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Preoperative Gemcitabine and Oxaliplatin in a Patient with Ovarian Metastasis from Pancreatic Cystadenocarcinoma

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Key Words

Pancreatic cancer · Mucinous pancreatic cystadenocarcinoma · Metastatic cystadenocarcinoma · Gemcitabine and oxaliplatin (GEMOX) · Chemotherapy

Abstract

We describe a case of clinical benefit and partial response with gemcitabine and oxaliplatin (GEMOX) in a young patient with ovarian metastasis from cystadenocarcinoma of the pancreas. A young woman complained of abdominal pain and constipation. Computed tomography (CT) and magnetic resonance imaging scans disclosed two bilateral ovarian masses with pancreatic extension. She underwent bilateral ovarian and womb resection. During surgery peritoneal carcinosis, a pancreatic mass and multiple abdominal lesions were found. The final diagnosis was mucinous pancreatic cystadenocarcinoma with ovarian and peritoneal metastases. She started chemotherapy with GEMOX (gemcitabine 1,000 mg/m²/d1 and oxaliplatin 100 mg/m²/d2 every 2 weeks). After 12 cycles of chemotherapy a CT scan showed reduction of the pancreatic mass. She underwent distal pancreatic resection, regional lymphadenectomy and splenectomy. Pathologic examination documented prominent fibrous tissue and few neoplastic cells with mucin-filled cytoplasm. Chemotherapy was continued with gemcitabine as adjuvant treatment for another 3 cycles. There is currently no evidence of disease. As reported in the literature, GEMOX is associated with an improvement in progression-free survival and clinical benefit in patients with advanced pancreatic cancer. This is an interesting case in whom GEMOX transformed inoperable pancreatic cancer into a resectable tumor.

Introduction

Mucin-producing cystic lesions of the pancreas currently constitute a well-recognized entity. Since they were first identified by Becourt in 1830, the major unsolved issue has been to have a definitive preoperative diagnosis, because different cystic neoplasms require different treatments [1]. In 1996, the World Health Organization distinguished two types of mucinous cystic tumors: intraductal papillary mucinous neoplasms and mucinous cystic neoplasms (MCNs) [2]. MCNs range from benign mucinous cystadenoma to malignant cystadenocarcinoma and have a potential for malignant degeneration, as originally reported by Compagno and Oertel in 1978 [3]. MCNs are defined as large, thick-walled, septated cysts with no communication with the ductal system and characterized by the presence of ovarian-type stroma. This stroma is not only morphologically similar to that of the ovarian cortex, but also expresses estrogen and progesterone receptors detectable by immunohistochemistry. This distinctive mesenchyma helps distinguish MCNs from other similar tumors (i.e. intraductal papillary mucinous neoplasms) [4].

The prognosis of resectable MCN is excellent whereas the prognosis of mucinous cystadenocarcinoma is poor. Complete surgical excision of benign MCNs is curative [3, 5, 6], whereas the long-term survival of patients with mucinous cystadenocarcinoma is controversial. Although the efficacy of neoadjuvant or postoperative adjuvant chemotherapy or radiation therapy for mucinous cystadenocarcinomas of the pancreas is unknown, two reports suggest a possible benefit of chemoradiation therapy [7, 8].

The present report describes a case of clinical benefit and partial response with gemcitabine and oxaliplatin (GEMOX) in a patient with pancreatic mucinous cystadenocarcinoma with ovarian metastasis, from inoperable disease into a radically resected neoplasm. We also review the literature and discuss the current principles of management.

Case Report

A 41-year-old woman presented with several months' history of dyspepsia, postprandial fullness, nausea, constipation, abdominal distension and epigastric pain, treated for a long time with proton pump inhibitors without benefit. Both her medical and family history were unremarkable. Because of the rapid aggravation of symptoms within a few months, the patient underwent an abdominal computed tomography (CT) scan that disclosed a hypodense area in the body and tail of the pancreas and a pelvic cystic mass of 129 × 80 mm. The pancreatic lesion (measuring 4 cm), confirmed by abdominal magnetic resonance imaging, was hypointense on T1-weighted scans and a large macrocystic mass of 14.5 cm with septations was seen in the pelvis involving the left ovary, with another mass of 7.1 × 5.3 cm involving the right ovary.

