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CASE REPORT

A Rare Complication of Diffuse Malignant Peritoneal Mesothelioma: Spontaneous Ileal Perforation

Orhan Kalaycı[1] · Güven Barış Cansu[2] · Bengür Taşkıran[2] · Özlem Eren[3]

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Introduction

Malignant mesothelioma is a rare type of malignancy involving the serosal lining of the pleura, pericardium, peritoneum, and tunica vaginalis. It has an incidence of three cases per million per year. It is characterized with poor prognosis. Although most cases arise from the pleura, peritoneum may be the site of origin in 30% [1]. Diffuse malignant peritoneal mesothelioma (DMPM), which is more prevalent in fifth to sixth decades of life, constitutes 90% of mesothelioma involving peritoneum [2, 3]. The clinical picture of DMPM is not clear cut from other cases. Abdominal pain, ascites, abdominal fullness due to masses, or systemic symptoms including malaise, decreased appetite, and weight loss are the most common complaints [4].

Spontaneous perforation of the small intestine due to either direct invasion or metastasis from pleural mesothelioma and DMPM is quite rare in English written literature. We present a case of spontaneous ileal perforation due to direct invasion from DMPM. According to the best of our knowledge, this is the first case reported in English written literature.

Case Report

A 64-year-old male coal miner was admitted to the Gastroenterology department because of increased abdominal girth, constipation, and abdominal pain and fullness for 1 month. He complained of poor appetite and weight loss (5 kg in 1 month). He denied any systemic chronic disease and previous surgeries. Fever, nausea, and vomiting were absent. He had been smoking for almost 30 years (40 pack-year).

On physical examination, his body temperature was 36.5 °C, blood pressure was 130/85 mmHg, and pulse rate 84/bpm. His abdomen was distended with marked diffuse tenderness, but rebound tenderness and guarding were absent. Bowel sounds were normoactive. Cardiac and chest auscultation was normal. A complete blood count revealed a hemoglobin level of 13 g/dL, white cell count of 7810/uL with 85.5% neutrophil, and a platelet count of 475.000/uL. Biochemical test results were as follows: total protein was 6.58 g/dl (6.4–8.3), albumin 3.5 g/dL (3.4–4.8), lactate dehydrogenase (LDH) 193 U/L (125–220), ferritin 99.2 ng/mL (21.8–274), alpha-fetoprotein 2.4 ng/mL (0.89–8.78), carcinoembryonic antigen (CEA) < 0.5 ng/mL (0.5–5), CA-125 6.8 U/mL (0–35), CA-19-9 2.32 U/mL (0–37.1), and erythrocyte sedimentation rate (ESR) 73 mm/h (0–20).

A diagnostic paracentesis was performed and exudative ascites was confirmed according to Light's criteria (protein 5.12 g/dL, albumin 2.8 g/dL, LDH 2416 U/L, glucose 17 mg/dL). Atypical cells were noted on cytological examination of the ascitic fluid. Histologic and immunohistochemical staining (IHC) examination of smears and cytoblock preparations revealed lymphocytes, a few polymorphonuclear leucocytes, mesothelial cells, and atypical epithelial cells with the papillary configuration on a granular background.

History of asbestosis exposure was absent and ascitic fluid was suspicious for malignancy; therefore, computed tomography (CT) studies of the abdomen and thorax were done. The thorax CT revealed pleural thickening along with calcifications. Bilateral pleural effusion was absent. Contrast-enhanced abdominal CT revealed abundant fluid in perihepatic and perisplenic space and between intestinal loops and in the pelvic region. Thickening of the neighboring soft tissue, while the abdominal wall was spared, supported the diagnosis of

✉ Güven Barış Cansu
bcansu74@hotmail.com

[1] Department of Surgery, Division of Surgical Oncology, Yunus Emre State Hospital, Eskişehir, Turkey

[2] Department of Internal Medicine, Division of Endocrinology and Metabolism, Eskişehir City Hospital, TR-26080 Eskişehir, Turkey

[3] Department of Pathology, Yunus Emre State Hospital, Eskişehir, Turkey

peritoneal carcinomatosis. [18F] Fluorodeoxyglucose (FDG) positron emission tomography (PET) showed minimally increased FDG uptake (maximum standardized uptake value (SUV_{max}) 2.63) corresponding to the 9-mm pleural thickening at the upper anterior segment of the left lung. Despite abundant free fluid within abdominal space, the pathologic diffuse FDG uptake over parietal (SUV_{max} 7.07) and visceral (SUV_{max} 9.89) peritoneal surfaces were noted. Increased FDG uptake (SUV_{max} 4.55) in paraaortic and paraaortocaval lymph nodes, the prominent one being at the level of second lumbar vertebra, was also noted.

