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GI ONCOLOGY (R BRESALIER, SECTION EDITOR)

Gastrointestinal Motility Issues in Cancer Patients

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Abstract

Purpose of Review This paper seeks to highlight GI motility disorders that are frequently present in patients with a malignancy. GI dysmotility can occur due to the cancer itself or as a consequence of medical and surgical treatments. Often, symptoms are nonspecific and the diagnosis requires a high index of suspicion. The goal of the paper is to review the common motility problems seen in patients with cancer, their clinical manifestations, and options for management.

Recent Findings Studies show that newer endoscopy techniques such as endoscopic mucosal dissection can cause esophageal dysmotility. Opioid-induced constipation is frequently encountered in patients with cancer.

Summary Motility disorders in cancer patient can lead to clinical morbidity, poor quality of life, and malnutrition. Newer diagnostic tests and medical and surgical treatments may be helpful in improving the diagnosis and management of these disorders.

Keywords Motility disorders in malignancy · Pseudoachalasia · Gastroparesis · Dumping syndrome · Paraneoplastic syndrome · Opioid-induced constipation

Introduction

A wide range of gastrointestinal (GI) motility disorders can be seen in patients with a variety of malignancies. These can be a manifestation of the cancer itself, as a paraneoplastic effect, from the presence of oncogene-related proteins or from the effects of treatment, including chemotherapy, surgery, use of opioids, and radiation therapy. GI dysmotility can present as abnormally rapid or slow GI transit, motor or sensory abnormality, or as functional obstruction. Motility disorders can be overlooked as a contributing factor in a cancer patient's symptoms (Table 1). Symptoms are often nonspecific and overlap with symptoms from the cancer itself. The dysmotility can affect the quality of life and may contribute to feeding difficulties and lead to malnutrition. Symptoms can be short-lived or chronic, and can even manifest years later, in the cancer survival population.

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The availability of newer diagnostic tests and medical and surgical treatments may be helpful with the diagnosis and management of these disorders (Table 2).

GI Physiology

Gastrointestinal (GI) motility function and its regulation is a complex process involving communication of the enteric nervous system (ENS), interstitial cells of Cajal (ICC), and gut smooth muscle cells [1]. The ENS is divided into two major ganglion plexuses, the myenteric and the submucosal, which control gut functions including motility, secretion, absorption, and vascular tone. The smooth muscles generate spontaneous electrical activity, the slow wave. The ICC, which are electrically coupled to the smooth muscle cells, act as pacemakers and initiate and propagate the electrical rhythm [1]. The contractile property of the smooth muscles is regulated by extrinsic parasympathetic and sympathetic pathways, intrinsic enteric sensory and motor neurons, neurotransmitters, GI hormones, and chemicals within the gastrointestinal tract [2]. Disruption at any level can affect normal GI motility and present as multiregional or localized disorders.

Table 1 GI motility disorders in patients with cancer

a. Esophageal
  i. Pseudoachalasia
  ii. Dysmotility following ESD
  iii. Post-laryngectomy
  iv. Post-esophagectomy
    1. Dumping syndrome
    2. Reflux disease
    3. Delayed gastric emptying
b. Gastric
  i. Dumping syndrome
  ii. Malignancy-associated gastroparesis
  iii. Post-surgical delayed gastric emptying
c. Intestinal
  i. Small intestinal bacterial overgrowth
  ii. Pseudo-intestinal obstruction
  iii. Radiation-induced enteritis
d. Colonc
  i. Chronic pseudo-colonic obstruction
  ii. Opioid-induced constipation
  iii. Pelvic floor neuropathy
e. Multiregional
  i. Radiation injury
  ii. Chemotherapy induced gastrointestinal dysfunction
  iii. Opioid-induced dysmotility
  iv. Paraneoplastic syndrome

Paraneoplastic Gastrointestinal Dysmotility

GI dysmotility that occurs in the setting of malignancy but not from direct tumor invasion, surgery, or chemotherapy is characterized as paraneoplastic GI dysmotility. This may result from an altered immune system response to tumor antigens [3]. Paraneoplastic syndromes evoke an inflammatory infiltrate targeting neurons in both submucosal and myenteric ganglia of the ENS. The cellular infiltrate along with circulating anti-neuronal antibodies is thought to damage the enteric reflexes, thereby contributing to paraneoplastic dysmotility. Onconeural antibodies selectively bind to enteric neurons in the myenteric plexus. The presenting symptoms usually precede the diagnosis of malignancy in up to 80% of cases. There can be a wide spectrum of presentation; the dysmotility can involve the entire GI tract or affect isolated segments, manifesting as pseudoachalasia, gastroparesis, intestinal pseudo-obstruction, or constipation.

