Perforation Due to Colon Cancer: Predisposing Factors and Clinical Presentation

Kolonik Tümör Perforasyonu: Predispozan Faktörler, Klinik Bulgu ve Semptomlar

Abdullah Bahadır ÖZ,[1] Hızır AKYILDIZ,[1] Erdoğan SÖZÜER,[1] Alper AKCAN,[1] Muhammet AKYÜZ,[1] İsmail BİRİ,[2] Ertan EMEK[1]

[1]Department of General Surgery, Erciyes University Faculty of Medicine, Kayseri;
[2]Department of General Surgery Clinic, Private Koru Hospital, Ankara

SUMMARY

Objectives

Large bowel perforation is a severe complication of colorectal cancer. Despite advances in surgery, antibiotics, and postoperative intensive care, the possibility of bowel perforation remains. The aim of this study was to evaluate the clinical presentation and predisposing factors of colonic perforation due to colorectal cancer.

Methods

We conducted a retrospective study that included 720 patients that received surgery to treat colorectal adenocarcinoma from June 2009 to May 2013. Patients were classified into 2 groups: group 1 included patients that received surgery for perforated colorectal cancer, and group 2 was comprised of patients that underwent elective surgery to correct hemorrhagic or obstructing colon cancer. Perforation at the tumor site was defined as a perforation in the immediate vicinity of the primary tumor. Medical records were retrospectively analyzed. A p-value less than 0.05 was statistically significant.

Results

Of all 720 patients, 28 qualified for placement into group 1 and 692 patients qualified for placement into group 2 (0.00389%, 95% confidence interval 0.0270-0.0556). No statistically significant difference was observed between groups in terms of demographic data, tumor differentiation, histological and nuclear grades, and local invasion. However, presence of perineural invasion, peritonitis carcinomatosa, and T4 stage classification were significantly different between groups 1 and 2 ($p<0.001$).

Conclusions

Risk factors for perforation due to colon cancer include presence of tumor perineural invasion, peritonitis carcinomatosa and T4 stage classification. This presentation may be utilized clinically to help guide and anticipate appropriate treatment.

Key words: Colorectal; peritoneal carcinomatosis; tumor perforation.

ÖZET

Amaç

Kolon perforasyonu, kolorektal kanserlerde kötü sonuçları düşündüren bir komplikasyondur. Cerrahi, antimikrobiyal tedavi ve ameliyat sonrası yoğun bakım uygulamalarında ilerlermeler olmasına rağmen bu durum kaçınılmaz şekilde devam etmektedir. Bu çalışmanın amacı kolorektal tümör perforasyonlarında predispozan faktöleri, klinik bulgu ve semptomları değerlendirmektir.

Gereç ve Yöntem

Haziran 2009-Mayıs 2013 tarihleri arasında kolorektal kanser nedeni ile ameliyata alınan 720 olgu geriye dönük olarak incelendi. Olgular iki gruba ayrıldı. Kolorektal kanser perforasyonu nedeni ile ameliyat edilen olgular grup 1, elektif ya da tümör tıkanıklığına bağlı veya kanama nedeni ile ameliyat edilen olgular ise grup 2 olarak ifade edildi. Tümör alanındaki peforasyon, primer tümörün olduğu yerde oluşan peforasyon olarak tanımlandı. Olgulardan elde edilen klinikopatolojik ve tıbbi verilerin analizi yapıldı. $P<0.05$ değeri istatiksel olarak anlamlı kabul edildi.

Bulgular

Yedi yüz yirmi olgu arasında 28 (%0.00389, %95 güvenlik aralığı 0.0270-0.0556) olgu kolorektal tümör perforasyonu nedeni ile ameliyat edildi ve grup 1' i oluşturmakta idi. Diğer 692 olgu ise ile grup 2'yi oluşturmaktaydı. Grup 1'de en çok görülen şikayet ani başlayan karın ağrısı tespit edildi. Her iki grup arasında demografik veriler, tümör faklılaşması, histolojik ve nüklear evresi açısından anlamlı bir fark görülmedi. Perinöral invazyon, peritonitis karsinomatoza ve T4 evre açısından ise gruplar arasında anlamlı fark tespit edildi ($p<0.001$).

Sonuç

Perinöral invazyon, peritonitis karsinomatoza ve T4 evre kolorektal tümör perforasyonu için istatiksel olarak anlamlı klinikopatolojik faktörler olduğunu saptadık.

