Audit of suspected chronic intestinal pseudo-obstruction in patients with gynecologic cancer

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Summary

Purpose: To describe chronic intestinal pseudo-obstruction (IPO) syndromes that occur after radiotherapy or chemotherapy (or both) for gynecologic cancer. *Methods:* All 48 patients in the study population had a history of gynecologic cancer, treatment with radiotherapy or chemotherapy (or both), and suspected chronic IPO. The final diagnosis was based on clinical symptoms, radiographic imaging, motility studies, and surgical findings. Treatment was expectant for 27 patients and surgical for 21. *Results:* In six of the 21 surgical patients, the final diagnosis was mechanical obstruction. In the other 15, it was IPO syndrome: six had an idiopathic dysfunction (ID) and nine had a thick fibrinous coating (FC) on the serosal surface. Intestines of these 15 patients had patent lumens but decreased motility. The ID and FC groups differed in mean age, chemotherapy administration, and mean time from radiotherapy to surgery. Symptoms improved in 67% of FC patients compared with 17% of ID patients. Among patients treated expectantly, symptoms improved in 50% of the ID patients and in 38% of the FC patients. Motility studies were useful for distinguishing ID from FC or mechanical obstruction. *Conclusion:* Clinical history and motility studies may assist in diagnosing IPO syndrome in gynecologic cancer patients treated with radiotherapy or chemotherapy (or both) and in identifying patients who might benefit from surgical intervention.

Key words: Chemotherapy; Gastrointestinal motility; Gynecologic cancer; Intestinal pseudo-obstruction; Radiotherapy.

Introduction

Intestinal pseudo-obstruction (IPO) is a clinical entity for which the signs and symptoms of intestinal obstruction are present but no intrinsic or extrinsic luminal occlusive process exists. Usually, this entity is caused by functional damage of the myenteric plexus or by a pathologic infiltrative process that involves the intestinal wall and impairs intestinal motility, leading to pseudo-obstruction [1, 2]. Radiotherapy and chemotherapy have been hypothesized to alter the myenteric plexus, causing functional intestinal obstruction [3-5].

Mechanical intestinal obstruction is a well known complication for patients with gynecologic cancer who have had surgical therapy or radiotherapy, or both. Preoperative evaluation of patients with intestinal obstruction may show obvious radiographic or clinical (i.e., recurrence of disease) signs of mechanical obstruction. However, one cannot always identify a clear point of intestinal stricture or kinking in patients who have an obstructive syndrome, and, on the basis of clinical and radiographic findings, the preoperative diagnosis may be intestinal obstruction of uncertain etiology.

Surgical treatment may not be necessary if no point of mechanical obstruction is identified. Moreover, surgical treatment may be accompanied by high morbidity in patients who have gynecologic cancer that was previously managed with radiotherapy [6, 7]. Therefore, one should identify women who have gynecologic cancer and functional obstruction of the intestine who will not benefit from surgical management [8]. Results of preoperative motility studies may potentially help distinguish mechanical from functional intestinal obstruction [9].

In our clinical experience, we observed patients with ovarian cancer who had whole abdominal radiotherapy, with or without chemotherapy, and who presented with intestinal pseudo-obstruction and did not benefit from surgical intervention. For this reason, we hypothesized that whole abdominal and pelvic radiotherapy, sometimes combined with cytotoxic chemotherapy, may cause chronic IPO in patients who have gynecologic malignancy. Our aim was to select and describe a case series of patients who had gynecologic cancer, a previous history of radiotherapy or chemotherapy (or both), and IPO. We attempted to identify clinical characteristics that might aid in selecting patients who may not benefit from surgical exploration.