Table 2 Diagnostic tests for motility disorders

1. High-resolution esophageal manometry
2. Timed barium esophagram
3. Modified barium swallow
4. 24 and 48 hour esophageal pHmetry
5. Endoluminal functional lumen image probe (EndoFLIP)
6. Gastric scintigraphy
7. Antroduodenal manometry
8. Hydrogen breath tests
9. Autonomic function tests
10. Wireless motility capsule
11. High-resolution anorectal manometry

The anti-Hu antibody (also called anti-neuronal nuclear antibody 1, ANNA-1) is the most common autoantibody associated with paraneoplastic dysmotility and is most frequently seen with small cell lung cancer. Up to 30% of anti-Hu antibody–positive patients show symptoms of GI dysmotility [3]. It is also seen with tumors of the stomach, esophagus, pancreas, breast, ovary, melanoma, and lymphoma [4••]. Other paraneoplastic antibodies associated with GI dysmotility include Purkinje cell cytoplasmic autoantibody type 1 (PCA-1) and collapsing response-mediator protein 5 (CRMP-5) which is present in 20% of patients with GI dysmotility.

Gastroparesis and chronic intestinal pseudo-obstruction are the 2 most common paraneoplastic GI dysmotility syndromes. Treatment centers are on management of the underlying malignancy. Management of dysmotility with antiemetics, prokinetics, or laxatives is often suboptimal, and can lead to malnutrition. Treatment with high-dose corticosteroids, cyclophosphamide, intravenous immunoglobulin (IVIG), rituximab, and methyl naltrexone [5] has met with variable response. Often the prognosis is poor and results in severe malnutrition.

Esophageal Motility Disorders

Abnormalities in esophageal motor function can be seen in malignancy-associated achalasia, post-esophagectomy syndrome, post-laryngectomy, and following extensive endoscopic submucosal dissection.

Achalasia

Achalasia is the quintessential motility disorder of the esophagus with an annual incidence of 1.6 per 100,000 people [6]. It is caused by the loss of neurons in the myenteric plexus which leads to incomplete relaxation of the lower esophageal sphincter and aperistalsis of the esophageal body. Achalasia is most commonly idiopathic, but "pseudoachalasia" can result from the presence of a malignancy, by direct invasion of the esophagus, infiltration of the myenteric plexus, or as part of a paraneoplastic syndrome.

Achalasia secondary to malignancy accounts for 1.5–5% of all patients with achalasia [7]. Pseudoachalasia is most commonly seen in cancers of the distal esophagus and the gastric cardia. It has also been associated with cancers of the lung, breast, pancreas, liver, and with lymphoma. Patients present with chest pain, regurgitation, and dysphagia, similar to idiopathic achalasia. Manometry features in pseudoachalasia can be indistinguishable from achalasia. A timed barium swallow will show retained contrast in the esophagus in both cases; therefore, the diagnosis of pseudoachalasia requires a high index of suspicion.

Concern for pseudoachalasia should be raised in patients with age over 55 years, a short duration of symptoms, and rapid weight loss [8]. The Eckardt symptom score adjusted for weight loss was found to be comparable between 315 idiopathic and 18 malignancy-associated achalasia patients, but higher with pseudoachalasia if weight loss was included. Endoscopy should be performed to evaluate the distal esophagus and cardia for infiltration. There may be a lack of balloon effacement with pneumatic dilation with pseudoachalasia. The American College of Gastroenterology guidelines recommend the use of endoscopic ultrasound when malignancy is suspected [9]. Functional lumen imaging probe, EndoFLIP, is a diagnostic catheter which focuses on measuring mechanical properties of the esophagus [10]. It is used to assess esophagogastric junction distensibility and stiffness of the esophageal wall [11]. The most common indications are for suspected achalasia. Distensibility measurement adds diagnostic information that can impact decision-making in the diagnosis of achalasia. Studies are needed to evaluate its utility in differentiating pseudoachalasia from the idiopathic disorder.