In November 2008 the patient underwent surgical removal of the bulky ovarian mass. Intraoperatively, peritoneal metastases were found with parietal lumps infiltrating the vagina, rectum and transverse colon. The voluminous pancreatic mass showed splenoportal venous confluence infiltration, with diffusion to the posterior gastric wall and lesser omentum. The surgical specimen included womb and ovaries infiltrated by two macrocystic lesions, producing mucoid material, of 6.5 × 6 × 4 cm and 10 × 9 × 5 cm, respectively. The final diagnosis was mucinous cystadenocarcinoma infiltrating the ovaries with a necrotic component and an extensive involvement of the capsule with peritoneal invasion ([fig. 1](#)). She was discharged on the ninth postoperative day.

In December 2008 the patient started chemotherapy with GEMOX (gemcitabine 1,000 mg/m²/d1 and oxaliplatin 100 mg/m²/d2 every 2 weeks). Here clinical condition was compromised and

ECOG performance status was 2. The serum CA19-9 level was 654.20 IU/ml (reference range 0.00–37.00 IU/ml) and the serum CA125 level was 98. IU/ml (reference range 0.00–35.00 IU/ml). After 6 cycles of chemotherapy a CT scan showed stable disease: a heterogeneously hypodense lesion at the pancreatic body (3 cm) and complete thrombosis of the splenic vein (G4) with opening of the perigastrosplenic collateral circulation. The tumor extended posteriorly, encompassing the origin of the celiac axis with artery thrombosis at splenic origin (G4) and was in close continuity with a missing adipose cleavage plane, with the lateral margin of the superior mesenteric artery at its origin (G1) (fig. 2). The serum CA19-9 level was 26.00 IU/ml (reference range 0.00–37.00 IU/ml) and the serum CA125 level was 16.90 IU/ml (reference range 0.00–35.00 IU/ml). Since the patient's clinical condition was good (ECOG performance status 0) with a reduction of abdominal pain and weight gain of 7 kg and since the therapy was tolerated well, she continued the medical treatment with another 6 cycles of chemotherapy.

In August 2009 a repeat CT scan showed further reduction of the pancreatic mass (fig. 3), measuring 2.4 × 1.2 cm, and serum CA19-9 and CA125 levels continued to be normal. The patient also underwent a CT/PET scan that showed no pathologic uptake of ¹⁸F-FDG. Surgical resection was then possible, so our patient underwent exploratory laparotomy with distal pancreatectomy, regional lymphadenectomy and splenectomy. During surgery there was no evidence of peritoneal carcinosis or ascites. The pancreatic specimen measured 6 × 3 × 1 cm and appeared to have an increased consistency. Histopathologic examination of surgical specimens revealed microscopic foci (<2 mm) of well-differentiated pancreatic ductal adenocarcinoma and extensive chemotherapy-induced fibrosis. Omental tissue was undamaged and there was no evidence of lymph node involvement. After surgery we decided to continue chemotherapy with gemcitabine as an adjuvant treatment for another 3 cycles. CT scan showed no disease, the patient's clinical condition was excellent, she stopped the treatment and underwent intensive follow-up. At present, 24 months after surgical resection, there is no evidence of disease relapse.

Discussion

The incidence of mucinous cystadenocarcinomas is 1% of pancreatic neoplasms. MCNs present most frequently in young women and in the body/tail of the pancreas (94.6%). Mean age at diagnosis is 47 years (range 18–95), whereas median age at diagnosis is higher for malignant MCNs with a difference of approximately 15 years [9]. The median diameter of the lesions is 8.7 cm, but they can be very large (range 0.6–35 cm), and many studies suggest that size is a reliable predictor of the tumor's malignant potential [10].

MCNs do not communicate with the pancreatic ductal system and, microscopically, the cysts are lined by tall columnar, mucin-containing cells [11]. The presence of ovarian-like stroma is a necessary element to confirm the diagnosis of MCN [5, 12]. Several theories have been proposed to explain the pathogenesis of ovarian-type stroma common to all MCNs. Theories include a common origin in epithelial cells that cover the embryonic gonads in early fetal life and the possibility that neoplastic epithelial cells of MCNs induce ovarian stromal differentiation [13]. Alpha-inhibin immunoreactivity has been found in the ovarian-like stroma of MCNs, suggesting that they may be embryologically derived from mullerian elements [14, 15]. However, the exact pathogenesis of MCNs remains unsettled.

During the past decade, several investigations have concluded that many cases previously diagnosed as primary mucinous carcinoma were actually metastatic to the ovary [16, 17]. Mucinous tumors may arise from a variety of sites, particularly within the gastrointestinal tract (including the colon, appendix and pancreas) and less often the stomach and biliary tract.

