Key Concepts

- Microscopic colitis is likely an underappreciated diagnosis. Although there is no “cure,” the quality of life for a patient can be improved significantly with treatment which is typically medical and rarely surgical.
- Budesonide is the only evidence-based treatment for microscopic colitis.
- Radiation colitis and proctitis spans a time course that ranges from acute to chronic which require different management strategies. Patients can present with problems even after 30 years of being asymptomatic.
- Colorectal cancer risk is increased with pelvic radiation and patients should be screened 5 years after completion of therapy.
- Surgical treatment for radiation proctitis/colitis should be individualized and based on the clinical context of the patient as morbidity and mortality rates are high postoperatively.
- Ischemic colitis represents the most common cause of gastrointestinal ischemia. The clinical picture has a wide spectrum ranging from mild cases with minimal mucosal ischemia to severe cases associated with transmural necrosis. Management and investigations need to be tailored depending on the clinical scenario encountered and patients require close vigilance by the surgeon.

Radiation Colitis

Introduction

An understanding of radiation injury to the colon and anorectal area is important for a coloproctologist. It is estimated that approximately 50% of treatment protocols for cancer involve the use of radiation [1]. With malignancies such as anal cancer increasing, and a higher number of cancer survivors, the colorectal surgeon will continue to encounter post-radiation problems. The areas covered in this section consist of (1) pathogenesis, (2) prevention, (3) presentation, and (4) treatment. An important aspect to keep in mind while reading this section is the lack of high-quality evidence; an attempt has been made to provide the reader with recommendations based on the best evidence available.

Pathogenesis of Radiation Injury

The two main forms of radiation delivery are external beam radiation therapy (EBRT) and brachytherapy [2]. External beam is what we encounter most and is delivered via linear accelerators which produce high-energy X-rays. The planning is typically done in three dimensions with CT (computed tomography) images. Gray (Gy) is the standard unit to indicate the amount of absorbed radiation. Fractionation refers to giving the total dose over multiple sessions—for example, 50 Gray of radiation could be given over 25 sessions with 2 Gy per session. Fractionation is done to minimize collateral tissue damage while maximizing tumor destruction. Conformal radiation refers to the use of metal plates (multileaf collimators) to bend the X-rays in order to target the tumor and minimize radiation to normal tissue.

Brachytherapy refers to placement of the radiation source inside the body—i.e., beads or pellets.

Radiation damage has been described through the “target cell” theory. This theory focused on the epithelium of the bowel and explained acute effects through the damage done to this layer which is rapidly proliferating. The delayed effects were explained by damage of other target cells such as endothelial cells or fibroblasts as their turnover is slower compared to intestinal epithelium. The main addition to this thinking is that other tissues/cells are part of the injury process [3]. Therefore, alterations to the gut microflora, immune system, microvasculature, and immune system are all thought to play a role in the symptoms induced by radiation [3].
When radiation is used in the treatment of abdominal or pelvic malignancies, the colon and rectum are sometimes included in the field of radiation. As a result, injury can occur. As with other treatments, there are patient and “radiation” factors that can influence outcomes.

Patient factors include Body Mass Index (BMI) with a higher BMI being protective. Smoking is a significant factor for worsening radiation-associated bowel complications [4], yet another reason to offer these patients a smoking cessation program. Additionally, previous surgery (fixing pieces of bowel in place—likely more relevant for small bowel injury), inflammatory bowel disease, diabetes, vascular and collagen vascular disease [3, 5, 6], and genetic predisposition are all predisposing factors [2].

The most important radiation factor is the dose. Other factors that play a role are the length of bowel radiated, fractionation, and use of chemotherapy [3].

Radiation effects can be considered acute or chronic. Acute symptomatology refers to those that occur during the actual treatment to 6 months after treatment is completed. Chronic radiation symptoms can continue on from the acute phase or after an asymptomatic period. Radiation symptoms can occur for up to 30 years after being latent; most patients will typically present with chronic changes 8–12 months after finishing their treatment [3, 7].

Prevention

The first question then is can anything be done to prevent acute changes especially because there appears to be a higher rate of chronic problems in patients who experience severe acute proctitis. The absence of acute symptoms does not preclude chronic changes and symptoms from occurring [7–9]. This process of severe acute injury leading to chronic changes is termed the “consequential” late effect [9, 10]. Prevention can be divided into those related to radiation delivery and those that are not.

The main goal with radiation delivery is to minimize damage to normal tissues surrounding the tumor. Conformal radiation therapy is one of the main methods of doing this. The 3D planning performed using CT and computer technology results in a higher dose of radiation delivery with less normal tissue being affected. Intensity-modulated radiation therapy (IMRT) is a technology whereby different intensities of radiation can be given (high and low) within the planned field. The neoplastic tissue is clearly identified as well as the normal tissue around it [11]. This modality has led to significant decrease in radiation toxicity and reduction in intestinal radiation during prostate cancer treatment even when compared to 3D planning/simulation [12]. In prostate cancer patients, acute and late radiation toxicity has also been reduced with the use of IMRT [13, 14]. In a study in prostate cancer, stereotactic radiation therapy has been found to cause lower rates of acute toxicity [14].

Brachytherapy, as mentioned previously, is when the source of radiation is implanted into the neoplasm (interstitial brachytherapy) or in a cavity which is close to the neoplasm (intracavitary brachytherapy). It can be used alone or with external beam radiation therapy and the goal again is to reduce normal tissue injury and is sometimes a good option for patients with inflammatory bowel disease [15, 16].

Proton beam radiation is an area where more research with respect to gastrointestinal toxicity is needed, but theoretically and with other tumors such as hepatocellular cancer the data looks promising [17]. The theory behind photon beams is that it “stops” in the target tissue and therefore collateral damage should be less.

With respect to non-radiation delivery factors, patient positioning has been found to be an effective way of reducing radiation to rectal wall, small bowel, and bladder—i.e., prone, Trendelenburg [18]. Other strategies employ bladder distension, abdominal wall compression, and determining position based on pretreatment contrast studies [11, 19].