Management includes treatment of the underlying malignancy, and addressing symptoms of reflux, pain, and malnutrition. There can be reversal of pseudoachalasia after successful treatment of the underlying cancer.

Dysmotility after Esophageal Submucosal Dissection

Endoscopic resection of early esophageal cancer has become the standard of care over the past 15 years [12]. Endoscopic resection is preferred over esophagectomy due to the potential of curative resection of cancers localized to the mucosa and superficial submucosa and lower postoperative morbidity than with esophagectomy.

Endoscopic submucosal dissection (ESD) involves en bloc removal of mucosal and superficial submucosa tumors. Dysphagia in the absence of esophageal strictures has been reported in up to 25% of patients after ESD for esophageal cancer [13, 14]. In one study, 52 patients were evaluated after ESD involving more than two-thirds of the esophageal circumference with esophageal manometry. Manometric abnormalities of both hyper and hypo motility were seen including jackhammer esophagus, esophageal spasm, EGJ outflow obstruction, and aperistalsis. Abnormalities were more common in patents with dysphagia (41%) but also seen in 13% of patient who did not report dysphagia [15].

In another study, nineteen patients underwent HRM before and after ESD for superficial esophageal carcinoma [14]. Non-obstructing dysphagia was reported in 1/19 (5.3%) before and 6/19 (31.6%) after ESD ($P = 0.131$). In patients with circumferential ESD appears to diminish the distal contractile integral (DCI) and increase the frequency of weak contractions seen by HRM. Circumferential mucosal resection and repeated ESD are predictors for impaired esophageal motility after ESD [16].

Post-esophagectomy Syndrome

Survival rates after radical surgery for esophageal cancer have steadily improved in recent years. About 40% of patients are expected to live 5 years after an esophagectomy. Motility-related symptoms that impact on the quality of life are common in the survivor population. These symptoms include reflux, early satiety, malabsorption, diarrhea, and post-prandial dumping [17].

Esophageal resection for malignant tumors leads to loss of major anti-reflux barriers. Gastric pull up, often performed along with an esophagectomy, results in the loss of the angle of His, resection of the lower esophageal sphincter predisposes to regurgitation of food. Weak contractions in the remnant esophagus result in decreased acid clearance. Reflux symptoms have been reported in 60% of post-esophagectomy patients. Anti-reflux maneuvers such as to prevent reflux and aspiration pneumonia in these patients.

Dumping syndrome, commonly associated with gastrectomy, is a known complication after esophageal resection. About 20% of patients have dumping syndrome after an esophagectomy [18]. Diarrhea, abdominal cramps, nausea, and dizziness are common symptoms seen in dumping after esophagectomy. The severity of dumping syndrome following esophagectomy is typically mild and can be managed without the need for medical therapy in most patients. Dietary recommendations to eat small-portion meals, following a low carbohydrate diet, appear to control dumping symptoms in the majority of patients.

Delayed gastric emptying is a frequently seen motility disturbance after esophagectomy with an incidence of 10–50%. The reduced stomach capacity and truncal vagotomy done with esophagectomy lead to delayed emptying [19]. The resulting nausea, early satiety, abdominal pain, and vomiting can prolong post op recovery, cause aspiration pneumonia, and lead to long-term poor quality of life. Pyloric drainage procedures are commonly done with the esophagectomy. However, a pyloromyotomy may contribute to an increase in reflux symptoms, dumping, and intestinal metaplasia of the remnant esophagus. The results of drainage procedures are variable. Studies have shown rates of dumping syndrome to be equivalent in patients who received any pyloric intervention including botulinum injection (11.7%), pyloromyotomy (2.4%), or pyloroplasty (8.6%, $P = 0.25$) [20, 21, 22••].