Although difficulties in distinguishing between primary and metastatic ovarian tumors are well recognized, since many years [18, 19] it is evident that a substantial proportion of tumors previously considered to be ovarian primaries actually represent secondary ovarian involvement by tumors elsewhere in the body and that it is important for the multidisciplinary team to have a low threshold of suspicion and that abdominal exploration at the time of surgery (appendicectomy) and radiological review are undertaken before a mucinous ovarian tumor is considered as primary.

Considering these data, the possibility of metastasis should always be considered in cases with a known extraovarian primary tumor. In our case the index of suspicion for secondary ovarian involvement was very high considering the pancreatic lesion and the following data: bilateral ovarian involvement, the metastatic tumor histologically similar to the primary but appearing little more mature, focal patterns almost exclusively seen in metastases, such as signet ring cells or abundant extracellular pools of mucin.

Fewer than 20% of patients with mucin-producing lesions present an invasive carcinoma (mucinous cystadenocarcinoma) with a 5-year disease-specific survival of 57%. The prognosis of a benign MCN is excellent, whereas the prognosis of mucinous cystadenocarcinoma is poor: its recurrence rate and the incidence of metastasis is unpredictable and reported within a wide range [5, 6, 20]. Sarr et al. [6] reported that, after pancreatic resection, patients with mucinous cystadenocarcinoma had a dismal prognosis.

Complete surgical excision of benign MCNs is curative [3, 5, 6], whereas the long-term survival of patients with mucinous cystadenocarcinoma remains controversial. It is largely accepted that the prognosis of unresectable mucinous adenocarcinoma is substantially better than that of the usual noncystic ductal adenocarcinoma of the pancreas [3]. However there is no consensus on this [5, 21], and widely varied and unpredictable recurrence rates and incidence of metastases have been noted [6]. Sarr et al. [6] reported a 5-year survival rate of patients with resected mucinous cystadenocarcinoma ranging from 50 to 70%, significantly better than that of ordinary ductal adenocarcinomas. However, in case of unresectable cystadenocarcinoma the prognosis is as poor as that for unresectable pancreatic adenocarcinoma [6, 22].

Few reports have investigated the use of chemotherapy, and occasionally radiotherapy, in the adjuvant setting, so the efficacy of neoadjuvant or postoperative adjuvant chemotherapy or radiation therapy for mucinous cystadenocarcinomas of the pancreas is unknown. Two reports suggest the possible benefit of chemoradiation therapy [7, 8]. Sarr et al. [6] suggested a role for adjuvant treatment if tissue invasion is present, even in the absence of lymph node metastasis. More studies are needed to prove the efficacy of chemoradiation, whether in the adjuvant or neoadjuvant setting [7, 8].

In conclusion, our case report documents the clinical benefit of and partial response to GEMOX in a patient with pancreatic mucinous cystadenocarcinoma with ovarian metastasis. This is the first report of metastatic mucinous cystadenocarcinoma of the pancreas responding to platinum-derived chemotherapy, transforming inoperable disease into a completely resectable pancreatic cancer.