The Multinational association of Supportive Care for Cancer and International Society of Oral Oncology has recently written a good paper to guide clinical practice with respect to Gastrointestinal Mucositis secondary to radiation injury [20]. Intravenous amifostine and sulfasalazine orally have been recommended as preventative measures for radiation proctitis and enteropathy. The panel also “suggested” that probiotics containing Lactobacillus could be used to prevent diarrhea in patients being treated with radiation for a pelvic malignancy. It was also specifically recommended based on the best available evidence that 5-ASA and related agents such as mesalazine not be used to prevent diarrhea in patients receiving radiation for a pelvic neoplasm. They also recommended against using misoprostol suppositories to prevent acute proctitis from radiation.

There are also operative maneuvers such as omental slings and tissue expanders that can be used to avoid radiation damage if it is planned post-resection.

Acute Radiation Colitis and Proctitis

Radiation damages the mitotic activity that is occurring at the base of crypts, where stem cells. Reside therefore the cells that migrate to line the bowel are damaged leading to a suboptimal mucosal surface and mucosal inflammation [21]. This can lead to diarrhea because of the impaired absorption. The barrier to bacteria is also affected because of this process and bacteremia can result [8]. Motility is also affected through the creation of Giant Migrating Complexes and this goes back to normal after treatment is complete; during treatment it is thought this alteration contributes to the diarrhea and cramping experienced by patients; diarrhea is the most common acute symptoms experienced by patients [22]. Other acute symptoms include nausea, tenesmus, fatigue, and abdominal pain [3]. Nearly all patients (50–75%) expe-
Chronic Radiation Colitis and Proctitis

Chronic symptoms and complications from radiation can range in severity but can be debilitating and significantly affect the quality of life of an individual. The Radiation Therapy Oncology Group (RTOG) and the European Organization for Treatment and Research of Cancer (EORTC) have devised a grading for late effects of radiation with grades of 0–5. Zero represents the effect of radiation that created no change compared to baseline and five is the effects that led to death (Table 54-1) [25].

There is not a lot written specifically about radiation colitis. There are articles written regarding non-rectal radiation-induced injury. Based on these reports some predictions can be made regarding colitis. The most common symptom is likely diarrhea. Patients can also present with more severe symptoms such as obstruction or perforation. Determining specific complication rates regarding radiation colitis specifically is difficult because studies that describe these usually include small intestine pathology as well [26].

The symptoms of chronic radiation proctitis are outlined well in Table 54-1. The pathophysiology of these complications is related to ischemic injury. The main pathology relates to fibrosis, atrophy, and vascular damage. Fibrosis which plays a prominent role in radiation injury is thought to occur because of the reaction of fibroblasts to cytokines, growth factors, and chemokines [2]. Atrophy results from the killing of cells and in concert with the other changes lead to malabsorption and strictures. The vascular damage from radiation can lead to dilation of small blood vessels—this is manifested as telangiectasias[2]. There can also be constriction of arterioles which leads to ischemia and in more severe cases necrosis; the fibrosis that occurs and which can progress over time can worsen the resultant ischemic injury [2, 3, 8]. The small vessel disease described is what distinguishes chronic from acute radiation changes.

Diagnosis

With an understanding of pathology, it is easier to understand chronic complications. Bleeding for example can be seen because of telangiectasias or ulcerations from ischemia. Malabsorption leading to diarrhea can be seen because of the atrophy of the mucosal lining or strictures leading to bacterial overgrowth. As mentioned earlier, radiation can also impact the nerves associated with gastrointestinal function and therefore accelerated small and large bowel motility can result [23]. With worsening ischemic strictures can occur leading to obstruction. With full thickness necrosis of the bowel wall, fistulas or free perforation can result. Surgery is complicated by the fact that anastomotic leak rates are higher when irradiated (with poorer blood supply) bowel is used [25].

Diagnosis is usually done with endoscopy and the features seen correspond to the pathological changes—telangiectasias, atrophy, and friable tissue. Biopsies, if necessary, can rule out processes such as inflammatory bowel disease, ischemic colitis, or drug-induced injuries. One should be cautious about taking biopsies in the radiated rectum as these have been implicated in a higher rate of fistula formation [27]. Histologic features of radiation therapy vary with the interval between completion of radiation treatment and onset of symptoms. Acute radiation injury (within 2–3 days after treatment) is characterized by surface epithelial damage, nuclear atypia with bizarre mitoses, attenuation and loss of crypts epithelium, increased apoptosis, and increased eosinophils with eosinophilic crypt abscesses. In the chronic phase of radiation injury, superimposed episodes of ischemia or the presence of mucosal or submucosal fibrosis can mimic primary acute or chronic ischemic colitis. The distinctive features of chronic

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<td>Mild diarrhea, mild cramping, bowel movement 5 times per day; slight rectal discharge or bleeding</td>
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<td>2</td>
<td>Moderate diarrhea and colic; bowel movement &gt;5 times per day; excessive rectal mucus and intermittent rectal bleeding</td>
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radiation injury include dilated, thickened, and hyalinized blood vessels, reactive or bizarre-shaped endothelial cells, fibroblasts and myofibroblasts, and foamy cells within the arteries (obliterative arteritis) [8] (Figure 54-1).

Management

Treatment of chronic radiation injury to the colon and rectum can be divided into medical, endoscopic, or surgical.

Medications

Medical treatment consists of topical versus systemic treatment. The main delivery method of topical treatment is via enema per rectum. Sucralfate enemas have been endorsed through the MASCC guidelines for the treatment of chronic radiation injury in patients who are having rectal bleeding [20, 28, 29]. There is one trial that showed oral sucralfate was beneficial in helping with diarrhea [30]; however, in their examination of the evidence, the MASCC recently suggested that oral sucralfate not be used [20].