In an analysis of 285 patients who did not undergo a drainage procedure post-esophagectomy, patients who retained the whole stomach were more likely to develop DGE than were patients with a tubularized stomach (13.2% versus 22.4%; $P = 0.05$) [22••]. Reflux and dumping syndromes are the most important functional complaints in patients after esophagectomy.

A study evaluated reflux symptoms and dumping in patients who underwent either minimally invasive (MIE) or open esophagectomy for cancer [18]. The reflux score was slightly worse in the MIE group (5.5 versus 3.5; $P = 0.021$). There was no difference in the dumping symptoms between the two groups.

Dysphagia Post-laryngectomy and Radiation Therapy

Total laryngectomy is performed to treat advanced laryngeal cancer; it is usually followed by chemoradiotherapy. Dysphagia following total laryngectomy is common and under-recognized. Estimates of post-laryngectomy dysphagia range from 17 to 72% [23].

The dysphagia is multifactorial, due to surgical changes, chemoradiation-related pharyngeal dysfunction, and stenosis at the pharyngoesophageal anastomosis. Esophageal motor dysfunction and symptoms of chest pain and regurgitation have been reported after laryngectomy.

Characteristics of esophageal dysmotility were studied with high-resolution esophageal manometry in 31 patients after a total laryngectomy.

Nearly half (49%) of the patients had significant disorders of LES function or a major peristaltic abnormality, including achalasia, EGJ obstruction, diffuse esophageal spasm, jackhammer, and absent contractility. There was no association between users of a voice prosthesis and specific patterns of esophageal motility disorders [23].

Chronic dysphagia is also reported after XRT for head and neck malignancies. Three years after radiation therapy (range 0.5–8 years), 116 patients were questioned about long-term dysphagia; impaired swallowing was reported by 59% of respondents. The dysphagia severity was not predicted by tumor site or stage, or by the time since therapy or adjuvant chemotherapy. Aspiration pneumonia was found to be responsible for 19% of non-cancer-related deaths in these patients [24]. This underscores the need for timely diagnosis and preventative measures.

Pharyngoesophageal (PEJ) strictures and outflow obstruction can also be seen after radiation treatment. Endoscopic functional luminal imaging probe (EndoFLIP) combined with manometry can give a comprehensive evaluation of motility and luminal capacity for distention. It can be applied across strictures to assess response to dilation. EndoFLIP was used to study the (PEJ) distensibility and treatment-related changes in 34 HNC patients with > 12 months of dysphagia. A PEJ stricture was confirmed in 22/34 (65%) patients. During distension, the mean EndoFLIP-derived narrowest cross-sectional area (nCSA) in patients with strictures and without strictures was measured. A cutoff of 114 mm [2] nCSA at the PEJ had perfect diagnostic accuracy in detecting strictures. EndoFLIP may be useful in detecting PEJ strictures and outflow obstruction [25].

Gastric Motility Disorders

Alterations in the upper GI function occur after gastric surgery for benign or malignant lesions. The stomach's accommodation response is impaired after partial gastric resection. Vagotomy can result in loss of fundus and pyloric relaxation and reduced antral contractions resulting in gastric retention [26]. These can lead to bloating, early satiety, and epigastric pain. Gastric dysmotility such as dumping syndrome, delayed gastric emptying, and Roux-en-Y syndrome can be seen following surgery. Delay in gastric emptying can be aggravated due to concomitant use of drugs such as opioids. Gastric dysmotility can impair adequate oral calorie intake and lead to malnutrition.

Dumping Syndrome

Truncal vagotomy and gastrectomy can result in dumping syndrome due to abnormalities in gastric and intestinal motility. Gastric surgery reduces gastric capacity and results in the rapid delivery of undigested solid food to the small intestine.

Patients experience vasomotor symptoms such as diaphoresis and flushing as well as GI symptoms such as nausea, cramping, and diarrhea. Clinically significant dumping symptoms occur in about 20% of patients after distal gastrectomy and in 40% after Roux-en-Y gastrectomy. Symptoms relate to the type of surgery and appear to be worse after total gastrectomy with Roux-en-Y, followed by proximal gastrectomy (PG), distal gastrectomy with Billroth-I, and least with pylorus-preserving gastrectomy (PPG) [27].