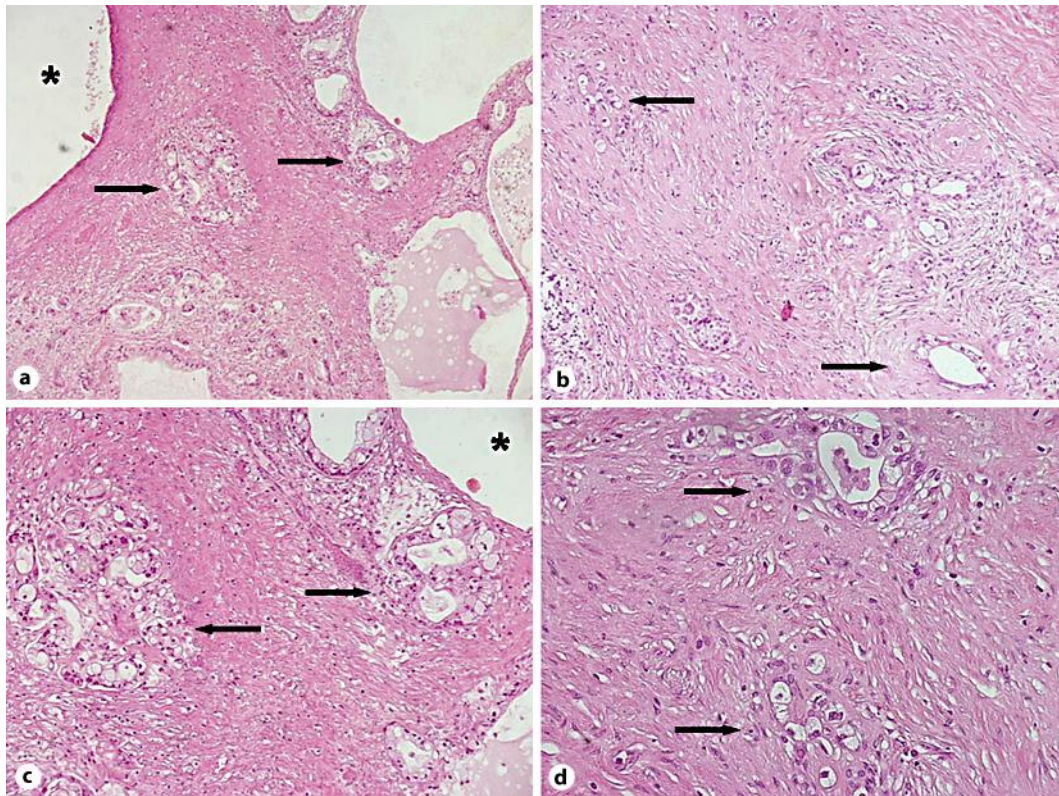


Fig. 1. Left column: **a** Low-power appearance of the ovarian lesion, displaying cystic spaces (asterisks) alongside with glandular areas (arrows). Both are lined by mucin-filled cells (H&E, $\times 10$). **c** Higher-power view of the glands depicted above showing infiltrating pattern and malignant cytology (H&E, $\times 20$). Right column: **b** Post-chemotherapeutic appearance of the pancreatic lesion. On a background of prominent fibrous tissue, few neoplastic cells (arrows) are noticeable (H&E, $\times 20$). **d** At higher magnification, the neoplastic cells show mucin-filled cytoplasm (H&E, $\times 40$).

