

CASE REPORTS PRIKAZI SLUČAJEVA

LARGE BOWEL OBSTRUCTION DUE TO METASTASIS OF PANCREATIC CANCER – CASE REPORT AND LITERATURE REVIEW

OPSTRUKCIJA DEBELOG CREVA IZAZVANA METASTAZOM KARCINOMA PANKREASA – PRIKAZ SLUČAJA I PREGLED LITERATURE

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Case report

Prikaz slučaja

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Abstract

Introduction. Pancreatic cancer is among the most aggressive malignancies, with a poor prognosis. The liver, peritoneum, lungs, and distant lymph nodes are the most common metastatic sites. However, metastasis of pancreatic cancer to the large bowel is extremely rare. **Case Report.** A 48-year-old male with pancreatic cancer underwent radical pancreateosplenectomy in August 2022, accompanied by subtotal gastrectomy, partial resection of the transverse colon, and resection with reconstruction of the splenic vein. He subsequently received six cycles of adjuvant therapy based on the 5-fluorouracil/Leucovorin protocol, which concluded in February 2023. Routine follow-ups revealed multiple liver metastases by June 2023. First-line systemic treatment with the mono-Gemcitabine protocol was initiated, but disease progression occurred after three cycles. The patient then transitioned to second-line therapy with the De Gramont/Cisplatin protocol. During the second cycle, he developed intestinal obstruction necessitating emergency surgery, during which a sigmoidostomy was performed. Intraoperative biopsy of a tumor mass in the sigmoid colon confirmed metastasis of the previously operated pancreatic ductal adenocarcinoma into the colonic wall. **Conclusion.** Metastasis of invasive ductal pancreatic adenocarcinoma to the colon wall, causing intestinal obstruction, is an extremely rare occurrence, with only a few cases documented in the literature. Histopathological analysis of any colonic mass in patients with a history of pancreatic ductal adenocarcinoma is crucial to differentiate between primary colorectal cancer and metastatic lesions originating from pancreatic cancer. **Key words:** Intestinal Obstruction; Colon; Colon, Sigmoid; Pancreatic Neoplasms; Neoplasm Metastasis

Introduction

Pancreatic cancer is one of the most aggressive malignant diseases, characterized by a poor prognosis.

Sažetak

Uvod. Karcinom pankreasa je jedan od najagresivnijih oblika malignih bolesti sa lošom prognozom. Najčešća mesta metastaza karcinoma pankreasa su jetra, peritoneum, pluća i udaljeni limfni čvorovi. Metastaza karcinoma pankreasa u debelo crevo je izuzetno retka pojava. **Prikaz slučaja.** Pacijent, muškog pola, star 48 godina koji boluje od karcinoma pankreasa bio je podvrgnut operaciji u avgustu 2022. godine kada je načinjena radikalna pankreatosplenektomija sa suptotalnom gastrektomijom, parcijalnom resekcijom transverznog kolona, resekcijom i rekonstrukcijom lijenalne vene. Pacijent je primio adjuvantnu terapiju po protokolu 5-fluorouracil/Leucovorin u šest serija do februara 2023. godine i redovno je bio praćen do pojave više metastaza u jetri do juna 2023. godine. Počeo je prvu liniju sistemskog lečenja po mono-Gemcitabin protokolu u tri serije, nakon čega je došlo do progresije bolesti. Pacijent je nastavio sa drugom linijom lečenja po De Gramont/Cisplatin protokolu i dok je primao drugu seriju terapije razvio je crevnu opstrukciju. Načinjena je hitna operacija sa kreiranjem sigmoidostomije, a intraoperativno je uočena i biopsirana tumorska masa u sigmoidnom debelom crevu. Definitivni histopatološki nalaz ukazivao je na metastazu prethodno operisanog karcinoma pankreasa u zid debelog creva. **Zaključak.** Metastaza invazivnog duktalnog adenokarcinoma pankreasa u zid debelog creva, sa posledičnom crevnom opstrukcijom, izuzetno je redak entitet sa samo nekoliko slučajeva opisanih u dostupnoj literaturi. Svaku masu debelog creva kod pacijenata sa istorijom pankreasnog adenokarcinoma treba patohistološki analizirati kako bi se razlikovao primarni kolorektalni karcinom i metastaza koja potiče od karcinoma pankreasa. **Cljučne reči:** opstrukcija creva; debelo crevo; sigmoidni kolon; karcinom pankreasa; metastaza