Materials and Methods

Our selection criteria were based on the presence of gynecologic cancer, IPO, and radiotherapy or chemotherapy (or both). Medical records were reviewed for 86 patients who had gynecologic cancer and a history of IPO, Ogilvie syndrome, or intestinal motility dysfunction and for 105 patients who had ovarian cancer and were treated with whole abdominal radiotherapy at Mayo Clinic between 1976 and 1997. Patients presenting with symptoms of intestinal obstruction or pseudo-obstruction (e.g., abdominal distension, abdominal pain, bloating, constipation,

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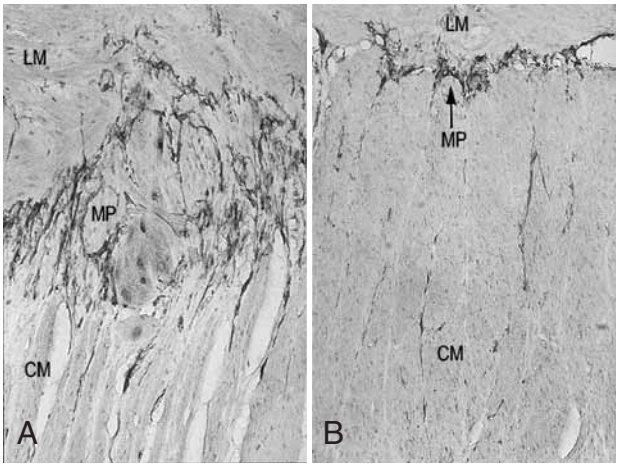

Figure 1. — Microscopic appearance of the myenteric plexus (MP) with interstitial cells of Cajal (c-kit antibody stain). *A*, Normal MP. *B*, Depleted MP. CM, circular muscle layer; LM, longitudinal muscle layer.

diarrhea, nausea, vomiting, and anorexia) without unequivocal clinical, radiographic, or endoscopic findings of mechanical obstruction (i.e., a massive recurrence of tumor or an area of stricture or obstruction) were suspected of having IPO syndrome. Of the 191 patients, 57 had received a diagnosis of IPO, but nine of the 57 were suspected of having IPO before they received treatment for gynecologic cancer (because of underlying disease, such as scleroderma) and were excluded from the study. Therefore, 48 patients were in the study population (34 had ovarian cancer, 10 had endometrial cancer, and 4 had other types of cancer). All had received radiotherapy (n = 17), platinum-based chemotherapy (n = 4), or both (n = 27). Radiotherapy was limited to the pelvis in six patients, and it included the whole abdomen in the remaining 38. Of the 48 patients with IPO, 21 were managed surgically and 27 expectantly (i.e., with restrictive diet or home total parenteral nutrition).

Clinical studies to distinguish mechanical obstruction from IPO included radiographic, histologic, and motility studies. Reports of radiographic findings were usually available in the medical records. The actual radiologic films were readily available for 17 patients. The films were reviewed to verify the presence of nonspecific findings and the lack of unequivocal evidence of mechanical obstruction. Hematoxylin-eosin–stained histologic specimens (available for 15 of the 21 surgical patients) were reviewed to compare histologic findings with clinical and surgical findings. For seven patients, available tissues were also stained with the antibody c-kit for interstitial cells of Cajal (ICC), and stained tissues were interpreted (Figure 1).

Motility studies were performed in a standard fashion [10] in accordance with previously published criteria for distinguishing mechanical obstruction from functional obstruction [9]. Motility tracings were reviewed blindly to distinguish IPO from mechanical obstruction. The results of the studies were available for 11 patients (Figure 2).

A diagnosis of IPO was assigned surgically when dilated bowel was present without a clear point of obstruction. IPO due to functional damage was distinguished from IPO with a fibrinous coating surrounding the intestine; intestinal lumens were patent in both types of IPO. The final clinical diagnosis for patients treated expectantly was mechanical obstruction if mechanical obstruction or progressive disease became evident. However, patients who did not subsequently demonstrate any