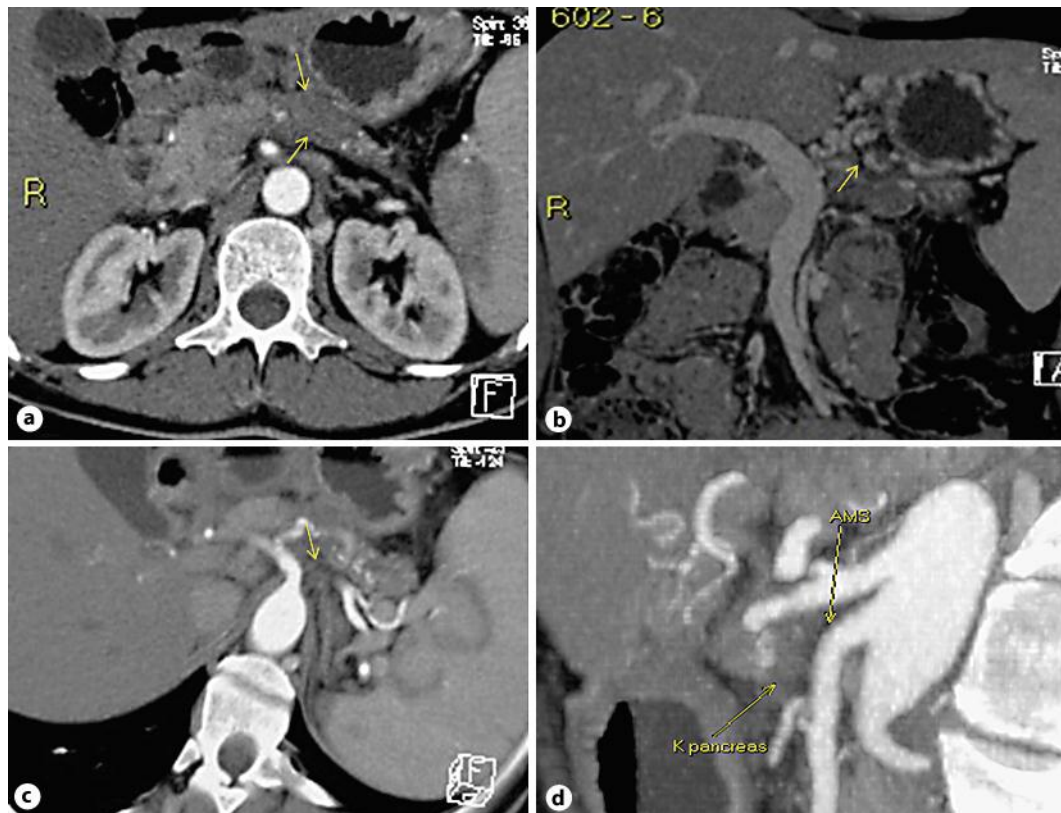


Fig. 2. CT scan after 6 cycles of chemotherapy showed stable disease. **a** Heterogeneously hypodense neoplasm at the pancreatic body. **b** Complete thrombosis of the splenic vein (G4) with opening of perigastrosplenic collateral circulation. **c** The tumor extended posteriorly encompassing the origin of the celiac axis with artery thrombosis at splenic origin (G4). **d** Close relationship of continuity, with a missing adipose cleavage plane, with lateral margin of the superior mesenteric artery at origin (G1).

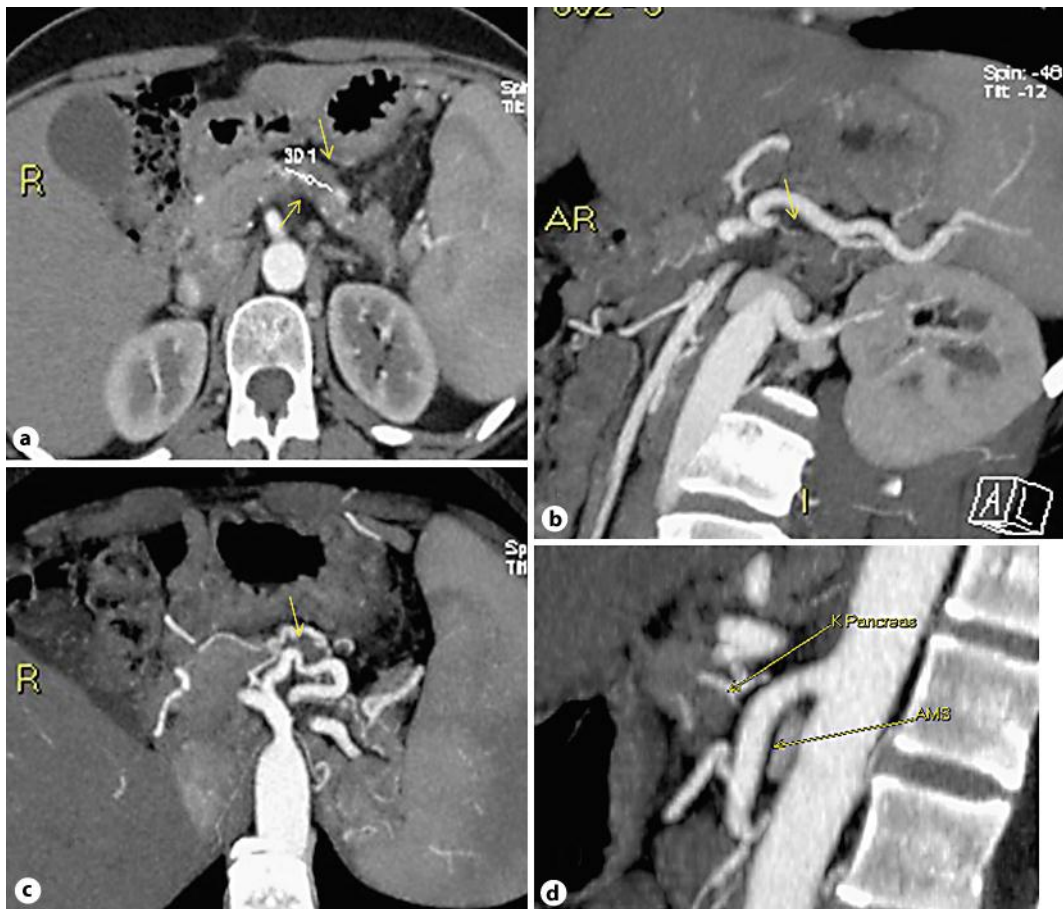


Fig. 3. In August 2009 a repeat CT scan showed further reduction of the pancreatic lesion (a) with partial revascularization of splenic artery origin (b, c) and the appearance of a cleavage plane with the left margin of the superior mesenteric artery (d).

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