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Short communication

Intestinal obstruction due to diffuse peritoneal fibrosis at 2 years after the successful treatment of malignant peritoneal mesothelioma with intraperitoneal mitoxantrone

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Summary. A 44-year-old man who had achieved a complete remission of malignant peritoneal mesothelioma after the intraperitoneal administration of 25 mg/m^2 mitoxantrone presented with clinical and radiological signs of intestinal obstruction suggestive of recurrent disease at about 2 years following the initial treatment. However, laporotomy revealed extensive adhesive fibrosis but no sign of malignant mesothelioma. The peritoneal complications of intraperitoneal cytostatic treatment are discussed.

Introduction

Primary malignancies of the mesothelium are uncommon. Their increased incidence during recent decades has been ascribed to the widespread exposure in the first half of this century to industrial products such as asbestos, which has been identified as the main risk factor for the development of malignant mesothelioma [3, 5, 6]. This disease commonly involves the pleura, but in 10%–20% of cases it is confined to the peritoneal cavity [5, 23]. The prognosis of malignant mesothelioma is poor and the therapeutic roles of surgery, radiotherapy, and chemotherapy are ill-defined. The rates of response to single-agent or combination chemotherapy do not exceed 30% in most series [6]. Occasionally, long-term survival has been reported following the combined application of several treatment modalities [5]. Among the therapeutic options is the intracavitary application of radioactive agents and, more recently, the intraperitoneal (i.p.) administration of cytostatic drugs in patients bearing peritoneal mesothelioma [6]. The i.p. administration of various cytostatic agents either alone or in combination with systemic cytostatics, surgery, and radiotherapy may yield significant response rates, with long-term survival being observed in some cases [4, 18, 25, 31].

Recently we treated a patient presenting with malignant peritoneal mesothelioma, who achieved a pathologically documented complete remission after the i.p. administration of mitoxantrone. After an interval of approximately 2 years, the patient presented with signs of intestinal obstruction suggestive of recurrent disease. At laparotomy, however, we found only diffuse peritoneal fibrosis that appeared to be the result of the initial treatment.

Case report

In 1987, a 44-year-old Caucasian man was admitted because of upper abdominal pain and a 5-kg weight loss. An upper gastrointestinal series and a barium enema showed no abnormalities. An ultrasound examination revealed ascites. At laparoscopy, multiple peritoneal lesions measuring 2 mm in maximal diameter became evident. Epithelial papillary malignant mesothelioma was diagnosed by histological examination of the peritoneal biopsies. A Tenckhoff catheter was inserted. After a total of six 3-weekly i.p. courses of 25 mg/m^2 mitoxantrone had been given, second-look laparoscopy was performed. Except for a blue discoloration of the peritoneum, no abnormalities were seen. Peritoneal biopsies showed no sign of tumor. After one additional i.p. course of mitoxantrone, the treatment was discontinued because of severe transient peritoneal irritation. In the following months the serum level of CA-125 gradually decreased from 520 to 20 IU/ml (normal value, <35 IU/ml).

The patient remained well until 22 months after the discontinuation of therapy, at which time abdominal cramps, nausea, vomiting, and weight loss occurred. Gastroscopy revealed reflux gastritis along with rigidity of the antrum. A computed tomography (CT) scan of the abdomen demonstrated thickened bowel walls and dilated loops (Fig. 1). Because the serum level of CA-125 had risen to 105 IU/ml, recurrent mesothelioma was considered and laparoscopy was performed. Extensive peritoneal