5-ASA enemas have had mixed results and there is no clear evidence on whether it is beneficial for the treatment of chronic radiation proctitis or sigmoiditis and has been found to be harmful in some [31–33]. In the trial cited in the previous paragraph, it would seem that sucralfate is likely a more efficacious agent compared to 5-ASA [28]. Short chain fatty acid enemas still require further research prior to being able to recommend them as a treatment in chronic radiation proctitis [34]. Steroid enemas have also not been found to be consistently effective in the treatment of radiation proctitis [11, 23].
There is one trial that divided 60 patients into either a group that had betamethasone enemas, mesalamine orally, and metronidazole orally or a group that did not include oral metronidazole. In this trial it was found that bleeding and ulceration were lower in the group with metronidazole even up to 1 year [35].

A topical treatment that has been shown to be effective in dealing with bleeding from chronic radiation proctitis is topical formalin therapy. The theory behind this is that the formalin is used to chemically cauterize the telangiectasias and ulcers that are bleeding. The two main methods of delivery are via irrigation of formalin or direct application of a formalin soaked gauze onto the mucosa usually via a rigid proctoscope—the concentration typically used is 4 % although there are papers that have utilized 10 % solutions [8, 36, 37]. After either method it is recommended that a washout of the formaldehyde is done. It should also be noted that multiple applications may be required to achieve high efficacy rates of around 80 % (and sometimes higher); those with severe proctitis or taking an antplatelet agent may require more applications [36–38]. For example, in one study the average number of applications of direct application with a cotton swab via a proctoscope was 3.5 with 1.5 more applications for patients taking aspirin or with severe proctitis [37]. Another important aspect of this treatment is to avoid contact with the anoderm as formalin can be irritating to this area. The irrigation or direct contact is done during an application until it can be visualized that cauterization has occurred of the affected rectal mucosa. For irrigation with formalin, it can be done in small aliquots ranging from 20–50 cc up to a total volume of 400–500 cc [38, 39]. It is important to be cognizant of the potential complications which includes anal or pelvic pain, stricture, rectal wall necrosis, and fistula formation [36, 39]. Finally, there may be a higher complication rate in patients who have received radiation for anal cancer [40].

Other medical treatments include use of vitamins—one study of 20 patients with chronic radiation proctitis looked at vitamin E and C use and whether a variety of symptoms could be managed with medical or endoscopic therapy and also for complications such as perforations, fistulas, or strictures/obstruction. For both patients and surgeons, surgery is not something to be taken lightly. Individualized management plans are likely required depending on the context of the patient and discussion with at least one colleague or at a multidisciplinary setting regarding the management is recommended. Luckily, only 10 % of patients require an operative intervention for colorectal complications post-radiation [52]. In any type of bowel resection, one needs to be aware that anastomotic leak rates are high when putting two pieces of radiated bowel together and is lower if only one of the pieces is irradiated [53].

Pelvic fistulas can be one of the difficult problems that surgeons can encounter post-radiation. Similar management principles can be employed as with other types of fistulas—i.e., management of any ongoing sepsis and trying to optimize the situation for healing (knowing of course that with irradiated tissue fistulas are more difficult to repair) through measures such as nutritional optimization. With many of these patients whether it is a rectovaginal or rectourethral fistula, diversion will likely be necessary. Surgery will then

Endoscopy

Endoscopic therapy plays a role not only in the diagnosis of radiation injury to the bowel but can be used for treatment of it.

With respect to bleeding, argon plasma coagulation (APC) likely plays the biggest role and for many would be the treatment of choice prior to using formalin. It is a safe and effective therapy with bleeding cessation in 80–90 % of cases. Its advantage is also related to the fact that it coagulates to a reliable superficial depth. As with formalin instillation, it can require multiple treatments. Not only has there been found to be a reduction in bleeding, but bowel function has improved as well. There are no randomized controlled trials examining this particular technology, but based on multiple retrospective studies it appears to be safe and efficacious [45–47]. One has to be careful to avoid the dentate line because it can cause pain. Complications are rare and typically consist of rectal pain and cramping.

In one randomized trial comparing APC to formalin there was no difference in outcomes and both were found to be very effective in stopping bleeding (94 % APC and 100 % Formalin) [48]. In another randomized controlled trial with approximately 60 patients in each group, it was found that the addition of oral sucralfate to APC did not make a difference to the success rate of APC [49]. Historically, Nd:YAG laser therapy was used endoscopically, but with APC this is rarely used at present. In previous studies, it was found to be safe with rare complications of stricture, ulcers, fistula, and mucus discharge [50]. Another endoscopic technology that may find a wider application in the future is radiofrequency ablation as it can target a larger area and theoretically may have a lower stricture rate [51]. It is also important to remember that individuals who receive abdominopelvic radiation are at a higher risk of developing colorectal cancer. If there is not a reason to screen those patients earlier, they should definitely get surveillance done at 5 years post-completion of therapy.

Surgery

Surgical treatment is required for patients whose symptoms cannot be managed with medical or endoscopic therapy and also for complications such as perforations, fistulas, or strictures/obstruction. For both patients and surgeons, surgery is not something to be taken lightly. Individualized management plans are likely required depending on the context of the patient and discussion with at least one colleague or at a multidisciplinary setting regarding the management is recommended. Luckily, only 10 % of patients require an operative intervention for colorectal complications post-radiation [52]. In any type of bowel resection, one needs to be aware that anastomotic leak rates are high when putting two pieces of radiated bowel together and is lower if only one of the pieces is irradiated [53].
depend on factors such as how high the fistula is. Is it ame-
nable to a perineal or abdominal approach and how will
well-vascularized tissue be incorporated. The repair can
therefore involve a flap reconstruction for a low rectovaginal
fistula (i.e., gracilis or Martius) or a coloanal anastomosis
with interposition of well-vascularized tissues such as omen-
tum if it is a higher fistula. In the most severe cases, proctec-
tomy or pelvic exenteration type procedures may be required.

