6] Kreis W, Petrylak D, Savarese D, et al: Colitis and docetaxel-based chemotherapy. Lancet 355:2164, 2000
- [7] Daniele B, Rossi GB, Losito S, et al: Ischemic colitis associated with paclitaxel. J Clin Gastroenterol 33:159-60, 2001

- [8] Tashiro M, Yoshikawa I, Kume K, et al: Ischemic colitis associated with paclitaxel and carboplatin chemotherapy. *Am J Gastroenterol* 98:231-2, 2003
- [9] Li Z, Ibrahim NK, Wathen JK, et al: Colitis in patients with breast carcinoma treated with taxane-based chemotherapy. *Cancer* 101:1508-13, 2004
- [10] Kaur H, Loyer EM, David CL, et al: Radiologic findings in taxane induced colitis. *Eur J Radiol* 66:75-8, 2008
- [11] Beck KE, Blansfield JA, Tran KQ, et al: Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 24:2283-9, 2006
- [12] Weber J: Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist* 12:864-72, 2007
- [13] Di Giacomo AM, Biagioli M, Maio M: The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Semin Oncol* 37:499-507, 2010
- [14] Kaehler KC, Piel S, Livingstone E, et al: Update on immunologic therapy with anti-CTLA-4 antibodies in melanoma: identification of clinical and biological response patterns, immune-related adverse events, and their management. *Semin Oncol* 37:485-98, 2010
- [15] Olithselvan A, Gorard DA: Vinorelbine and ischaemic colitis. *Clin Oncol (R Coll Radiol)* 15:166-7, 2003
- [16] Alexandrescu DT, Dutcher JP, Wiernik PH: Capecitabine-induced pancolitis. *Int J Colorectal Dis* 22:455, 2007
- [17] Wenner WJ, Jr., Piccoli DA: Colitis associated with alpha interferon? *J Clin Gastroenterol* 25:398-9, 1997
- [18] Schellhaas E, Loddenkemper C, Schmittel A, et al: Bowel perforation in non-small cell lung cancer after bevacizumab therapy. *Invest New Drugs* 27:184-7, 2009
- [19] Lecarpentier E, Ouaffi L, Mir O, et al: Bevacizumab-induced small bowel perforation in a patient with breast cancer without intraabdominal metastases. *Invest New Drugs*, 2010
- [20] Ardelean DS, Gonska T, Wires S, et al: Severe ulcerative colitis after rituximab therapy. *Pediatrics* 126:e243-6, 2010
- [21] Shimokaze T, Mitsui T, Takeda H, et al: Severe hemorrhagic colitis caused by dasatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 26:448-53, 2009
- [22] Sears S, McNally P, Bachinski MS, et al: Irinotecan (CPT-11) induced colitis: report of a case and review of Food and Drug Administration MEDWATCH reporting. *Gastrointest Endosc* 50:841-4, 1999
- [23] Sandmeier D, Chaubert P, Bouzourene H: Irinotecan-induced colitis. *Int J Surg Pathol* 13:215-8, 2005
- [24] Takaoka E, Kawai K, Ando S, et al: Neutropenic colitis during standard dose combination chemotherapy with nedaplatin and irinotecan for testicular cancer. *Jpn J Clin Oncol* 36:60-3, 2006
- [25] Davila ML: Neutropenic enterocolitis. *Curr Opin Gastroenterol* 22:44-7, 2006
- [26] Wade DS, Nava HR, Douglass HO, Jr.: Neutropenic enterocolitis. Clinical diagnosis and treatment. *Cancer* 69:17-23, 1992