Pancreatic ductal adenocarcinoma (PDAC) accounts for over 85% of all pancreatic cancer cases and represents the most common form of this malignancy [1]. The disease is marked by a prolonged asymp-

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Abbreviations

PDAC	– pancreatic ductal adenocarcinoma
MRI	– magnetic resonance imaging
CT	– computed tomography
AP	– anterior-posterior
LL	– laterolateral
CC	– craniocaudal
5FU/LV	– 5 fluorouracil and leucovorin
HE	– hematoxylin eosin
WBC	– white blood cells
CRP	– C-reactive protein
IHC	– immunohistochemistry
CK	– cytokeratin

tomatic course and early metastasis to distant organs, making its progression highly unpredictable. The liver, peritoneum, lungs, and distant lymph nodes are the most common metastatic sites, while rarer locations include the bones, kidney, and skin [2]. Metastasis to the large intestine is an extremely rare occurrence, with only a few cases reported in the literature. Documenting such cases is essential to enhance understanding of PDAC's metastatic behavior and its clinical implications.

Acute abdomen is a clinical entity characterized by sudden and severe abdominal pain. The differential diagnosis is broad, encompassing various potential causes, which can complicate diagnosis and management. In patients with a history of malignancy, acute abdomen poses a significant challenge, requiring a multidisciplinary approach to achieve optimal care.

Case Report

This report details the case of a 48-year-old male undergoing treatment for pancreatic cancer. The patient had a significant history of smoking (one pack daily for 30 years) and regular alcoholic consumption. His past medical history included childhood epilepsy, and there was no family history of malignancy.

Clinical suspicion of pancreatic cancer arose in July 2022 after the patient underwent magnetic resonance imaging (MRI) of the abdomen due to severe epigastric pain radiating to the back and unintentional weight loss of 10 kg over three months. Radiological findings revealed a poorly defined, partially cystic soft-tissue mass located at the transition line between the body and tail of the pancreas, measuring approximately 47x55x48 mm (APxLLxCC). The mass appeared to infiltrate the splenic vein, the greater curvature of the stomach, and possibly a part of the transverse colon. A multidisciplinary team deemed the tumor resectable, and radical surgical treatment was performed in August 2022. The procedure included a radical antero-grade modular pancreatosplenectomy, subtotal gastrectomy and "Roux-en-Y" reconstruction, resection

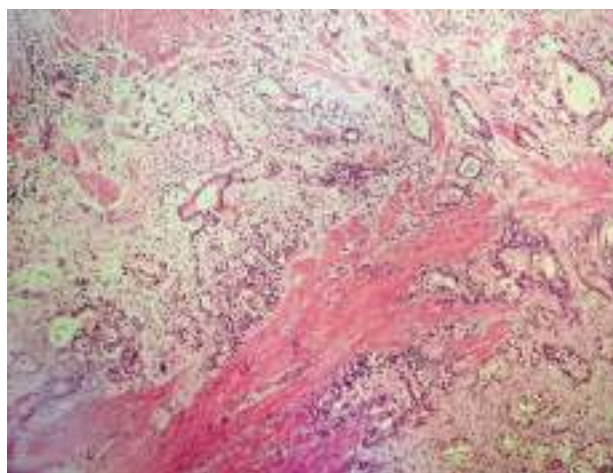


Figure 1. Moderately differentiated invasive pancreatic ductal adenocarcinoma with lymphovascular and perineural invasion (HE, 40x)

and reconstruction of the splenic vein, and resection of the transverse colon with T-T anastomosis. Histopathological examination confirmed a moderately differentiated invasive ductal adenocarcinoma with lymphovascular and perineural invasion (**Figure 1**). Malignant infiltration was found in 2 of 25 resected locoregional lymph nodes. The disease was staged as pT3N1, corresponding to stage IIB per the American Joint Committee on Cancer.