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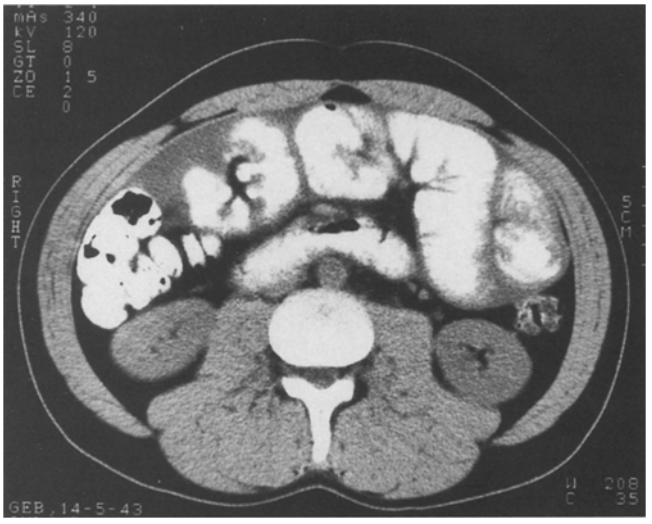

Fig. 1. CT scan of the abdomen, showing intestinal obstruction at 22 months after treatment with i.p. mitoxantrone. The scan shows thickened bowel walls and dilated small-bowel loops

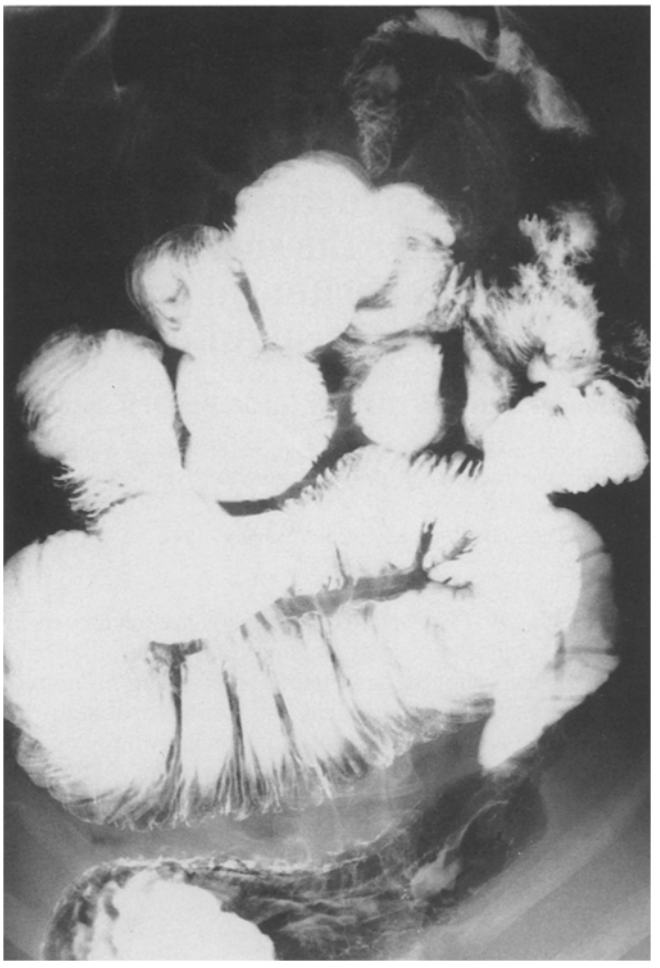

Fig. 2. The upper gastrointestinal series demonstrates rough gastric mucosal folds along with narrowing of the antrum. The small-bowel loops are dilated due to a stenosis in the distal jejunum

adhesions were found, and histological examination of the peritoneal biopsies revealed fibrosing inflammation but no sign of malignancy. The abdominal symptoms gradually increased, and an upper gastrointestinal series showed narrowing of the antrum and dilation of small-bowel loops due to localized jejunal stenosis (Fig. 2). Because of persistent vomiting, exploratory laparotomy was undertaken. Both the parietal and the visceral peritoneum exhibited a 1- to 2-mm-thick fibrotic layer along with extensive adhesions. Because no localized stenosis was found, only careful adhesiolysis was performed. Histological examination of multiple biopsies revealed extensive fibrosis but no malignant mesothelioma. After experiencing an uneventful recovery, the patient obtained excellent symptomatic relief and his serum CA-125 level normalized.