Diversion may be helpful in non-fistula cases as well.
Studies have shown that a colostomy or ileostomy may
resolve symptoms of pain, tenesmus, sepsis, incontinence,
and obstruction and improve quality of life to the point where
further surgical intervention may not be needed [52, 54].
Because dissection can be difficult in an irradiated pelvis,
transverse and descending colostomies were found to be
safer than a sigmoid colostomy [52]. Diversion does not
always help with bleeding, but there has been at least one
retrospective study that has shown improvement in bleeding
with a stoma [55].

Overall, on a 30-year retrospective review (looking at
colorectal surgery for radiation injuries), the approach—
resection versus diversion versus bypass—did not lead to a
difference in success. It is not surprising, considering that it
was a retrospective review where the surgeons picked an
operative approach based on what was most reasonable [54].
The promising finding was that 70 % of patients had symp-
tomatic relief. Of the different indications fistula repair had
the lowest success rate (55 %) compared to stricture (78 %),
hemorrhage (64 %), and perforation (100 %). It is sobering
to note that the morbidity rate was 65 % with a mortality rate
of 7 % [54]. The conclusion of this 30 years review is that
treatment plans should be highly individualized and this les-
son is likely the one that the surgeon should remember when
dealing with these patients.

Microscopic Colitis

Introduction
First described in 1976, microscopic colitis (MC) is an
inflammatory colitis and a relatively common cause of non-
bloody diarrhea [56, 57]. Two main types of MC have been
described: collagenous colitis and lymphocytic colitis [58].
Although considered to be a milder disorder when compared
to other inflammatory bowel diseases such as ulcerative col-
itis and Crohn’s disease [58], MC can have a significant
impact on patients’ quality of life [59, 60].

Epidemiology
The incidence of microscopic colitis is increasing [61–63].
In 2001, the estimate prevalence in the United States was
103 cases/100,000 persons [63]. It has been found in all age
groups; however, it is more common in the older population
and believed to be present in 10–30 % of patients older than
70 investigated for chronic diarrhea and presenting with a
normal colonoscopy [58, 61, 62]. Collagenous colitis is more
common in women, while lymphocytic colitis is equally dis-
tributed between genders [63, 64]. Relative incidence of col-
genous vs. lymphocytic colitis varies between series; in a
recent report, it was estimated that the prevalence of collag-
enous colitis was 39.3 per 100,000 persons vs. 63.7 for lym-
phocytic colitis [62, 63].

Etiology and Risk Factors
The cause of MC remains unknown; it is hypothesized to be
multifactorial [65].

Genetics
A limited number of Familial cases of MC have been reported
[62]. It is interesting to note that members of the same family
can develop either collagenous or lymphocytic colitis [66].
An association has been found with HLA-DQ2 and TNF2
allele carryage and microscopic colitis suggesting a possible
association with the pathogenesis of coeliac disease [67, 68].
On the other hand, NOD2/CARD15 gene, known to be
linked to Crohn’s disease susceptibility, was not found to be
more frequent in MC patients compared to healthy controls
[69]. MMP-9, another marker of inflammatory bowel dis-
ease, has been found more frequent in MC patients, but
MMP 1 and 7 were not found to be associated with MC [70].

Infection
Stool cultures are negative in most patients with
MC. However, onset after infection with *Yersinia enterocol-
itica*, *Clostridium difficile*, and *Campylobacter jejuni* has
been described [58].

Smoking
In case–control study, smoking has been associated with an
increased risk of MC (OR 2.12) [71]. In a retrospective
review of 184 patients, smokers tended to develop symptoms
earlier in their life: in one study the mean age at onset of
diarrhea was 50.4 years old vs. 65.5 in the nonsmoking
group. In the same study, smoking habits were not associated
with increased risks of relapse [72].

Medications
Evidence regarding the association between MC and medi-
cations is equivocal. Some studies suggest a link between
MC and nonsteroidal anti-inflammatory drugs (NSAIDS),
MC rarely leads to complications [62]. Cases of spontaneous perforation have been reported, but it is more common for perforation to occur as a result of a colonoscopy [78, 79]. “Fractured colon” associated with linear ulceration developing during colonoscopy has been described in collagenous colitis [80]. Collagenous deposition on the wall of colon is thought to render the wall less pliable and more likely to “fracture” during colonoscopy [81].

MC has not been found to be associated with an increased risk of colorectal cancer in a retrospective analysis of 547 MC cases [82]. A recent case–control study of 647 patients with MC followed for an average of 4.63 years found that MC was associated with a lower risk of colon cancer or adenomatous polyps [83].

Diagnosis

Histopathology is the mainstay of the diagnosis of MC. Because of the nonspecific clinical presentation the differential diagnosis is wide and includes inflammatory bowel disease, infectious colitis, medication-induced changes, celiac disease, bile salt malabsorption, lactose malabsorption, and irritable bowel disease [62, 84]. Colonoscopy with two or more biopsies in each of areas of the ascending, transverse, descending, and sigmoid colon respectively is the exam of choice to diagnosis MC. Biopsies should be sent separately [85]. The pathologic findings tend to be patchy involvement occurring anywhere in the colon; however, the disease is classically more severe in the right colon [84, 86]. Up to 30% of rectal biopsies are normal in patients with MC, underscoring the need to obtain biopsies throughout the colon. MC was originally described in patients with a normal endoscopic exam and most patients with MC do have a normal exam. However, endoscopic abnormalities have been described in a small number. In a recent literature review of 42 articles (total number of patients included not mentioned), 88 patients with abnormal colonoscopy and a diagnosis of collagenous colitis were found. The most frequent findings were mucosal nodularity, alteration of the vascular pattern, and mucosal defects [87].