Given the disease stage, the multidisciplinary oncology team indicated adjuvant therapy with six cycles of 5-fluorouracil and leucovorin (5FU/LV) over three months. The patient completed treatment by February 2023 without delays or significant side effects. Follow-up imaging in March 2023, including chest computed tomography (CT) scan and abdominal MRI showed no signs of disease dissemination or local recurrence.

In June 2023, routine MRI of the abdomen detected multiple focal lesions in the liver with metastatic characteristics, localized in the following segments: S8/S4a (12 mm), S2 (12 mm) and subcapsular in S5 (10 mm). Chest CT findings were negative for metastasis. Due to the progression of the disease, first-line treatment with mono-Gemcitabine protocol was initiated, and the patient received three cycles by September 2023 without side effects and complications. However, subsequent abdominal MRI showed disease progression, with enlargement of the liver lesions and new retroperitoneal lymphadenomegaly, with the largest one located in the coeliac trunk area with a short diameter of 10.5 mm. Second-line treatment with 5-fluorouracil and cisplatin (De Gramont/CDDP protocol) was started.

The first cycle of the second-line treatment proceeded without any adverse events. Two weeks after

the initial chemotherapy session, the patient was routinely hospitalized for the second cycle but reported abdominal discomfort upon admission. Laboratory findings before hospitalization were satisfactory, and the initial clinical examination revealed no anomalies. The patient was administered a nonsteroidal painkiller, and the planned chemotherapy was initiated. On the second day of chemotherapy, the patient experienced an acute exacerbation of his abdominal pain and called for urgent medical assistance.

His clinical presentation included diffuse abdominal pain resistant to pain relief medication, nausea, persistent vomiting, and the absence of stool and gas passage. Clinically, the patient appeared pale, with unstable vital signs. Abdomen examination showed absence of peristalsis, metallic high-pitched bowel sounds in the lower left quadrant, distention, meteorism, and diffuse tenderness to superficial and deep palpation, with clinical signs of peritoneal irritation.

Laboratory test revealed a significantly elevated white blood cell (WBC) count of $14.36 \times 10^9/L$ (reference range: $4-10.0 \times 10^9/L$), primarily due to an elevated neutrophil count (absolute neutrophil count $11.77 \times 10^9/L$; reference range: $2-7.0 \times 10^9/L$), along with a high level of C-reactive protein (CRP 193.7 mg/L; reference value: <5 mg/L). Combined with his unstable vital signs, these findings indicated an acute inflammatory response. An abdominal X-ray demonstrated multiple air-fluid levels without signs of pneumoperitoneum, indicative of bowel obstruction without bowel perforation.

The oncology surgeon on duty was consulted and, after reviewing the patient's medical history, transferred him from the Department of Differential Oncology Treatment to the Department of Oncological Surgery. Emergency surgery was performed the following day. Intraoperatively, multiple metastatic deposits were found in the abdominal cavity, with severe distention of both the small and large intestines. Complete luminal obstruction of the distal sigmoid colon was caused by a tumor mass, while the proximal ileum was partially obstructed due to external compression from peritoneal metastasis. The sigmoid colon was mobilized, a loop sigmoidostomy was created, and the tumor mass was biopsied. Additionally, the subocclusive segment of the ileum was resected, followed by an L-L ileo-ileo anastomosis. Histopathological analysis of the sigmoid tumor confirmed metastasis of previously diagnosed ductal adenocarcinoma of the pancreas (**Figure 2**). Postoperatively, the patient's general condition improved, and the planned systemic treatment regimen resumed. He received a total of five cycles of chemotherapy by February 2024. At a follow-up in March 2024, abdominal MRI re-

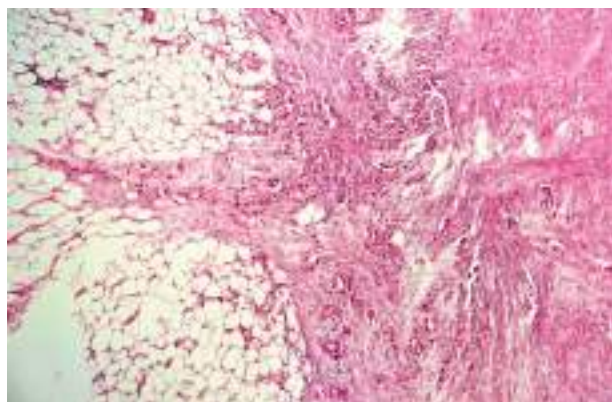


Figure 2. Metastasis of moderately differentiated invasive ductal adenocarcinoma infiltrating sigmoid colon wall (HE, 40x)