The patient underwent diagnostic laparoscopy because of failure to localize the tumor and the appearance of peritonitis carcinomatosa on CT. Diffuse peritoneal involvement giving the appearance of the omental cake was noted during laparoscopy. Numerous implants measuring 5–20 mm in size were observed over mesothelium of the small intestine. Ten liters of ascites were drained during laparoscopy. The ligamentum teres hepatis was excised and removed for histological diagnosis. The procedure was ended without any complication after checking for bleeding and perforation. After resumption of oral intake, he evacuated gas and stool. He was discharged from the hospital uneventfully on the third day of operation until the final pathology report would be obtained. Histopathological evaluation of the biopsy from ligamentum teres was positive for mesothelin, calretinin, CK 5/6, and vimentin. EMA was focally positive and MUC-1 was weakly positive. Stains for WT-1, CEA, CD15, BER-EP-4, CA 72-4, TTF-1, and mucicarmine were all negative.

About 10 days after discharge, he was admitted to the hospital again due to abdominal pain and distention. Peritoneal irritation signs including abdominal distention and rebound tenderness were present. Abdominal radiograph demonstrated air-fluid levels in the loops of small bowel and the plain chest film was normal. Laboratory tests revealed neutrophilic leukocytosis (WBC 19450/uL with 95.1% neutrophil) and increased CRP (372 mg/L) (0–8). Oral intake was halted and supportive therapy along with a broad-spectrum antibiotic therapy was initiated. He underwent emergency surgery due to fecal discharge from the laparoscopic trocar insertion site. Spontaneous perforation was evident at the mesenteric border of the ileum 20 cm proximal to the caecum, and loop ileostomy was performed. The intra-abdominal cavity was rinsed with saline and iodine. He was transferred to the intensive care unit after the operation. Clear fluid from surgical drains was collected until 72 h following operation. Thereafter, intestinal contents began to drain and he was re-operated. A second perforation 15 cm proximal to the ileostomy loop was detected during abdominal exploration. Therefore, the portion between the perforation site and stoma was resected and double barrel colostomy was performed. He died on the fifth day of the third operation due to severe respiratory infection.

Histopathologic examination of the specimen obtained during surgery for ileal perforation, which was 16 cm in length, showed malignant mesothelioma (epithelioid type) invading all layers of intestine from serosa to mucosa (Fig. 1). The surgical margin was positive for tumor invasion. Active chronic inflammatory process and fibrin deposits were present in serosa. Perineural and vascular invasion was observed. Immunohistochemical staining of the specimen was positive for mesothelin, calretinin, cytokeratin (CK) 5/6, vimentin, and D2 40, and focally positive for EMA. Napsin A, WT 1, and TTF 1 stains were negative (Fig. 2). These stains aid to diagnose MM and are also used in differential diagnosis to exclude other types of malignancies (squamous cell cancer and adenocarcinomas). EMA stain was used to differentiate epithelioid type MM from reactive mesothelial cells. He was diagnosed with stage IV MPM (T4N1M0) according to the criteria of the International Mesothelioma Interest Group.

Discussion

Metastasis of primary cancers to the small intestine may cause perforation, obstruction, or bleeding. The most common primary sites are the lung, cervix, kidney, and skin [5]. Perforation of the small intestine due to metastasis of pleural mesothelioma to the intestine or direct invasion of the small intestine by peritoneal malignant mesothelioma is a quite rare incident. We searched PubMed database on literature about perforation of small intestine published between 1974 and 2016. We found four cases of perforation due to either direct invasion or metastasis of small intestine [5–8]. Three of them had primary pleural mesothelioma which metastasized to the small intestine. The fourth one was a jejunal perforation case due to direct invasion of peritoneal mesothelioma. Our case is the first report of ileal perforation secondary to direct invasion of DMPM.

There are a few reports about the direct invasion of intra-abdominal organs and intestinal lumen by DMPM. In a study published in 1977, it was shown that DMPM may directly invade the gastrointestinal tract as well as liver parenchyma, abdominal wall, diaphragm, retroperitoneum, pancreas, and bladder [9]. In this study, Kannerstein M et al. showed the involvement of GI lumen in 22 out of 28 patients with local invasion. Most of the data were driven from autopsy studies. Involvement of mucosa was evident in four and submucosa in five cases. However, there is no mention of perforation.