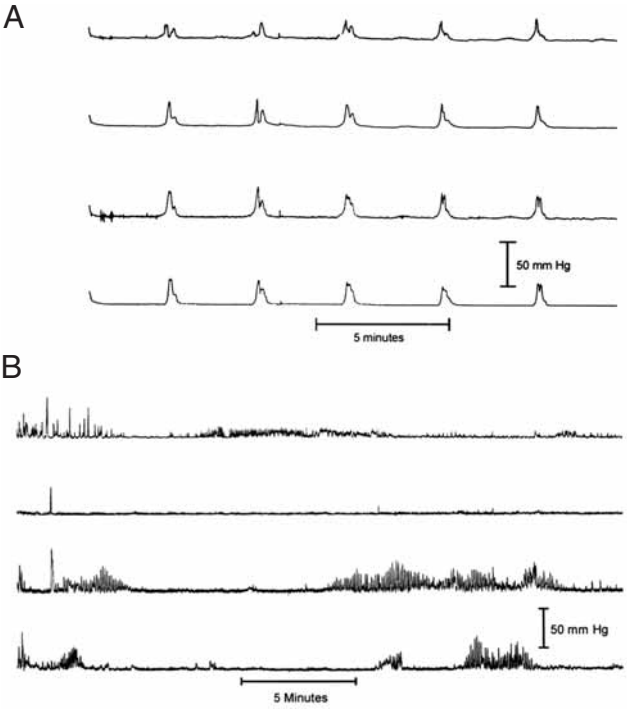

Figure 2. — *A,* Motility tracing showing simultaneous clusters and prolonged contractions in the jejunum during fasting. The tracing is compatible with a mechanical obstruction. *B*, Motility tracing showing retrograde clusters and propagated bursts in the jejunum during the postprandial period. The tracing is compatible with a neuropathic pseudo-obstruction.

clear sign of mechanical obstruction were categorized as having a chronic IPO syndrome. When the diagnosis remained uncertain, owing to the presence of inadequate follow-up information, the clinical entity was defined generically as late radiation enteropathy.

Three months postoperatively (for surgical patients) and six months after nutritional therapy began (for patients treated expectantly), the outcome was defined as the persistence or resolution of IPO, depending on whether the patient was able to reestablish oral nutrition. Surgical complications were defined as those occurring within one month postoperatively. The following were evaluated as indications of surgical morbidity: the preoperative American Society of Anesthesiologists physical status score (11), operative time, estimated blood loss, febrile morbidity (defined as having a temperature > 38°C at 2 different times, at least 6 hours apart, after the first 24 hours postoperatively), perioperative transfusions, and duration of hospital stay.

Descriptive statistics were used for the clinical and pathologic characteristics of patients. Fisher exact test, χ^2 test, and Student t-test were used when appropriate. Differences between groups were considered statistically significant at $p < .05$. SAS System 6.10 statistical software (SAS Institute, Inc, Cary, NC) was used for the analysis.

Results

For the 21 patients who were managed surgically, surgical morbidity was as follows: nine patients (43%) needed perioperative transfusions, median operative time was 179 minutes (range, 95-469 minutes), median esti-