vealed persistent small bowel distention due to progressing peritoneal carcinomatosis. However, the liver metastases in segments S2, S5, and S8 showed regression (12 mm to 8 mm, 12 mm to 9 mm, 10 mm to 9 mm, respectively). A CT scan of the chest indicated newly developed thrombosis in the intralobar pulmonary arteries on the right and in individual branches for the left basal lobe. Following this outpatient follow-up, the patient ceased attending regular visits and hospitalizations for continued differential oncology treatment.

Discussion

This case highlights the rare occurrence of pancreatic ductal adenocarcinoma (PDAC) metastasizing to the colonic wall, resulting in intestinal obstruction. To the best of the authors' knowledge, only a limited number of such cases have been reported cases in the literature.

Pancreatic ductal adenocarcinoma accounts for more than 85% of all pancreas cancer cases [1]. It is one of the most aggressive malignancies, with a 5-year survival rate of less than 5% and a median survival of 17 to 23 months. In the absence of treatment for metastatic disease, life expectancy is typically less than three months [3]. The incidence of PDAC peaks in the seventh decade of life, ranking as the 11th most common malignancy globally and the 7th leading cause of cancer-related deaths [4]. Its poor prognosis is underscored by the near equivalence of its annual incidence and mortality rates.

The etiology of PDAC remains unclear, likely multifactorial, with several identified risk factors. These are categorized into non-modifiable factors such as age, gender, race, family history, and hereditary genetic syndromes [5], and modifiable factors, including smoking, alcohol consumption, type 2 diabetes, obes-

ity, and chronic pancreatitis. Men are twice as likely to develop pancreatic cancer compared to women of the same age [4]. Hereditary pancreatic cancers account for about 10% of all cases, one-third of which are caused by hereditary genetic syndromes and two-thirds belong to the group of family cancers with a positive family history. Multiple studies have identified smoking as the leading risk factor for developing pancreatic cancer not only for passionate smokers but also for people smoking several cigarettes a day, and even for passive smokers [6]. Alcohol consumption was also studied thoroughly, emphasizing its role in carcinogenesis of pancreatic cancer, especially in heavy-drinkers (>60 g of ethanol per day) [7]. Type 2 diabetes is the third most significant modifiable risk factor that increases the risk 1.5- to 2-fold, with most cases manifesting 2-3 years before the initial diagnosis [8]. Obesity has shown to increase risk of developing pancreatic cancer by 2-fold. Increase in body mass index by 5 kg/m² was associated with a 12% greater risk of the disease [9]. Recent studies have revised the link between chronic pancreatitis and PDAC, indicating the highest cancer risk occurs shortly after diagnosis, emphasizing the need for close monitoring especially in the first year after diagnosis [10].

Surgical resection remains the only potentially curative treatment for PDAC [11]. However, more than 80% of cases are diagnosed in advance stages, precluding curative intervention. Approximately half of newly discovered PDAC cases present with metastatic disease. This is mainly due to its prolonged asymptomatic period and early propensity for distant spread. Even after potentially curative resection followed by adjuvant chemotherapy, most patients will experience recurrence with a five-year survival rate of 25% [12]. Nevertheless, recurrence of pancreatic cancers, either as a local or metastatic disease, occurs even after R0 residual status in up to 80% of patients [12]. A retrospective study by Kovač JD, et al. estimated a mean recurrence time after radical surgical resection was 17.4 months [13]. PDAC, like most malignancies, can spread in any part of the body. The most common metastatic sites are liver (21-80%), lungs (7-28%), distant lymph nodes (18-25%), and peritoneum (11-23%). Less common sites of metastasis are bones, kidney and skin. Metastasis of pancreatic cancer to the intestinal wall is an extremely rare entity, with only few cases reported so far [14-25].

A detailed literature review using PubMed, by implementing the criteria “metastatic PDAC OR pancreatic ductal adenocarcinoma OR PC OR pancreatic cancer AND large intestine OR colon OR large bowel”, identified 12 case reports meeting the above criteria, which are presented in **Table 1**.