In a review published in 2008, Huang-Chi Chen et al. defined five cases of gastrointestinal intraluminal metastasis (large bowel, ileum, stomach, duodenal bulb) of mesothelioma (4 pleural and 1 peritoneal mesothelioma). As a result, the authors presumed that luminal metastasis of mesothelioma was an exceptional finding [10].

Perforation of the small intestine due to direct invasion or metastasis of pleural or peritoneal mesothelioma to GIT is a

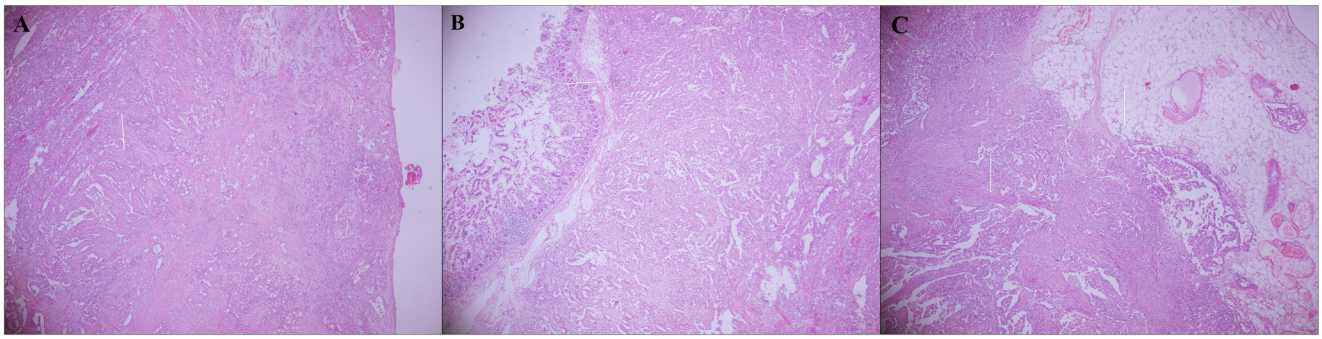

Fig. 1 The histological examination of the specimen retrieved in laparoscopy shows that all layers of the small intestine were involved with malignant mesothelioma. The layers of the small intestine: **a** muscularis and serosa, **b** submucosa, and **c** muscularis, serosa, and fat tissue surrounding serosa (H & E, × 25)

rare finding and only four cases have been reported in English written literature [5–8]. The features of these cases are summarized in Table 1. Three of them are due to metastasis of pleura and one case resulted from the direct invasion of peritoneal mesothelioma. All of them were male patients over 50 years of age. Acute surgical abdomen with peritoneal irritation signs was the initial presentation of mesothelioma in two cases (case 1, 4). The time interval between the diagnosis of mesothelioma and intestinal perforation ranged between 7 days (case 2) and 13 months (case 3).

Although perforation of small intestine occurs rarely, it may present as the first sign of pleural mesothelioma or DMPM and mesothelioma should be kept in mind among the other causes of perforation.

The association between asbestos exposure and mesothelioma is well established. It has been proposed that chronic peritonitis, remote abdominal radiation, exposure to other mineral fibers, and simian virus 40 may also play a role in the pathogenesis [11, 12]. We did not detect any possible cause except the fact that our patient was working for 30 years at a coal mine, some of which may bear asbestos. However, information about the asbestos content of the mine was not available.

Sugarbaker et al. defined three types of clinical presentation. The wet type is associated with increased abdominal girth due to ascites; a painful mass visible on CT in the dry-painful type; the combination of these [13]. Ascites occurs in 90% of the patients; the patients frequently complain of epigastric or right upper quadrant abdominal pain and distension. Anorexia, weight loss, and malaise are other common symptoms. Bowel obstruction may occur in advanced disease [2, 14, 15]. The major complaint of our patient was increased abdominal girth due to ascites, followed by constipation, abdominal pain, poor appetite, and weight loss. Differential diagnosis of ascites was made and DMPM was diagnosed according to the test results. Despite the rarity of the disease, it must be kept in mind among the other possible causes of ascites.

CT, MR, and PET-CT are imaging modalities aiding diagnosis of DMPM [4]. Computed tomography findings are the thickening of the pleura, peritoneum, and mesentery; nodules in various sizes and shapes; omental caking; and ascites. Bone destruction and lymphadenopathy may be also present. These findings are not pathognomonic for MM; they may be observed in peritoneal carcinomatous, primary peritoneal carcinoma, ovarian carcinoma, lymphomatosis, and tuberculosis peritonitis [16]. Although the imaging features on contrast-enhanced CT including thickening of the neighboring soft tissue and sparing abdominal wall were compatible with peritoneal carcinomatosis, a definite diagnosis was established only after diagnostic laparoscopy.