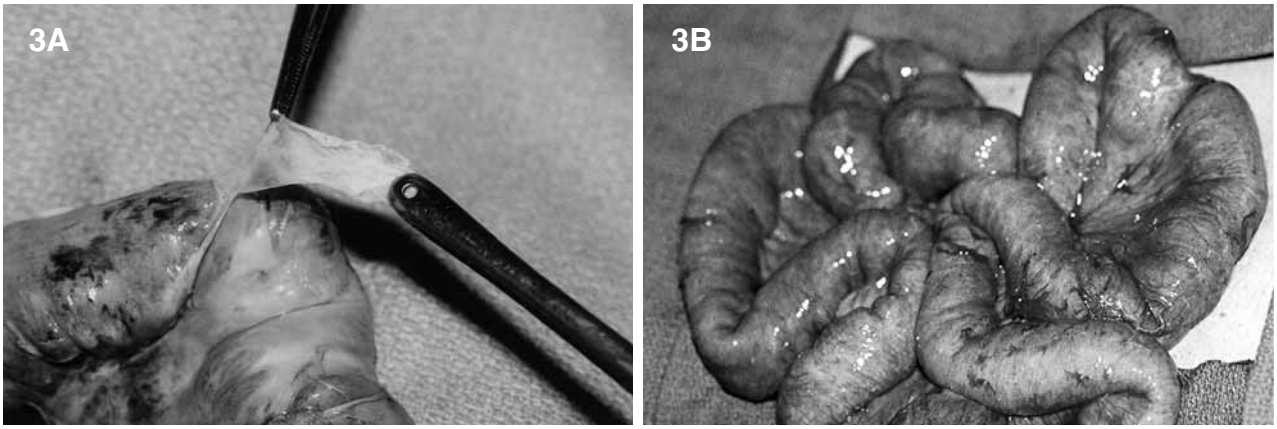

Figure 3. *A,* Macroscopic appearance of the small intestine encased in fibrinous coating. *B,* Resolution of FC six months after surgical documentation of intestinal pseudo-obstruction due to the fibrinous coating.

mated blood loss was 500 ml (range, 50-3,000 ml), and median duration of hospital stay was 19.5 days (range, 12-50 days). The following postoperative complications occurred: thromboembolic episode in one patient, dehiscence of the stoma and subsequent reoperation in one patient, and death in one patient.

Of these 21 patients, six (29%) had a final surgical diagnosis of mechanical obstruction. No point of obstruction was identified in 15 patients (71%): six demonstrated IPO reflecting probable idiopathic dysfunction and nine had a thick fibrinous coating on the serosal surface (Figure 3). Intestines of these 15 patients had patent lumens but markedly decreased motility. All 21 patients had received prior radiotherapy. Significant differences in age, mean time from cancer diagnosis to development of IPO syndrome, and mean time between radiotherapy and surgical diagnosis were observed between patients with IPO resulting from fibrinous coating and those with IPO from idiopathic dysfunction (Table 1). No differences existed between patients with fibrinous coating and idiopathic dysfunction for mean operative time, estimated volume of blood loss, duration of hospital stay, dose of radiotherapy, duration of preoperative symptoms, preoperative American Society of Anesthesiologists score, need for perioperative transfusions, or febrile morbidity.

Symptoms improved for six of the nine patients (67%) with fibrinous coating three months postoperatively, compared with one of the six patients (17%) with ID. The patient with idiopathic dysfunction whose symptoms mildly improved postoperatively needed endoscopic decompression of the intestine. The other five patients needed to be treated subsequently with long-term home total parenteral nutrition. Seven of the nine patients (78%) with fibrinous coating were receiving fluids and nutrition orally at latest follow-up, compared with three of the six patients (50%) with idiopathic dysfunction.

Among the 27 patients who were managed expectantly, mechanical obstruction became evident in six, whereas five patients were classified as having late enteropathy, owing to the scarcity of data and follow-up. Therefore, 16 patients with a final clinical diagnosis of IPO were treated expectantly. On the basis of direct intraoperative assessment and subsequent outcomes analyses in surgical patients, we identified time from completion of radiotherapy to IPO symptoms as an important clinical characteristic that could assist in the classification of the IPO syndrome (Table 1). Therefore, on the basis of time from completion of radiotherapy (radiotherapy had been administered to 14 of the 16 patients) to suspected IPO, we identified patients in whom symptoms developed within two years after treatment (clinical history consistent with fibrinous coating) and patients in whom symptoms developed after two years (clinical history consistent with idiopathic dysfunction). The clinical history was consistent with idiopathic dysfunction in six patients and with fibrinous coating in eight patients. Six of the eight patients with suspected fibrinous coating but none of the six with suspected idiopathic dysfunction had received chemotherapy before radiotherapy (Table 2). Outcomes of expectant therapy were evaluated six months after diagnosis of IPO. Improvement of symptoms was

Table 1. — *IPO characteristics associated with surgically determined FC and ID.*

Characteristic	FC (n = 9)	ID (n = 6)	p
Mean age, yrs.	53	65	<.01
Chemotherapy, no. of patients (%)	8 (89)	2 (33)	.08
Mean time from Ca Dx to IPO, mos.	22	93	.02
Mean time from RT to surg, mos.	11	85	.02

Ca Dx, cancer diagnosis; FC, fibrinous coating; ID, idiopathic dysfunction; IPO, intestinal pseudo-obstruction; RT, radiotherapy; surg, surgical diagnosis.