Early dumping syndrome, the most frequent type, occurs about 30 min of eating.

Hyperosmolar nutrients' rapid entry in the small bowel causes a shift of fluid to the intestinal lumen, resulting in a decrease in plasma volume, tachycardia, and bloating and diarrhea.

Late dumping usually occurs 1 to 3 h after a meal and is a result of a hyperinsulinemic response after carbohydrate ingestion. Rapid delivery of undigested carbohydrates to the small intestine results in high glucose concentrations that induce a hyperinsulinemic response, resulting in subsequent hypoglycemia. Hypoglycemia-related symptoms such as weakness, confusion, asyncope, and irritability can occur. It may result in either weight loss or weight gain.

Isolated late dumping with hypoglycemia as the only symptom affects up to 25% of patients. In severe cases, dumping syndrome is associated with a substantial reduction in quality of life [28].

Management includes dietary modifications, medications, enteral nutrition, or surgery in refractory cases. Acarbose, an α-glycosidase hydrolase inhibitor that slows carbohydrate digestion in the small intestine, has been shown to reduce

the incidence of post-prandial hypoglycemia in patients with dumping syndrome [29].

Somatostatin analogs slow gastric emptying and improve hypoglycemia in both early and late dumping symptoms. Liraglutide, a GLP-1 analog in case reports, has been effective in treating hyperinsulinemic hypoglycemia associated with late dumping syndrome [30].

Gastroparesis Associated with Malignancy

Gastroparesis, defined as delayed gastric emptying with symptoms of nausea, vomiting, early satiety, and abdominal pain, in the absence of an obstruction, has been reported in several malignancies, including gastric, pancreatic, gallbladder, esophageal, and lung. The prevalence of malignancy-associated gastroparesis (MAG) is unknown.

Gastroparesis can result from malignant infiltration of the autonomic nervous system, from paraneoplastic dysmotility with autoantibody-mediated destruction of the ICC, or of the myenteric plexus [31]. It can be a consequence of post-vagotomy syndrome after surgery or radiation. In addition, there may be benign coexisting conditions such as diabetes that contribute to the gastroparesis.

Mechanical obstruction should be excluded by imaging or upper endoscopy. Next, gastric emptying delay should be assessed with a gastric emptying scintigraphy or with a wireless motility capsule. Treating MAG involves ensuring adequate hydration and nutritional intake, and the use of prokinetics and antiemetics. For refractory MAG, a neurostimulation device (Enterra, Medtronic) can be placed temporarily by endoscopy or permanently by surgery. There are reports of symptom improvement after in MAG with Enterra, despite minimal changes in the gastric emptying time [32].

Post-surgical Delayed Gastric Emptying

Post-surgical gastroparesis is commonly seen after surgery of the stomach or the pancreas. Gastroparesis after pancreatoduodenectomy occurs in up to 60%of patients undergoing this procedure. Delayed gastric emptying (DGE) can result from post-surgical atony or vagal denervation, or from a small gastric remnant. DGE in the immediate postoperative period has been attributed to a loss of phase III activity of the migrating motor complex normally seen in the fasting state. Another important mechanism involves the increased release of GI hormones including vasoactive intestinal peptide (VIP), incretins, and insulin, glucagon. Enhanced release of these GI hormones can induce discoordinated GI motility [28].

One study showed an incidence of delayed gastric emptying of 24% after distal pancreatic resection. DGE was associated with higher rate of fistula and significantly prolonged hospital stay. A periampullary malignancy was shown to be a significant factor for DGE development.

Gastric emptying delay has been reported at 1 and 8 weeks after ESD for gastric cancer, compared with before ESD. The delay appears greater for proximal stomach lesions than for distal stomach lesions ($P = 0.028$, $P < 0.001$) [33•].

The Roux-en-Y Stasis Syndrome

The Roux-en-Y stasis syndrome (RSS) is a postgastrectomy syndrome caused by dysmotility of the Roux-en-Y limb (RYL). Ten to 67% of patients undergo Roux-en-Y surgery experience RSS [34]. This results from abnormal motility of the RYL with net propulsive movement towards instead of away from the stomach. This causes stasis in the gastric remnant or in the RYL. Patients predisposed to it are those with a greater than 50% gastric remnant or with a truncal vagotomy. Evaluation requires upper GI series and endoscopy. If prokinetic medicines are not helpful, surgical reconstruction with a subtotal gastrectomy or a Billroth-2 anastomosis may be required [34].