Biopsies can be obtained during laparoscopic or open surgery for diagnostic purposes. The characteristic appearance of

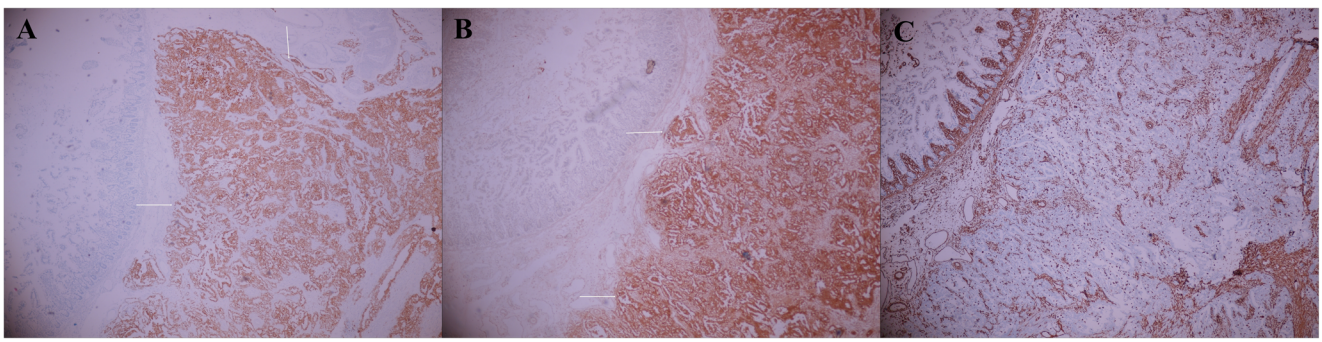

Fig. 2 Immunohistochemical staining malignant mesothelioma of the small intestine (× 40) **a** Submucosa with CK 5/6. **b** Strong HBME and mesothelin staining of the membranous layer. **c** Vimentin

Table 1 Reported cases of intestinal perforation due to malign mesothelioma

Case	Year	Author	Age/sex	Interval between primary malignancy and perforation	Primary origin	Metastasis or invasion site	Histological type	Symptoms	Survival after perforation
1	2007	Salemis NS	62/M	Same time	Peritoneum	Jejunum	Epithelioid	Severe abdominal pain, nausea, vomiting	7 months
2	2010	Gocho K	52/M	7 days	Pleura	Jejunum	Biphasic	Severe abdominal pain of acute onset	12 months
3	2015	Navarro Garcia MI	67/M	13 months	Pleura	Jejunum	Epithelioid	Peritoneal irritation findings	No data
4	2016	Alkhayal K	65/M	Same time	Pleura	Jejunum	Epithelioid	Peritoneal irritation findings	No data
Our case		Kalaycı O	64/M	10 days	Peritoneum	Ileum	Epithelioid	Peritoneal irritation findings and discharge of intestinal contents from trocar incision sites	10 days

mesothelioma is soft, grayish-white papillary masses measuring millimeters to centimeters in size scattered all over peritoneal surfaces. Malignant mesothelioma is positive for stains including calretinin, cytokeratin 5/6, epithelial membrane antigen (EMA), Wilms tumor 1 (WT-1), anti-mesothelial cell antibody-1, podoplanin (D2–40), and mesothelin. Markers of other malignancies (CEA, B 72.3, MOC-31, Leu-M1, and Ber-EP4) should be negative [17–19]. At least two mesothelial immunohistochemical markers are warranted to establish the diagnosis of MPM [20]. In our case, stains for mesothelin, calretinin, CK5/6, vimentin, and D2 40 were positive, and EMA was focally positive.

There are three histological subtypes of mesothelioma: epithelioid being the most common, sarcomatoid, and the mixed/biphasic type. Epithelioid subtype has a more favorable outcome than the other subtypes [21]. Our patient had an epithelioid subtype of mesothelioma.

DMPM is a rare disease. Diagnosis is difficult to establish and may have various presentations.

The course of the disease is variable and the prognosis is poor. Survival varies from 4 to 12 months in patients without treatment and those managed with conventional measures [22]. However, in recent years some data showed that debulking surgery along with heated intraperitoneal chemotherapies may prolong survival.

Finally, DMPM should be kept in mind among the other possible causes of ascites in addition to chronic liver diseases and solid organ metastasis. In addition, advanced mesothelioma may be a rare cause of intestinal perforation.

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