Pathologic findings of collagenous colitis include preserved crypt architecture and expanded lamina propria by a mixed inflammatory infiltrate, including plasma cells, eosinophils, and occasional neutrophils, mostly on the superficial portion underneath the surface epithelium. The crypt epithelium shows regenerative nuclear changes. Focally the subepithelial collagen layer is thickened, which is the main diagnosis feature, has a lacy appearance, and incorporates inflammatory cells and small capillaries. The surface epithelium shows markedly increased intraepithelial lymphocytes and focally may be detached from the mucosa. The pathologic findings of lymphocytic colitis include preserved crypt architecture and expanded lamina propria by numerous plasma cells, lymphocytes, and eosinophils. The surface and crypt epithelium are diffusely infiltrated by numerous T lymphocytes (diagnostic if >20 IELs per 100 epithelial cells), which by immunohistochemistry express CD3 and CD8 and lack CD4. The crypt epithelium shows hyperchromatic, regenerative nuclei (Figures 54-2 and 54-3).

Autoimmunity

In a recent survey of 116 patients with MC, 30.4% had an autoimmune condition [75]. Some diseases have a particularly strong association: celiac disease and thyroid disease. Other conditions that have been linked to MC include diabetes mellitus, arthritis, alopecia, psoriasis, and Sjögren’s syndrome [75]. In contrast to Crohn’s and ulcerative colitis, no association has been found with autoimmune liver conditions [58].

Clinical Manifestations

Clinical Presentation

Chronic, non-bloody, watery diarrhea is the hallmark of this disease [62]. It can occasionally lead to fecal incontinence, especially in the elderly. In a retrospective cohort study, fecal incontinence was present in 25% of patients [76]. Watery diarrhea, even during flare-ups, rarely leads to dehydration [65]. Bile salt malabsorption can make diarrhea worse and therefore cholestyramine is sometimes used for treating these patients [77].

Weight loss is also common, being found in 41–46% of patients [64, 76]. Abdominal pain is more common in MC patients compared to controls. Interestingly, patients considered to be in remission also have more abdominal pain compared to healthy control [65]. Fatigue is another frequent complaint of patients with MC, present in 50–60% of patients; it is unclear if it is due to nocturnal diarrhea preventing rest or to the disease itself [58, 65].

Lymphocytic and collagenous colitis cannot be differentiated based on clinical presentation [62]. Interestingly, the pathologic abnormalities found in MC have been found in asymptomatic and constipated patients [65].

Complications

MC rarely leads to complications [62]. Cases of spontaneous perforation have been reported, but it is more common for perforation to occur as a result of a colonoscopy [78, 79]. “Fractured colon” associated with linear ulceration developing during colonoscopy has been described in collagenous colitis [80]. Collagenous deposition on the wall of colon is thought to render the wall less pliable and more likely to “fracture” during colonoscopy [81].

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HMG-CoA reductase inhibitors (statins), proton pump inhibitors (PPI), and selective serotonin reuptake inhibitors (SSRI), while others did not find a similar association [64, 73]. Some classes of drugs potentially linked to MC such as NSAIDS and PPI are known to cause watery diarrhea as a common side effect confounding the potential causal relationship. Because they can exacerbate symptoms of a preexisting MC, further investigations may be prompted and lead to an MC diagnosis [74].
Figure 54-4 presents an algorithm to illustrate pathologic diagnosis of MC. The term incomplete MC is used when a patient has pathological alterations not meeting the criteria for MC [85, 89]. A study conducted to assess observer variability in the diagnosis of MC found a high intra-observer and interobserver reliability for assessment of samples containing normal colon, inflammatory bowel disease samples, and MC samples. The reliability assessment for differentiating collagenous and lymphocytic colitis was lower but still good ($\kappa=0.64–0.70$ for types of MC vs. $\kappa=0.84–0.86$ for diagnosis of MC) [89].

Laboratory analysis usually shows nonspecific abnormalities such as mildly elevated inflammation markers. Fecal calprotectin and lactoferrin are not consistently elevated (in contrast to inflammatory bowel disease), limiting their use in the diagnosis of MC [90]. Research to identify reliable
Figure 54-3. Lymphocytic colitis. (a, b) The colon shows preserved crypt architecture. The lamina propria is markedly expanded by numerous plasma cells, lymphocytes, and eosinophils (thick arrow). The surface and the crypt epithelium are diffusely infiltrated by numerous lymphocytes (thin arrow). The surface and crypt epithelium shows hyperchromatic, regenerative nuclei. Hematoxylin and eosin, ×40, ×100, ×200. Reproduced with permission from Celia Marginean MD.

Figure 54-4. Algorithm for pathological diagnosis. Adapted from Warren, Edwards & Travis, 2002 [86].
biomarkers is ongoing [58, 65]. Imaging is typically normal and does not have a role in the diagnosis of MC [58].

Management

There is no curative treatment for MC. The goal of the treatment is to control the symptoms. In 2009, after conducting multiple surveys, Hjortswang et al. published criteria to define clinical remission based on the impact of the symptoms on patient quality of life. According to their work, patient with a mean of <3 stools per day and a mean of <1 watery stool per day should be considered in remission [91]. The role of pathologic response in recurrence rate and quality of life is not known currently [62]. Patients should be advised to stop smoking and dietary factors (dairy product, alcohol, caffeine) should be controlled. Long-term remission has been documented in 63–80 % of patients depending on the series [77]. The treatment and frequency of treatment course varies and the main options will now be discussed:

Budesonide

In a meta-analysis of nine randomized controlled trials, budesonide was shown superior to placebo to induce clinical and pathological response. However, the recurrence rate with treatment cessation was high [92]. Two Cochrane reviews have been published on the treatment of collagenous colitis and lymphocytic colitis [93]. When budesonide therapy was continued for 6 months after clinical remission, it was shown to prolong the disease-free interval from 45 to 207 days with 83 % of patients maintaining response vs. 28 % in the placebo group [94]. Increased stool frequency (>5 per day) and symptom duration longer than 12 months have been identified as factors associated with shorter duration of remission [95].

Prednisolone

The role of prednisolone in the treatment of MC is limited. It is associated with more side effects than budesonide [58]. In a recent meta-analysis, it was not shown to be superior to placebo [92].