- [27] Wagner ML, Rosenberg HS, Fernbach DJ, et al: Typhlitis: a complication of leukemia in childhood. *Am J Roentgenol Radium Ther Nucl Med* 109:341-50, 1970
- [28] Williams N, Scott AD: Neutropenic colitis: a continuing surgical challenge. *Br J Surg* 84:1200-5, 1997
- [29] Amromin GD, Solomon RD: Necrotizing enteropathy: a complication of treated leukemia or lymphoma patients. *JAMA* 182:23-9, 1962
- [30] Gildenhorn HL, Springer EB, Amromin GD: Necrotizing enteropathy: roentgenographic features. *Am J Roentgenol Radium Ther Nucl Med* 88:942-52, 1962
- [31] Katz JA, Wagner ML, Gresik MV, et al: Typhlitis. An 18-year experience and postmortem review. *Cancer* 65:1041-7, 1990
- [32] Sloas MM, Flynn PM, Kaste SC, et al: Typhlitis in children with cancer: a 30-year experience. *Clin Infect Dis* 17:484-90, 1993
- [33] Ikard RW: Neutropenic typhlitis in adults. *Arch Surg* 116:943-5, 1981
- [34] Alt B, Glass NR, Sollinger H: Neutropenic enterocolitis in adults. Review of the literature and assessment of surgical intervention. *Am J Surg* 149:405-8, 1985
- [35] Pokorney BH, Jones JM, Shaikh BS, et al: Typhlitis. A treatable cause of recurrent septicemia. *JAMA* 243:682-3, 1980
- [36] Urbach DR, Rotstein OD: Typhlitis. *Can J Surg* 42:415-9, 1999
- [37] Quigley MM, Bethel K, Nowacki M, et al: Neutropenic enterocolitis: a rare presenting complication of acute leukemia. *Am J Hematol* 66:213-9, 2001
- [38] Cunningham SC, Fakhry K, Bass BL, et al: Neutropenic enterocolitis in adults: case series and review of the literature. *Dig Dis Sci* 50:215-20, 2005
- [39] Bremer CT, Monahan BP: Necrotizing enterocolitis in neutropenia and chemotherapy: a clinical update and old lessons relearned. *Curr Gastroenterol Rep* 8:333-41, 2006
- [40] Rizzatti M, Brandalise SR, de Azevedo AC, et al: Neutropenic enterocolitis in children and young adults with cancer: prognostic value of clinical and image findings. *Pediatr Hematol Oncol* 27:462-70, 2010
- [41] Gorschluter M, Mey U, Strehl J, et al: Neutropenic enterocolitis in adults: systematic analysis of evidence quality. *Eur J Haematol* 75:1-13, 2005
- [42] Dorantes-Diaz D, Garza-Sanchez J, Cancino-Lopez JA, et al: [Prevalence of neutropenic enterocolitis in adults with severe neutropenia and associated mortality.]. *Rev Gastroenterol Mex* 74:224-9, 2009
- [43] Furonaka M, Miyazaki M, Nakajima M, et al: Neutropenic enterocolitis in lung cancer: a report of two cases and a review of the literature. *Intern Med* 44:467-70, 2005
- [44] D'Amato G, Rocha Lima C, Mahany JJ, et al: Neutropenic enterocolitis (typhlitis) associated with docetaxel therapy in a patient with non-small-cell lung cancer: case report and review of literature. *Lung Cancer* 44:381-90, 2004
- [45] Gadducci A, Gargini A, Palla E, et al: Neutropenic enterocolitis in an advanced epithelial ovarian cancer patient treated with paclitaxel/platinum-based chemotherapy: a case report and review of the literature. *Anticancer Res* 25:2509-13, 2005
- [46] Ferrazzi E, Toso S, Zanotti M, et al: Typhlitis (neutropenic enterocolitis) after a single dose of vinorelbine. *Cancer Chemother Pharmacol* 47:277-9, 2001