Table 2. — *IPO characteristics associated with clinically suspected FC and ID managed expectantly.*

Characteristic	FC (n = 8)	ID (n = 6)	p
Mean time from RT to IPO Dx, mos. (range)	9 (4-16)	104 (32-208)	.002
Chemotherapy, no. of patients (%)	6 (75)	0 (0)	.009
Mean age, yrs.	55	58	.73

FC, fibrinous coating; ID, idiopathic dysfunction; IPO Dx, intestinal pseudo-obstruction diagnosis; RT, radiotherapy.

described in three of the six patients (50%) with idiopathic dysfunction and in three of the eight patients (38%) with fibrinous coating.

Motility studies were available for 11 patients with IPO syndrome; five were managed surgically and six expectantly. Studies demonstrating IPO (n = 4) were all associated with idiopathic dysfunction, whereas studies suggestive of both mechanical obstruction and IPO (n = 3) were associated with fibrinous coating. Of the three patients for whom motility study findings suggested mechanical obstruction, surgical exploration confirmed mechanical obstruction in one and fibrinous coating in another; the third patient was treated expectantly, and the final clinical diagnosis was uncertain (late radiation enteropathy) (Table 3).

Table 3. — *Comparison of diagnoses from motility studies and definitive diagnoses for 11 patients with intestinal pseudo-obstruction.*

Motility study diagnosis	Definitive diagnosis
Surgical treatment	
MO	MO
MO	PO (FC)
MO and PO	PO (FC)
MO and PO	PO (FC)
PO	PO (ID)
Expectant treatment	
MO	PO*
MO and PO	PO (FC)
Equivocal	PO (FC)
PO	PO (ID)
PO	PO (ID)
PO	PO (ID)

FC, fibrinous coating; ID, idiopathic dysfunction; MO, mechanical obstruction; PO, pseudo-obstruction. *Late radiation enteropathy.

As expected by use of the selection criteria, radiographic findings were equivocal and did not help in distinguishing mechanical obstruction from functional obstruction. These equivocal findings had been confirmed by the review of a sample of films from 17 patients.

Histologic and immunohistochemical assessments showed mild to moderate damage of the myenteric plexus/ICC in six of the seven patients analyzed but did not correlate with surgical diagnosis or postoperative outcomes (Table 4). Likewise, serosal adhesions were associated with obstruction from either mechanical causes or fibrinous coating.

Table 4. — *Comparison of damage of the ICC network with clinical findings in seven patients*.*

ICC (MY/CM)†	Surgical diagnosis	Postoperative outcome
++/+	MO	No change
+/+	MO	Improved
+/+	MO	Improved
+++/+++	PO (FC)	No change
++/ns	PO (FC)	Improved
++/++	PO (FC)	No change
+/+	PO (FC)	No change

CM, circular muscle; FC, fibrinous coating; ICC, interstitial cells of Cajal; MO, mechanical obstruction; MY, myenteric plexus; ns, no staining; PO, pseudo-obstruction. *All tissue samples were from the small bowel. †The number of plus signs indicates the intensity of staining. Normal ICC network is indicated by "+++." No staining, "+," and "++" indicate damage.

Discussion

Radiotherapy may damage the myenteric plexus, thus leading to a functional intestinal obstruction [3, 4]. Reports of only a few patients with gynecologic malignancy and IPO have been published. Most of the patients experienced acute colonic pseudo-obstruction [12-15] rather than chronic IPO [3, 16, 17]. This is probably because IPO is an underrecognized clinical entity for patients who have intestinal obstructive symptoms after radiotherapy or chemotherapy. Alternatively, this underreporting might be due to the relatively infrequent use of whole abdominal radiotherapy for the treatment of ovarian cancer. In fact, most of the patients in our series had ovarian cancer that had been managed with postoperative whole abdominal radiotherapy.