Cholestyramine and Loperamide

Antidiarrheals are often recommended as the first line of treatment. They seem to have the most benefit in patients with mild symptoms. They are unlikely to induce a pathologic response and the long-term efficacy has not been proven. Patients with MC not responding to budesonide or recurring symptoms after multiple cycles of treatment should be tested for bile salt malabsorption; affected patients could benefit from cholestyramine [58, 62, 65].

Aminosalicylates

The evidence supporting the use of aminosalicylates in MC is limited. In a three-arm randomized controlled trial comparing budesonide, placebo, and mesalamine, there was no statistically significant difference between placebo and mesalamine at 8 weeks in terms of clinical remission [96]. A previous trial comparing mesalazine alone and mesalazine with cholestyramine for 6 months reported a remission rate >85 % in both groups, with a 13 % relapse rate in the remission group at 2 years. There was no placebo arm in this study [97].

Immunosuppressive and Anti-TNF Medications

This class of medication is generally reserved for patients refractory to other types of medical management because of their potential side effects. The role of azathioprine and mercaptopurine in budesonide refractory MC was studied through a retrospective review of 46 patients. Overall, thiopurines achieved remission in 41 % of patients; side effects included elevated liver enzymes and nausea/vomiting [98]. The evidence supporting the use of methotrexate in budesonide refractory MC is conflicting with one study reporting a clinical response in 16 of 19 patients and another study showing no improvement in nine patients [99, 100, 102]. Small series (less than ten patients) refractory to standard medical management report symptom improvement with the use of anti-TNF medication [103–104]. Larger studies are needed to better define the role of immunosuppressants in MC.

Bismuth Subsalicylate

Bismuth subsalicylate has been widely used, but there is limited evidence to support its use. A recent Cochrane review found only one partially published trial on bismuth subsalicylate including nine patients [105]. It was found to induce remission in 100 % of patients at a dose of 262 mg, eight tablets divided into three doses for 8 weeks [84]. The same authors published a 13-patient series with a response rate of 85 % and a 7 months remission in 69 % of patients [106]. Interestingly, bismuth subsalicylate has been found to be useful in treating chronic intractable diarrhea in up to 74 % of patients in a 31-patient case series [107].

Other Medications

Many other medications have been used to treat MC. *Boswellia serrata* extract and probiotics were not associated with a statistically significant response to treatment [94]. Antibiotics such as metronidazole and erythromycin have been used, but their effects have not been formally studied [65].
Surgery has a limited role in the treatment of MC. Loop ileostomy, subtotal colectomy, and proctocolectomy with J-Pouch have been described to treat severe intractable disease [108, 109]. Indications for surgery are ill defined and likely to be less frequent as our understanding of the optimal medical regimen improves [58, 62, 65].

Ischemic Colitis

Introduction

The term ischemic colitis was coined by Martson and published for the first time in 1966 [110]. Colon gangrene had been recognized since the late 1800, but the physiopathology of the disease had remained unsolved until the mid-twentieth century [113]. Ischemic colitis (IC) can be defined as “the condition that results when blood flow to the colon is reduced to a level insufficient to maintain cellular metabolic function” [111]. It is a fairly common disease usually self-limited. Affected patients are often frail which explain the relatively high rate of mortality associated with this disease [112].

Anatomy and Physiology

Branches from the superior mesenteric artery and the inferior mesenteric artery supply the colon. Splanchnic vessels are amongst the most reactive in the body, with blood flow varying from 10 to 35 % of cardiac output depending on physiologic or pathologic conditions [112]. This characteristic partially explains the high frequency of a low flow state in the colon. Two watershed regions have been described in the colon where ischemia is most likely: the splenic flexure (area of Griffith) and the recto-sigmoid junction (Sudeck’s point) [113]. This is superimposed on the fact that the colon receives the least amount of blood flow in the gastrointestinal tract as measured by blood flow to 100 g of tissue [113].

Epidemiology and Risk Factors

The incidence of IC varies between 4.5 and 44 cases per 100,000 person-years. It is the most frequent site of gastrointestinal ischemia [113]. It is more common in females and in patients over the age of 65 [114]. It is recognized as a disease affecting older, comorbid patients. Chronic obstructive pulmonary disease, thrombophilia, history of irritable bowel disease, constipation, diabetes, renal failure, hypertension, extreme exercise, myocardial infarction, and history of vascular disease have been identified as risks factors [111, 114, 115]. Multiple drugs are known to increase the risks of developing colonic ischemia—a literature review published in 2007 documented drug classes having been linked with development of ischemic colitis [116] (Table 54-2).

Pathophysiology

Mechanisms of ischemic colitis can be divided into non-occlusive arterial ischemia, embolic or thrombotic arterial occlusion, and mesenteric vein thrombosis. The mucosa is the first layer of the bowel to show ischemic changes, after which if there is a progression all layers of the bowel wall can be involved. Because it is furthest from the mesentery, the antimesenteric part of the bowel is affected first [111]. Transmural changes occurring after 8–16 h [121, 122].
Non-occlusive Ischemia

Non-occlusive ischemia is responsible for 95% of IC cases [120]. Non-occlusive ischemia can be idiopathic without identifiable cause or may be secondary to a medical or surgical condition diminishing colonic blood flow [111]. Colorectal vascular anatomy explains why IC happens on the left side of the colon in >75% of cases but affects the rectum in only 5% of patients [116, 117]. When the ascending colon is diseased, the cecum is the most frequently affected colonic segment [112]. Colonic injury and the systemic response to IC are due to both the hypoxic state and reperfusion injury [115]. Most of the evidence presented in the chapter is based on the management of this type of IC.

Arterial Thrombosis and Emboli Related Ischemia

An embolic source of ischemia is a less frequent cause of colonic ischemia. It is often seen with concomitant small bowel ischemia and the distribution is less likely to follow the zones of watershed area. In a case–control study on 60 patients with segmental non-transmural ischemia, patients with IC were 2.5 times more likely to have a cardiac source of embolism than control patients with similar comorbidities and medications but without IC. Thirty-two percent of patients were placed on anticoagulation and 25% on antirhythmic therapy after cardiac work-up including transthoracic echocardiogram, electrocardiogram, and rhythmic Holter monitoring [112, 123].