Anahtar sözcükler: *Kolorektal; peritonitis karsinomatoza; tümör perforasyonu.*

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Correspondence *(İletişim):* Dr. Abdullah Bahadır Öz. Erciyes Üniversitesi Gevher Neshibe Hastanesi, 6 Kat, Genel Cerrahi Servisi, 38039 Kayseri, Turkey.
e-mail *(e-posta):* drbahadir01@gmail.com

Introduction

Colorectal cancers are among the most commonly diagnosed cancers in developed countries. Large bowel perforation is a severe complication of colorectal cancer. Besides diverticulitis, colon cancer is the second most common cause of peritonitis requiring emergent surgery.[1,2] Despite advances in surgical techniques, antimicrobial therapies, and postoperative intensive care, secondary peritonitis due to colonic perforation continues to be a potentially fatal outcome for which the operative mortality ranges from 12% to 43%.[3,4] Moreover, the reported incidence of perforations due colorectal cancer is between 1.2% to 10%.[5,6]

Comorbid medical problems, overall patient health, peritonitis severity, and cause of perforation all influence prognosis and the decision as to whether surgery should be performed.[1] Colonic perforation due to malignancy is difficult to treat because both the cancer and perforation are to be treated simultaneously. Though many studies have evaluated nondiverticular colon perforation risk factors, emergent operation techniques, and tumor recurrence in the colon and rectum, there is a paucity of data regarding the predisposing factors and clinical presentation of colon perforation due to cancer.[7,8] Therefore, the aim of this retrospective study was to investigate the clinical presentation and risks leading to cancer-mediated colon perforations.

Materials and Methods

A retrospective chart review was performed for patients that received surgery for colorectal adenocarcinoma at Erciyes University Medical Faculty in the Department of General Surgery between June 2009 and May 2013. Patients were stratified into 2 groups: group 1 included patients that received surgery for perforated colorectal cancer and group 2 underwent elective surgery for obstructing or bleeding colon tumors that were proximal to the perforation. Perforation at the cancer site was defined as a perforation in the immediate vicinity of the primary tumor. An adherent tumor was defined as a tumor attached to an adjacent organ or structure in a manner that limited colon motility. Tumor adherence to organ structures may occur via direct tumor infiltration, an inflammatory process, or both. The term peritonitis carcinomatosa was used to describe patients with widespread peritoneal dissemination of the cancer with omental involvement.

Medical data were obtained and retrospectively analyzed from the emergency outpatient clinic, general surgery discharge notes, and pathology and imaging archives including computed tomography, abdominal X-rays, and chest X-rays. Patient demographics and clinical data that were studied included patient gender; age; initial presenting complaints; findings on physical exam; depth of tumor invasion; number of lymph node metastases and distant metastases; extent of tumor cell differentiation; presence of lymphatic, vascular, and/or perineural invasion; cancer location; degree of inflammation; coexistence of peritoneal carcinomatosis; and histological and nuclear grade. Extent of intraperitoneal tumor spread and the determination of the presence of liver metastases were based on findings during surgery. Tumors were classified according to the tumor node metastasis (TNM) system (International Union Against Cancer). Tumor size was determined based on the greatest surface dimension.

Patients with clinical signs of peritonitis, sepsis with fever, or leukocytosis were evaluated clinically and imaging was performed including abdominal ultrasonography or computed tomography. All patients with colon perforations were admitted to the hospital from the emergency department and underwent surgery within 24 hours after admission. Preoperative evaluation included blood tests and abdominal and chest radiographs. Parenteral antibiotic therapy against both aerobic and anaerobic bacteria was started immediately after admission if there was suspicion of perforation. This study was reviewed and approved by the ethics committee prior to the commencement of the investigation.

Statistical analysis

The independent sample t-test and the chi-squared test were used to compare the differences between groups. Data were analyzed with SPSS version 13.0 software package (SPSS, Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

Results

In this retrospective study 720 patients underwent surgery for colorectal cancer. Among the 720 patients, 28 subjects (0.00389%, 95% confidence interval [CI] 0.0270-0.0556) had colon cancer with perforation in the immediate vicinity of the primary tumor and so were placed into group 1. Group 2 was comprised of 692 patients. The most common presenting complaint was sudden onset of abdominal pain (100%) followed by abdominal distension (89.3%), nausea (67.9%), and vomiting (42.9%) in group 1. Furthermore, tenderness to abdominal palpation was present in every group 1 patient. The great majority of colonic perforations were clinically diagnosed. Free air in the abdomen was evident in abdominal and chest radiographs in 75% of patients in group 2. Malignant tumors were mainly localized in the left colon and were diagnosed in 71.4% of group 2 patients. Colon perforations occurred most frequently in the sigmoid colon and was observed in 50% of all bowel perforations. Demographic and clinical data are organized in Table 1. Tumor infiltration and subsequent organ adhesion was dem-

Table 1. Statistical analysis of possible risk factors of cancer-mediated colon perforation

Variables	Perforated colon cancer (n=28)			Colon cancer without perforation (n=692)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			59.6±12.1			58.2±11.7	0.5
Gender							1.0
Female	15	53.5		358	51.7		
Male	13	46.5		334	48.2		
Vascular invasion	12	42.8		208	30		0.2
Perineural invasion	18	64.2		97	14		**<0.001**
Mucinous component	9	32.1		196	28.3		0.8
Inflammatory response	22	78.5		622	89.8		0.1
Peritonitis carcinomatosa	22	78.5		47	6.7		**<0.001**
T_4 stage	26	92.8		114	16.4		**<0.001**
Frequent mitoses	15	57.6		378	54.6		1.000
Tumor size (cm)			6.2±3.1			5.3±2.9	0.08

onstrated histologically in 41.3% of colonic tumors and 31.2% of rectal tumors. There were no significant differences regarding tumor size, histological and nuclear grades, and local invasion between both groups. However, the presence of perineural invasion (p<0.001), peritonitis carcinomatosa (p<0.001), and advanced T4 stage classification (p<0.001) were all found to be significant risk factors contributing to colon perforation.