The first documented case of large bowel obstruction due to metastasis of pancreatic cancer was reported by Tresadern C. John in 1981 [14]. This case laid the groundwork for subsequent descriptions of this rare clinical phenomenon. Analysis of the available literature suggests a significant rise in interest over the past decade, with an increasing number of cases being reported each year. This trend may be attributed to the introduction of novel therapeutic regimens that have extended the overall survival of pancreatic cancer patients, thereby allowing more time for such metastases to develop. Additionally, advancements in radiology and pathology have likely improved diagnostic accuracy and efficiency, contributing to the identification of more cases.

The mean age at diagnosis of intestinal obstruction due to PDAC metastasis was 68 years, consistent with the epidemiological data, indicating that the disease incidence is highest in the seventh decade of life [4]. The youngest recorded patient was 45 and the oldest was 91 years old. In terms of gender, there were seven men and five women, suggesting that the male sex is more likely to suffer from this disease compared to female [1, 4].

The clinical presentation at diagnosis varied, with abdominal pain and constipation being the dominant ones. In some cases, constipation preceded the onset of abdominal pain [16, 19, 24]. Unintentional weight loss and appetite loss [15, 20, 23, 25] were also frequently reported, which was expected as that these are the most common manifestation of malignant diseases, especially pancreatic cancer. These nonspecific symptoms overlap with those of primary gastrointestinal malignancies, complicating the diagnosis.

Regarding the localization of PDAC metastases in the large bowel, they were predominantly found on the left side of the colon, particularly in the sigmoid region. This localization complicates the differentiation between pancreatic cancer metastases and primary colon cancer, as primary malignancies are also more commonly observed on the left side of the colon. In all reported cases of intestinal obstruction, the initial assumption was that the obstruction was caused by a primary colon tumor. However, post-resection histopathological analysis confirmed the presence of PDAC metastasis in the colon. While most cases involve a single metastasis site, some reports documented multiple metastatic sites [18, 20].

The analysis of **Table 1** reveals a higher incidence of synchronous presentations of pancreatic cancer and colonic metastases. In these cases, the primary tumor manifested with a nonspecific clinical symptoms until the onset of intestinal obstruction. The synchronous discovery of the primary tumor and metastasis is like-

Table 1. Comprehensive Overview of Metastatic PDAC to the Large Intestine: Case Summaries

Author	Age/ Gender	Manifestation	PDAC Diagnosis history	Histopathology (Primary tumor)	Metastasis location	Histopathology (Metastatic PDAC)	Treatment
Tresad- ern. (1981) [14]	68/M	Colicky abdominal pain and alternating constipation and diarrhea for 5 weeks	synchronous	N/A	Transverse colon	N/A	Palliative care
Bellows et al. (2009) [15]	45/M	Several months of severe epigastric pain and unintentional weight loss	synchronous	N/A	Ascending colon	CA 19-9+, EMA+ and CEA+, CK7 -, CK20 - CDX2 -	N/A
Ogu et al. (2012) [16]	85/F	One week obstipation and intermittent abdominal pain	post-pancreaticoduodenectomy 24 months prior	Stage IIA	Mid sigmoid colon	Strong CK7 + and weak CK20 +, CA 19-9+	Hartmann's operation with adjacent lymphadenectomy
Inada et al. (2013) [17]	62/M	Abdominal distension and pain	Pancreatoduodenectomy 7 years prior	pT2N1M0 stage IIB	Ascending colon	Strong CK7+ and CK20 -	Right hemicolectomy with adjacent lymphadenectomy
Kim et al. (2015) [18]	64/M	Diffuse abdominal pain for 2 weeks	Distal Pancreatectomy 2 years prior	pT3N0M0 stage IIA	Ileocecal valve	Strong CK7+ and CK20 -	Right hemicolectomy
Kelley et al. (2016) [19]	67/F	Four day of worsening abdominal pain and ten day Obstipation	synchronous	N/A	Distal sigmoid colon and rectum	N/A	Excision of the obstructed bowel and end colostomy
Gizzi et al. (2017) [20]	70/F	Progressive weight loss and reduction of appetite	synchronous	N/A	Transverse and descending colon	Strong CK7+ and CK20 -	N/A
Nogueira et al. (2018) [21]	60/M	Low abdominal pain for two months	synchronous	N/A	Sigmoid colon	CK7+ and CK20 -, CDX2 -	Resection of the sigmoid tumor and colostomy placement after perforation
Miyasaka et al. (2018) [22]	63/M	Abnormal laboratory tests (elevated CRP 3 months post operation), later abdominal pain	Pancreatoduodenectomy (R0 resection) after neoadjuvant therapy	Poorly differentiated PDAC pT2N0M0 stage IB	Transverse colon and jejunum	Poorly differentiated PDAC	Extirpation of the tumor mass
Kahl et al. (2019) [23]	91/F	Unintentional weight loss, constipation and nausea	synchronous	N/A	Sigmoid colon	Well differentiated PDAC CK7+ and CK20 -, CDX2 -	Palliative resection of the sigmoid with end colostomy
Park et al. (2019) [24]	73/F	Lower abdominal pain radiating in the back and obstipation for 10 days	synchronous	Moderately differentiated PDAC within a desmoplastic stroma CK7+ and CK20 - Stage IV	Sigmoid and descending colon	Moderately differentiated PDAC pT3N2 CK7+ and CK20 -, CDX2-, SATB2 -	Subtotal colectomy and ileostomy
Meng et al. (2023) [25]	65/M	Lower abdominal pain and unintentional weight loss	synchronous	Stage IV PDAC Strongly CK7+ and CK20 -	Sigmoid colon	Strongly CK7+ and CK20 -	Systemic treatment with mono Gemcitabine and Nab-paclitaxel