Venous Thrombosis

Venous thrombosis is more frequently related with small bowel ischemia; and it is the rarest cause of IC [113]. It tends to affect the ascending colon more frequently than the descending. The management of this entity is usually nonoperative: systemic anticoagulation and occasional catheter-directed thrombolysis are typically used to improve the situation.

A new entity, mesenteric phlebosclerotic colitis, has been described in 2003. Its etiology is still unknown. Patients present with abdominal pain, mesenteric venostasis, and fibrotic and calcified veins. The optimal management of this condition remains to be defined, so far it has been mostly surgical for severe cases [114].

Clinical Presentation

Abdominal pain and rectal bleeding are the most frequent symptoms associated with acute IC [125]. Nine to twenty-four percent of lower GI bleeds are caused by ischemic colitis [111]. In a review of 401 IC cases, 5% required a blood transfusion [125]. Abdominal pain is usually combined with an urgent desire to defecate [115]. Other symptoms include nausea, vomiting, abdominal distension, diarrhea, dizziness, and syncope [125]. Right-sided colitis is less likely to be associated with rectal bleeding and this diagnosis should be kept in mind in patients with isolated right-sided abdominal pain [111].

IC can evolve from an acute reversible colopathy (70%) into different clinical patterns including gangrene (10%), chronic colitis (18%), and fulminant colitis (2%) [126, 127]. Strictures form in 3.3%–9.4% of patients—they are asymptomatic in the majority of cases [111].

Diagnosis

Laboratory Studies

Results from laboratory studies are often nonspecific. Increased white blood count and acidosis are associated with infarction. There is no reliable marker of ischemia. Increased lactate, LDH, CPK, or amylase can sometimes indicate tissue damage [120].

Stool culture should be sent in patients with uncertain diagnosis. *Salmonella, Shigella, Campylobacter, Yersinia, E. coli* O157:H7, and parasites can cause a similar clinical picture. *C. difficile* should be considered even though it is usually not associated with bloody diarrhea [119]. *Klebsiella oxytoca* has been found in patients with right-sided hemorrhagic colitis mimicking ischemic colitis. It has been found more commonly in patients exposed to penicillin derivatives [128, 129].

Imaging

Plain films and contrast enema

In IC, plain abdominal films can be normal or show nonspecific findings of distention and ileus. Free air can be seen with perforation. Classic findings of bowel ischemia (i.e., thumbprinting and pneumatosis) are present in 21–30% of plain films in patients with IC [111, 120]. Contrast enemas have a limited use in the acute phase as they may make ischemia worse by increasing intraluminal pressure. Contrast studies can be used after the acute process has resolved to assess stricture formation [115].

Abdominal CT scan

CT scans are frequently performed in the Emergency Room to evaluate patients with abdominal pain; CT scan with intravenous contrast is currently the imaging modality of choice to assess IC [111]. The accuracy of CT scan in determining bowel ischemia varies between 74 and 79% depending on the study protocol and the experience of the radiologist [130]. In a recent review of CT imaging at different clinical phases during ischemia, 100% of patients presenting in the acute phase had a radiologic abnormality, most frequently pericolonic fluid and free fluid, change in bowel wall densities, and
bowel wall thickening [131]. Pneumatosis was present in <5 % of patient in acute phase. The clinical significance of pneumatosis and portal venous gas is becoming controversial. It used to represent a definite sign of bowel wall necrosis and was associated with a dismal prognosis. However, recent reports have suggested that pneumatosis and portal venous gas can be associated with different conditions. Lassandro et al. described 25 other conditions presenting with pneumatosis [132]. In their review, pneumatosis and portal venous gas were a sign of transmural necrosis in 62–92 % [132]. When portal venous gas and pneumatosis were found in combination with bowel necrosis, the mortality rate was 71 % [132]. CT angiography has not been found to increase diagnostic accuracy in the acute setting [133]. It can be used to rule out superior mesenteric occlusion if clinically suspected; inferior mesenteric occlusion is of limited clinical significance as it is found in 10 % of asymptomatic patients older than 60 years old [111].

Endoscopy
Colonoscopy can be used to confirm the diagnosis of ischemic colitis and to exclude other etiologies for colitis. It should not be performed in patients with findings of peritonitis or known perforation. Findings indicating ischemia at the time of endoscopy include erythema (84 % of cases), edema (70 %), friability (43 %), superficial ulceration (57 %), deep ulceration (22 %), stenosis (8 %), and intraluminal blood (8 %) [117]. Disproportionate involvement of the antimesenteric side with occasional single linear antimesenteric ulcer and segmental involvement are also signs of IC. Hemorrhagic nodules can be seen if the ischemia reaches the submucosa. In severe and transmural ischemia, the bowel wall may be gray, green, or black [115]. It is difficult to evaluate the severity of the disease with endoscopy. In 2011, Beppu et al. presented a case series of 106 patients and compared their clinical course based on endoscopy findings. Patients with longitudinal and circumferential ulcers stayed in the hospital longer than patients with only redness and erosion [134]. Endoscopic findings should be integrated into the complete clinical context when making decisions regarding whether surgical or medical management should be undertaken [111]. If severe ischemia is suspected a biopsy should not be taken as the risk of perforation would be high. The endoscopy should be aborted when an ischemic segment is reached [111].

The features of acute ischemic colitis include preserved architecture of the colonic crypts, necrosis of the superficial portion of the crypts, sparing the deep portion of the crypts (with or without ghost of crypts), mucin depletion, and reactive changes in the residual crypt epithelium, which may mimic dysplasia. The lamina propria is hypocellular, with very rare or completely absent acute inflammatory cells (neutrophils), and shows hyalinization. Sloughed necrotic mucosa may produce a microscopic appearance of a pseudomembrane which is composed of fibrin admixed with numerous neutrophils and mucin. Numerous small intravascular hyaline thrombi are seen in small mucosal capillaries (Figure 54-5). Montoro et al. noted that those findings were more commonly observed in the first 48 h [124]. In more chronic presentation, mucosal atrophy and area of granulation tissue may be found as well as fibrosis in area of stricture [110].