In a study, 8 patients who had undergone total gastrectomy with Roux-en-Y reconstruction for proximal gastric cancer were evaluated with high-resolution manometry (HRM) of the esophagus and the Roux limb. The esophageal motility was not affected by the surgery. Peristalsis was found to be present but abnormal in the roux limb [35].

Small Bowel Dysmotility

Causes of small bowel dysmotility in cancer patients include intestinal pseudo-obstruction, radiation enteritis, and bacterial overgrowth.

Pseudo-intestinal obstruction can occur as a paraneoplastic syndrome as noted earlier. This is most closely associated with small cell lung cancer. The mechanism of action is not clear. Treatment of the underlying malignancy may reverse the symptoms. Octreotide has been used to treat this successfully as well [36].

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) results from alterations in GI anatomy, motility, gastric acid, and intestinal secretions [37]. Once the gut microbiome is altered, the bacterial overgrowth causes an inflammatory response in the intestinal mucosa resulting in chronic diarrhea, weight loss, and malabsorption. The prevalence of SIBO post-total gastrectomy and gastric bypass may be as high as 77%.

In a study, 76 patients who had undergone gastrectomy for early gastric cancer were evaluated with a hydrogen breath test. SIBO was significantly more prevalent in the

postgastrectomy patients compared with the controls (77.6% vs. 6.7%, $P < 0.01$) [37]. A higher incidence of SIBO has also been reported after surgical resection in patients with colorectal cancer compared with controls [38]. Response to rifaximin treatment for 10 days was favorable.

Malabsorption and malnutrition are also prevalent in survivors of esophageal and stomach cancer [39•]. Malabsorption was reported in 73% of patients, and 38% had evidence of SIBO after esophageal or gastric oncologic resections.

Radiation-Induced Bowel Injury

Up to 90% of patient's experience GI symptoms after radiation to the abdomen and pelvis, both in the acute period and chronically resulting in permanent change in their bowel habit.

Three to 10% of such patients develop severe radiation-induced bowel injury with evidence of dysmotility, strictures, and fistulae. One-third of patients with severe radiation-induced bowel injury will require surgery that is associated with a mortality rate of 10–22%. The integrity of the intestinal mucosa barrier is impaired as a consequence of the damage by the tumor or as a side effect of radiotherapy and chemotherapy. These treatments often result in reduced functionality of cellular and humoral immune system, inadequate nutritional intake, and secondary infection [40]. Irradiation also results in significant changes in the gut microbiota.

Common symptoms of radiation-induced bowel injury include diarrhea, abdominal pain, bloating, fecal incontinence, bleeding per rectum, and weight loss. "Acute" symptoms occur within 3 months of radiotherapy and usually resolve within 3 months. The chronic phase can occur 6 months to years later and is characterized by chronic inflammation, fibrosis, vasculitis, ischemia, and gut dysmotility [41]. Treatment is focused on control of symptoms, prevention of infection, and in providing adequate nutritional support (Table 3).

Tabl7e 3 Treatment of motility disorders

a) Pharmacotherapy
  i. Prokinetics
    1) Dopamine receptor antagonists (metoclopramide, domperidone)
    2) Motilin agonist (erythromycin)
    3) Ghrelin receptor agonist (relamorelin, in trials)
    4) 5HT4 receptor agonist (prucalopride)
  ii. Antiemetics
    1) Phenothiazines (promethazine)
    2) 5HT3 receptor antagonist (ondansetron, granisetron)
    3) Neurokinin 1 receptor antagonist (aprepitant)
  iii. Peripherally acting mu-opioid receptor antagonists (methylnaltrexone, naloxegol, alvimopan)
  iv. Antidiarrheals
    1) (loperamide, octreotide)
  v. Secretory agents
    1) Guanylate cyclase-C receptor agonists (linaclotide, plecanatide)
b) Surgical
  i. Heller myotomy
  ii. Gastric electrical stimulation
  iii. Gastric bypass surgery
  iv. Subtotal colectomy
c) Endoscopic
  i. Botulinum toxin injection
  ii. Per oral endoscopic myotomy (POEM), (gastric, G-POEM)
  iii. Endoscopic submucosal dissection
  iv. Venting G-tubes
  v. Feeding G and J tubes
d) Nutritional
  i. Enteral feeding
  ii. TPN