Legend: PDAC - Pancreatic Ductal Adenocarcinoma; N/A - Not Available; M - male; F - female; IHC - Immunohistochemistry; CA 19-9 - Carbohydrate Antigen; EMA - Epithelial Membrane Antigen; CEA - Carcinoembryonic Antigen; CK 7/20 - Cytokeratin; CDX2 - Caudal-Type Homeobox gene, CRP - C-Reactive Protein; SATB2 - Special AT-rich Sequence-Binding Protein 2

ly due to the unpredictable biological behavior of pancreatic cancer, characterized by its propensity for early and distant metastases, even when the pancreatic tumor is relatively small and subclinical. Conversely, the

occurrence of metachronous PDAC metastasis in the colon varied significantly, with timelines ranging from a few months [22] to several years [17] following the radical resection of the primary tumor.

Case reports on this topic emphasize the importance of additional histopathological diagnostics, particularly immunohistochemical (IHC) analyses, to reliably differentiate pancreatic cancer metastases from primary colon cancer. The most commonly utilized IHC markers in these cases are cytokeratin (CK) 7 and CK20, where CK7-positive and CK20-negative findings indicate an extraintestinal origin of the tumor in the bowel [16, 18, 20]. IHC analyses are especially beneficial in cases of synchronous presentation of pancreatic cancer and colon tumor changes. Furthermore, the presence of tumor cells in the submucosa without mucosal invasion, combined with the absence of precursor lesions such as adenomas or serrated polyps, strongly support the metastatic origin of colonic tumor changes [14].

Therapeutic strategies in most reported cases have involved palliative resection of the tumor mass and/or the creation of a protective stoma. Since ileus is a medical emergency, it requires prompt intervention to preventing fatal outcomes. Notably, the case described by Meng et al. [25] highlights systemic therapy as a viable

treatment option for this clinical entity. The authors underscore the importance of achieving a preoperative diagnosis, emphasizing that in cases where PDAC metastases in the colon do not result in mechanical obstruction, systemic therapy may serve as the primary treatment modality.

Conclusion

Metastasis of invasive ductal pancreatic adenocarcinoma to the colonic wall with subsequent intestinal obstruction is an extremely rare clinical entity. Its diagnosis and management require a multidisciplinary approach, with treatment plans tailored to the individual patient. In cases of bowel obstruction in patients with a history of ductal pancreatic adenocarcinoma, metastases in the colonic wall should be considered, and any tumor changes in the colon should undergo thorough histopathological evaluation to differentiate between primary colorectal cancer and metastasis originating from pancreatic cancer.

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