Figure 54-5. Ischemic colitis. (a) Colonic mucosa shows necrosis of the superficial portion of the crypts, sparing the deep portion of the crypts. The lamina propria is hypocellular and shows hyalinization (dense, eosinophilic color). Hematoxylin and eosin, ×100. (b) Sloughed necrotic mucosa may produce a microscopic appearance of a pseudomembrane erupting from a crypt, composed of fibrin admixed with numerous neutrophils and mucin (arrows). Numerous hyaline thrombi are seen in small vessels (thick arrow). Hematoxylin and eosin, ×200. Reproduced with permission from Celia Marginean MD.
Arteriography
Arteriography has a limited use in diagnosis of IC since it is usually an arteriolar disease. It can be used to exclude small bowel ischemia and large vessels occlusion. In the elderly and comorbid population usually presenting with IC, arteriography should be used cautiously, balancing the benefits of the information gained from the exam with the potential risks of a contrast load [115].

Ultrasound
Criteria suggestive of colonic ischemia include bowel wall thickening, altered pericolonic fat, and absence of Doppler flow with a thickened bowel wall. In a study of 62 patients with IC, the sensitivity of ultrasound was 93.5%. Repeated exams showed improvement in patients successfully treated conservatively and no improvement in patients with transmural necrosis [135]. Ultrasound has its usual limitations—user dependent and limited by body habitus and the presence of bowel gas [116].

Management
There is limited empirical evidence to guide management of ischemic colitis [136]. Guidelines and recommendations are based on case series and expert consensus.

General Principles
Many patients with IC have a self-limited disease and would improve without specific intervention [111]. Treatment is usually supportive and includes the maintenance of hydration. Patients with an ileus may benefit from nasogastric tube decompression. Medications should be reviewed and those promoting splanchnic vasoconstriction should be stopped if possible and cardiac output should be optimized. Steroids should not be used to treat IC unless it is the consequence of a vasculitis [111].

Improvement should be seen in 1–2 days with complete clinical resolution in 1–2 weeks. Absence of improvement may suggest development of chronic ischemia or progression towards transmural ischemia.

If an endoscopy is performed in the acute phase, bowel preparation is contraindicated [115]. After complete resolution of the initial episode, patients should undergo a colonoscopy to ensure complete healing and assess for possible stricture [118]. Asymptomatic strictures can be observed; symptomatic strictures can be managed through surgical resection or endoscopic dilatation. Since no evidence supports the use of dilatation specifically for ischemic stricture, its use should be reserved for patients with too much comorbidity to undergo surgery [111]. The potential benefits of stent insertion in benign stricture remain to be defined [137]. In a retrospective study, balloon dilatation was associated with longer patency time than self-expandable stent and a lower rate of complications [138].

Antibiotics
Broad-spectrum antibiotics are recommended considering that the loss of mucosal integrity caused by ischemia can lead to bacterial translocation. However, there is no empirical evidence to support their use [111]. The use of antibiotics is based on older studies describing diminished bowel damage with antibiotics during an ischemic event [111]. Some studies conducted in animals documented bacterial translocation from bowel to mesentery and liver and also support the use of antimicrobials [120, 121].

The choice of antibiotic is based on expert opinions. Considering the possibility of translocation associated with bowel ischemia, the ACG guidelines recommend broad-spectrum antibiotics, and animal studies support the use of metronidazole [111].

Antithrombotic
Anticoagulation is not routinely recommended for patients with ischemic colitis secondary to microvascular pathology or low flow states. If bowel ischemia is due to venous thrombosis or arterial thromboembolic events, anticoagulation is indicated. Patients should be investigated for thrombophilia if no other risk factors are found on history. Antiplatelet agents are not generally recommended [120].

Surgical Management
Surgical indications include peritonitis, sepsis, radiologic evidence of perforation, suspicion of transmural ischemia on endoscopy, absence of improvement or deterioration under medical management (persistent sepsis or protein losing colopathy), and stricture causing obstruction [111, 115].

In the acute setting anastomosis creation is controversial especially on the left side. Huguier et al. published a series of 31 patients undergoing surgery for ischemic colitis: 17 had a primary anastomosis with a 11.7% leak rate; the factors leading to primary anastomosis or stoma were not described [139].

Prognosis
Overall mortality rates vary from 4 to 12% depending on the study [111]. In a recent literature review, 19.3% required surgical intervention [140]. IC necessitating surgery is associated with higher mortality: 39% in surgically treated patients vs. 6% in medically managed patients [140].

The recurrence rate is difficult to compare amongst different patient cohorts because of the many factors involved in the development of the disease and its treatment. A retrospective review of 401 patients with IC found a recurrence
rate of 10% at 5 years [125] and, not surprisingly, has been shown to increase with time [111]. Factors commonly associated with poor prognosis include right-sided colitis, male gender, peritonitis on presentation, absence of rectal bleeding, and concomitant renal dysfunction [140]. In a recent effort to establish a “prognostic scoring model” for IC, Chung et al. [141] reviewed 153 cases of IC. They identified ulceration on endoscopy, tachycardia, and shock in the first 24 h of presentation as the strongest predictor of poor outcomes defined as death, need for resection, and improvement delayed for more than 2 weeks [141].

Conclusion

There is no doubt that the term and conditions that encompass colitis span a varying spectrum of pathologies. Medical providers who care for these patients must have a thorough understanding of the medical, interventional, and surgical approaches to the diagnosis and treatment in order to optimize outcomes for this complex group of colonic pathologies.

Acknowledgments Thanks to Celia Marginean for her help with the pathology sections of this chapter.

References


colon tissue 