Colon and Rectum Dysmotility

Dysmotility involving the colon includes opioid-induced constipation and chronic pseudo-colonic obstruction.

Chronic Pseudo-colonic Obstruction

Chronic pseudo-obstruction is a syndrome that presents with signs and symptoms of small or large bowel obstruction (present for at least 6 months) in the absence of a mechanical obstruction [42]. It is characterized by the presence of dilation of the bowel on abdominal imaging. The etiology is multifactorial, involving a neuropathic, smooth muscle myopathic disorder, or abnormality in the ICC. Paraneoplastic association has been reported with small cell lung cancer, carcinoid tumor, and malignant thymoma. These patients often have anti-neuronal nuclear (anti-Hu) antibodies which along with the cellular inflammation damage the enteric reflexes, thereby contributing to paraneoplastic dysmotility. The most common symptoms are abdominal pain, vomiting, constipation, and diarrhea. Treatment options focus on correcting nutritional deficiencies, minimizing symptoms, and preventing malnutrition. Medication trails have included cisapride, domperidone, metoclopramide, and octreotide with limited success [19, 36].

Opioid-Induced Constipation

A distinct category of constipation is opioid-induced constipation (OIC), which is a change in bowel habits associated with opioid use [43]. It can result in a decreased bowel frequency, straining, and incomplete evacuation. OIC affects 60 to 90% of patients with cancer who use opioids. It results from the binding of exogenous opioids to peripheral m-opioid receptors in the submucosal and myenteric plexuses of the enteric nervous system (ENS) [44••]. This alters neural output from the ENS, which impairs gut motility, and limits fluid secretion in the GI tract [44••]. Peripherally acting mu-opioid receptor antagonists (PAMORAs) act by minimizing

the action of exogenous opioids at peripheral m-opioid receptors, without affecting the central analgesic effect.

Methylnaltrexone is a naltrexone derivative available in oral and subcutaneous forms [45].

Several studies have shown that oral and subcutaneous methylnaltrexone is effective in improving stool frequency in OIC [45]. In a phase III trial, 97 adults with OIC and cancer were treated with daily oral naldemedine. The primary end point of 3 or more spontaneous bowel movements (SBM) a week with naldemedine was 71.1% compared with placebo (34%) [46].

Multiregional Dysmotility

Many of the motility disorders described above are not isolated to one organ. Drugs such as opioids and chemotherapy-induced changes frequently cause multiregional changes in GI motility [47]. Widespread chemotherapy-induced gastrointestinal dysfunction is seen in 40% of patients receiving standard dose chemotherapy [48]. Nearly all patients receiving high-dose chemotherapy exhibit pain, bloating, vomiting, diarrhea, and/or constipation over the course of their treatment. Chronic treatment with cisplatin results in myenteric neuronal loss. Platinum-based chemotherapeutics increase the incidence of chronic diarrhea and constipation which can persist for up to 10 years after treatment has been completed [49, 50]. Enteric neuropathy has been linked to a variety of GI pathologies, due to its regulation of intestinal epithelial function and colonic motility. Enteric neuropathy may be an underlying cause of chemotherapy-induced GI dysmotility. Similarly, paraneoplastic syndromes often present with multiregional signs and symptoms which must be considered in the diagnosis and management of these disorders.

Conclusion

Motility disorders in cancer patients are common and are frequently overlooked. These disorders can have considerable impact on the quality of life and the nutritional well-being of the patient. Symptoms are often nonspecific and similar to those from the cancer. A high clinical suspicion is required to diagnose and manage these disorders which can persist for years in the survivor population. Newer diagnostic tools and medications are improving the diagnosis and management of these syndromes.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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