Discussion

This case report demonstrates that long-term complete remission of non-bulky malignant peritoneal mesothelioma can be achieved by the i.p. administration of mitoxantrone. Although i.p. treatment with various cytostatic agents in the presence or absence of other therapy modalities may yield remissions of occasionally long duration in patients presenting with malignant peritoneal mesothelioma, only three cases of pathologically documented complete remission have been reported [25, 26, 31]. The treatment given to these patients had consisted of single-agent i.p. cisplatin, i.p. cisplatin in combination with systemic doxorubicin, and i.p. cisplatin alternating with i.p. doxorubicin followed by whole abdominal radiation, respectively.

In the present case, the clinical signs and features arising at the time of intestinal obstruction due to peritoneal fibrosis illustrate the nonspecificity of the CT findings and the limitations of CA-125 as a tumor marker [16, 32]. Although serum levels of CA-125 may be elevated in many malignant diseases and malignant peritoneal mesotheliomas may express this antigen, CA-125 must be considered to be a nonspecific marker of mesothelial irritation and its levels can be elevated in any patient exhibiting ascites [7, 9].

Mitoxantrone is an anthracenedione derivative that displays structural similarities to doxorubicin and comparable antitumor effect [28]. Although doxorubicin is the most active single agent for the treatment of malignant mesothelioma, mitoxantrone shows only minor activity against this disease [6, 11]. However, because of the low peritoneal absorption of drugs such as mitoxantrone, the i.p. administration of relatively high doses may result in long-standing cytotoxic concentrations in the peritoneal fluid without producing significant systemic toxicity [10, 17, 21]. The i.p. administration of these high doses may be associated with local abdominal symptoms. Chemical peritonitis is a frequent dose-limiting, acute complication of i.p. treatment with mitoxantrone, mitomycin C, methotrexate, and doxorubicin [2, 8, 14, 22, 24]. This local toxic reaction may lead to the formation of fibrous bands around the indwelling i.p. catheter, with function being impaired in approx. 30% of the patients treated [19]. Intestinal obstruction that occasionally requires surgery may

occur during or shortly after the i.p. administration of mitoxantrone at a dose of 20–38 mg/m^2 and is considered to be a dose-limiting side effect [2, 20]. The dose of i.p. mitoxantrone recommended in early clinical studies varies from 23 to 30 mg/m^2 every 3–4 weeks [2, 8]. It has recently been suggested that i.p. mitoxantrone be given at lower doses and shorter intervals to overcome the peritoneal toxicity [20]. Bowel obstruction may also be caused by paralytic ileus such as that observed after i.p. treatment with vinblastine [1].

Fibrosing or sclerosing peritonitis as a delayed complication of i.p. treatment has been reported in experimental animals receiving i.p. mafosfamide (a cyclophosphamide analog), doxorubicin, and the epipodophyllotoxin derivates VM 26 and VP 16-213 [15, 27, 30]. In humans, only a few cases of sclerosing or fibrosing peritonitis have been reported [12, 19]. Two well-documented cases of extensive sheet-like adhesions requiring exploratory laparotomy for small-bowel obstruction as in our patient have been described [19]. In these ovarian cancer patients, this complication occurred at 1 month after the completion of six monthly i.p. courses of cisplatin, cytarabine, and doxorubicin and at 2 months following the administration of three monthly i.p. courses of cisplatin and cytarabine, respectively.

In our patient, the i.p. treatment with mitoxantrone is the most likely cause of the extensive peritoneal fibrosis. Because the fibrosis was much more extensive than the original disease, it is unlikely that the former represented residual lesions of malignant mesothelioma in complete remission [29]. However, it cannot be excluded that the fibrosis represented a nonspecific reaction to i.p. treatment per se, because this complication has also been observed in patients undergoing chronic ambulatory peritoneal dialysis and in subjects treated with i.p. catheters such as the LeVeen shunt [13]. In conclusion, abdominal symptoms arising after i.p. treatment for malignant peritoneal disease should not a priori be considered to be indicative of recurrent disease. A "benign" complication of the treatment must also be considered.

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