- [47] Kouroussis C, Samonis G, Androulakis N, et al: Successful conservative treatment of neutropenic enterocolitis complicating taxane-based chemotherapy: a report of five cases. *Am J Clin Oncol* 23:309-13, 2000
- [48] Cardenal F, Montes A, Llort G, et al: Typhlitis associated with docetaxel treatment. *J Natl Cancer Inst* 88:1078-9, 1996
- [49] Avigan D, Richardson P, Elias A, et al: Neutropenic enterocolitis as a complication of high dose chemotherapy with stem cell rescue in patients with solid tumors: a case series with a review of the literature. *Cancer* 83:409-14, 1998
- [50] Cloutier RL: Neutropenic enterocolitis. *Hematol Oncol Clin North Am* 24:577-84, 2010
- [51] Aksoy DY, Tanriover MD, Uzun O, et al: Diarrhea in neutropenic patients: a prospective cohort study with emphasis on neutropenic enterocolitis. *Ann Oncol* 18:183-9, 2007
- [52] Gorschluter M, Marklein G, Hofling K, et al: Abdominal infections in patients with acute leukaemia: a prospective study applying ultrasonography and microbiology. *Br J Haematol* 117:351-8, 2002
- [53] Cartoni C, Dragoni F, Micozzi A, et al: Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. *J Clin Oncol* 19:756-61, 2001
- [54] Kirkpatrick ID, Greenberg HM: Gastrointestinal complications in the neutropenic patient: characterization and differentiation with abdominal CT. *Radiology* 226:668-74, 2003
- [55] Davila ML: Neutropenic enterocolitis. *Curr Treat Options Gastroenterol* 9:249-55, 2006
- [56] Davila ML: Neutropenic enterocolitis: current issues in diagnosis and management. *Curr Infect Dis Rep* 9:116-20, 2007
- [57] Pestalozzi BC, Sotos GA, Choyke PL, et al: Typhlitis resulting from treatment with taxol and doxorubicin in patients with metastatic breast cancer. *Cancer* 71:1797-800, 1993
- [58] O'Brien S, Kantarjian HM, Anaissie E, et al: Successful medical management of neutropenic enterocolitis in adults with acute leukemia. *South Med J* 80:1233-5, 1987
- [59] Varki AP, Armitage JO, Feagler JR: Typhlitis in acute leukemia: successful treatment by early surgical intervention. *Cancer* 43:695-7, 1979
- [60] Glenn J, Funkhouser WK, Schneider PS: Acute illnesses necessitating urgent abdominal surgery in neutropenic cancer patients: description of 14 cases and review of the literature. *Surgery* 105:778-89, 1989
- [61] Liu Z, Geboes K, Hellings P, et al: B7 interactions with CD28 and CTLA-4 control tolerance or induction of mucosal inflammation in chronic experimental colitis. *J Immunol* 167:1830-8, 2001
- [62] Fong L, Small EJ: Anti-cytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. *J Clin Oncol* 26:5275-83, 2008
- [63] Ribas A, Hanson DC, Noe DA, et al: Tremelimumab (CP-675,206), a cytotoxic T lymphocyte associated antigen 4 blocking monoclonal antibody in clinical development for patients with cancer. *Oncologist* 12:873-83, 2007

- [64] Beelen DW, Elmaagacli A, Muller KD, et al: Influence of intestinal bacterial decontamination using metronidazole and ciprofloxacin or ciprofloxacin alone on the development of acute graft-versus-host disease after marrow transplantation in patients with hematologic malignancies: final results and long-term follow-up of an open-label prospective randomized trial. *Blood* 93:3267-75, 1999
- [65] Minor DR, Chin K, Kashani-Sabet M: Infliximab in the treatment of anti-CTLA4 antibody (ipilimumab) induced immune-related colitis. *Cancer Biother Radiopharm* 24:321-5, 2009



## **Colitis**

Edited by Dr Fukata

ISBN 978-953-307-799-4

Hard cover, 196 pages

**Publisher** InTech

**Published online** 05, January, 2012

**Published in print edition** January, 2012

Inflammation of the colon is collectively called "Colitis". Since a variety of conditions may cause colitis and its manifestations are similar among the causes, selection of the right treatment based on the correct diagnosis is important in the management of this group of illnesses. Over the last few decades, a major shift has been observed in the clinical attention to the pathogenesis of colitis from infectious to idiopathic inflammatory bowel diseases. Colitis cases that are associated with chemical therapeutics and specific pathogens such as amoeba, have become prominent in hospitalized individuals and immune deficient patients, respectively. In addition, a great deal of progress has been made in colitis research triggering the need for updating our knowledge about colitis. This book Colitis provides comprehensive information on the pathogenesis, mechanism of resolution, and treatment strategies of colitis.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Carlos H. Barcenas and Nuhad K. Ibrahim (2012). Chemotherapy–Induced Colitis, Colitis, Dr Fukata (Ed.), ISBN: 978-953-307-799-4, InTech, Available from: <http://www.intechopen.com/books/colitis/chemotherapy-induced-colitis>

**INTech**  
open science | open minds

#### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

#### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.