Discussion

Emergent operative interventions are performed to treat colorectal cancer in 7% to 40% of patients with colon cancer.[9] The majority of emergent surgeries are due to complete obstruction rather than perforation as 8% to 40% of cases are obstructions versus the 3% to 10% that are colonic perforations.[10] Perforation due to colorectal cancer may occur due to tumor necrosis or proximal perforation resulting from a marked colonic dilatation.

Most colonic perforations present without obstruction. Perforations occur commonly at the tumor site due to tissue necrosis; however, perforations secondary to acute obstruction is even less frequent.[7] Many reports describe the high morbidity and mortality associated with colorectal perforations due to colon cancer.[11-14] Interestingly, neoplastic perforation was also reported to be the only significant indicator for increased disease-free survival. In fact, patients with large bowel perforations at the tumor site generally had a better 5-year survival rate than patients that had perforations that were proximal to the cancer site.[8] Fecal peritonitis secondary to perforation is a life-threatening condition, as it may progress to septic shock and is a known contributor of higher intraoperative mortality. Furthermore, for patients that survive an operation to correct a large bowel perforation secondary to fecal peritonitis, there remains high postoperative morbidity that delays and complicates chemotherapy protocols. However, early diagnosis of cancer-mediated colon perforation may improve survival and decrease morbidity, and so greater knowledge regarding its risks and clinical presentation may positively influence clinical outcome.

Our study demonstrated that cancer-induced colonic perforation is independently associated with T4 stage classification, peritoneal carcinomatosis and perineural invasion. Perforation may be due to the tumor inducing vascular and stromal changes resulting from direct invasion by tumor cells.[15] Tumor cells in the perineural space spread in a continuous fashion. Together the changes in tissue architecture and the means by which tumor cells spread may account for how late stage tumors contribute to large bowel perforations. The incidence of perineural invasion in gastric and pancreatic carcinomas is high and has been reported to correspond with disease progression, but perineural invasion is relatively rare in rectal carcinoma.[16-18] In group 2, perineural invasion was present in only 14% of the patients while in group 1 it was present in 64% of patients. Thus, perineural invasion might be a good clinical predictor of large bowel perforation due to colorectal cancer.

Patients with colonic perforations also had significantly higher rates of peritoneal carcinomatosis (p<0.001). These higher rates may be due to the degree of tumor aggres-

siveness and might reflect the degree of neoangiogenesis and lymphatic obstruction that facilitate both local tissue invasion and systemic spread.[19] Patients with clinical presentations consistent with an acute bowel perforation were much more likely to have an adherent tumor.[15] Surgical or spontaneous bowel perforations occur more commonly in adherent tumors versus nonadherent tumors. Moreover, it has been reported that tumor adherence to organs is associated with a poorer prognosis. Tumor adherence limits the mobility of the attached colonic segment by direct tumor infiltration and/or an inflammatory process, which likely facilitate perforation.

Malignant perforation occurred in 3.8% of all patients in our study, which is in accord with previously reported data. Perforated colorectal cancer has two major complications including generalized peritonitis caused by leaking fecal material and tumor cell spillage into the peritoneal cavity through the perforation site. Additionally, the incidence of local tumor recurrence becomes even more likely if the tumor perforates through the colon wall. As such, cancer-mediated colonic perforation has a poor prognosis. More than 15% of colorectal carcinomas present either as acute large bowel perforations or obstructions despite routine colon cancer screening and endoscopy.[9]

Accurately evaluating risk factors for large bowel perforation preoperatively may aid in stratifying patients according to their morbidity and mortality so to facilitate making treatment decisions. If patients are at high risk for large bowel perforations, then considering adjuvant therapy may be warranted. With the knowledge that the patient is at high risk for bowel perforation, the treating physician may be more alert to symptoms that indicate this condition and may be more likely to treat the patient with preoperative adjuvant therapy.

Our study had several limitations as it was conducted retrospectively and the number of patients stratified between each group was very unequal, which caused a reduction in statistical power.

Conclusion

Perineural invasion, peritonitis carcinomatosa and T4 stage classification were found to be statistically significant risk factors contributing toward cancer-mediated colonic perforation. Sudden onset of abdominal pain was the most common presenting complaint for patients with colon perforations. We suggest that further studies explore the risks contributing to large bowel perforations in colon cancer patients so to create a standardized preoperative protocol such that physicians may plan their treatments accordingly to prevent perforation.

Conflict of Interest

The authors declare that there is no potential conflicts of interest.

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