For our analysis, we excluded patients who had IPO unrelated to radiotherapy or chemotherapy and selected only women for whom previous treatment for cancer was the only identifiable possible cause of IPO. For patients who had surgical therapy, a definitive diagnosis of mechanical obstruction or IPO was made, and patients with IPO due to fibrinous coating were correctly distinguished from those with idiopathic dysfunction. Diagnoses for patients treated expectantly are questionable, however, and they were made on the basis of clinical findings (i.e., time between radiotherapy and onset of symptoms of IPO) (Table 2).

As expected by use of the selection criteria, radiographic findings were not helpful in distinguishing between mechanical obstruction and functional obstruction. On the contrary, motility tracings were often predictive of surgical findings (Table 3). In fact, motility tracings helped to correctly predict mechanical obstruction and IPO due to idiopathic dysfunction. IPO due to fibrinous coating was often interpreted as being a mechanical obstruction or as having a mixed cause. Whether or not the function of the myenteric plexus in patients with fibrinous coating was altered (Table 4), the fibrinous coating was a mechanical obstacle for motility. Two-thirds of patients with fibrinous coating improved after surgery (compared with only one-third when treated expectantly), and motility studies assisted in distinguishing patients who might benefit from surgical treatment. As described in the study, surgical morbidity may be high in these patients and must be avoided whenever possible.

Histologic findings did not usually add useful information to the surgical findings, as previously reported [18]. For this reason, we looked for possible damage to the ICC, which had been previously reported from findings in patients with intestinal pseudo-obstruction [19]. Unfortunately, staining for ICC has been limited to seven patients with available tissue and has not been performed for any patient with demonstrable idiopathic dysfunction. The analysis of the ICC demonstrated mild to moderate damage of the ICC network in six of seven patients who had previous radiotherapy with or without chemotherapy (Table 4). The status of the ICC did not correlate with the surgical diagnosis or with the clinical outcome postoper-

atively. These findings suggest that there was damage to the ICC (due to radiotherapy or chemotherapy, or both) that was not always clinically evident. In fact, ICC are responsible for normal, coordinated gastrointestinal tract motility, and radiotherapy-induced damage to ICC may possibly contribute to the development of IPO or may simply make a mechanical obstruction more evident. Other authors previously described abnormalities in the ICC causing IPO [20].

With the selection criteria in our study, we cannot draw conclusions about the frequency of IPO syndrome in gynecologic cancer patients treated with external radiation with or without chemotherapy. However, this case series does permit recognition of the existence of IPO after radiotherapy in gynecologic cancer patients presenting with symptoms of intestinal obstruction but equivocal radiologic findings.

Conclusions

Our sample size was too small to draw definitive conclusions but, as demonstrated in Table 1, patients with the following may have idiopathic IPO that is extremely unlikely to benefit from surgery: gynecologic cancer, symptoms of chronic intestinal obstruction, unclear radiologic findings, history of previous radiotherapy, and time from initial radiotherapy to symptoms of IPO longer than two years. In those patients an operation should be avoided (or at least preceded by a trial of conservative nonsurgical therapy), and as many as 50% of them may benefit from expectant management. By contrast, patients with a mechanical obstruction or clinical characteristics consistent with an IPO due to fibrinous coating (Table 1) may benefit from surgical intervention. In fact, although surgical intervention did not always lead to a good outcome (probably some cases of obstruction had mixed causes), surgical treatment may have been more efficacious than expectant treatment in patients with fibrinous coating. Among patients with a history of gynecologic cancer, previous radiotherapy or chemotherapy, or symptoms consistent with chronic intestinal obstruction or partial obstruction but equivocal radiologic findings, the clinical history and motility studies may assist in making the correct diagnosis preoperatively, thereby guiding subsequent management decisions.

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