Carcinoma of the Jejunum with Multideposit Peritoneal Seeding

Resection and Intraperitoneal Chemotherapy

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ABSTRACT

Jejunal adenocarcinoma is rare, often presenting late with widespread intraperitoneal disease. Intraperitoneal chemotherapy (IPC) has been shown in non-randomized studies to improve the survival of patients presenting with intraperitoneal metastases from carcinoma of the colon, appendix and stomach and in primary peritoneal malignancies including mesothelioma and pseudomyxoma peritonei, providing that adequate operative cytoreduction can be performed. A case is presented of obstructive jejunal adenocarcinoma in which 19 intraperitoneal deposits were excised. The patient was treated successfully with immediate postoperative IPC followed by systemic chemotherapy. This condition is reviewed along with the rationale for IPC.

Carcinoma del Yeyuno con Siembra Peritoneal – Depósito Múltiple

Resección y Quimioterapia Intraperitoneal

M Innis[1], N Sandiford[1], RK Shenoy[1], PR Prussia[2], A Zbar[3]

RESUMEN

El adenocarcinoma del yeyuno es raro, presentándose a menudo de forma tardía con enfermedad intraperitoneal extensa. Estudios no randomizados han demostrado que la quimioterapia intraperitoneal (QIP) mejora la supervivencia de pacientes que presentan metástasis intraperitoneal del carcinoma de colon, apéndice y estómago, así como en malignidades peritoneales primarias, incluyendo el mesotelioma y el pseudomixoma peritoneal, siempre que se realice una adecuada citoreducción quirúrgica. Se presenta un caso de adenocarcinoma yeyunal obstructivo en el que se extirparon 19 depósitos del intraperitoneal, tratándose inmediatamente al paciente exitosamente con quimioterapia intraperitoneal postoperatoria, seguida de quimioterapia sistémica. Se examina esta condición junto con las razones para practicar la QIP.

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INTRODUCTION

The small bowel accounts for only 1% of all gastrointestinal neoplasms (1, 2). Small bowel tumours frequently present comparatively late in their natural history with widespread intraperitoneal seeding (3). Extensive surgical eradication of metastatic disease in patients with peritoneal malignancy has been pioneered by Sugarbaker and colleagues (4, 5), where it has been applied with long-term survival in non-randomized studies for disseminated peritoneal cancers of appendiceal (6), colorectal (7) and gastric (8) origin as well as for abdominopelvic sarcomas (9) and primary peritoneal surface malignancies including pseudomyxoma peritonei (10), mesothelioma (11), primary peritoneal adenocarcinoma and papillary serous carcinoma. This approach has been supplemented by cytoreductive formal peritonectomy procedures (12) and the use of supplemental intraperitoneal chemotherapy (IPC) (13).

There is only one report of which the authors are aware highlighting peritoneal resection and IPC for disseminated intraperitoneal malignancy derived from primary small bowel adenocarcinoma (14). The authors report their recent experience of such a case where a radical approach towards multisite tumour deposit excision followed by IPC plus systemic chemotherapy has resulted in a successful outcome.

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Case Report

A 54-year old Afro-Caribbean male presented with a five-month history of cramping, postprandial upper abdominal

pain, vomiting, distension and constipation with an attendant 50 lb weight loss. Clinical examination was unremarkable with preoperative ultrasound demonstrating a central 3 cm x 3 cm epigastric mass with a normal liver and proximal small bowel dilatation. Barium meal and follow-through showed a mid-jejunal obstruction with a meniscus consistent with a primary small bowel tumour (Fig. 1). Preoperative serum CEA level was 0.8 ng/mL (normal range for male non-smokers = 0–3.4ng/mL with a CA 15–3 level of 27 U/mL (normal range = 9–51 U/mL).

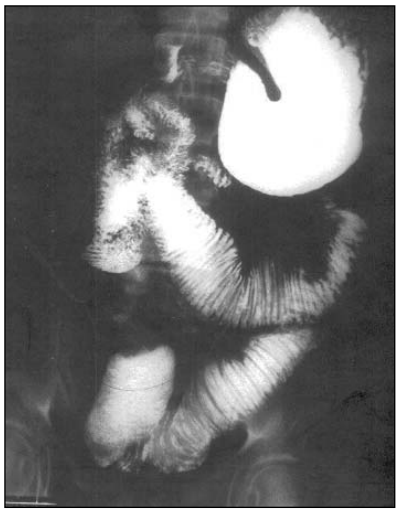

Fig. 1: Small bowel barium meal and follow-through showing the mid-jejunal obstruction.

Laparotomy revealed no evidence of liver metastases but a napkin-ring lesion in the upper jejunum and extensive regional lymphadenopathy not extending to the main superior mesenteric vessels (Fig. 2). There were 19 separate

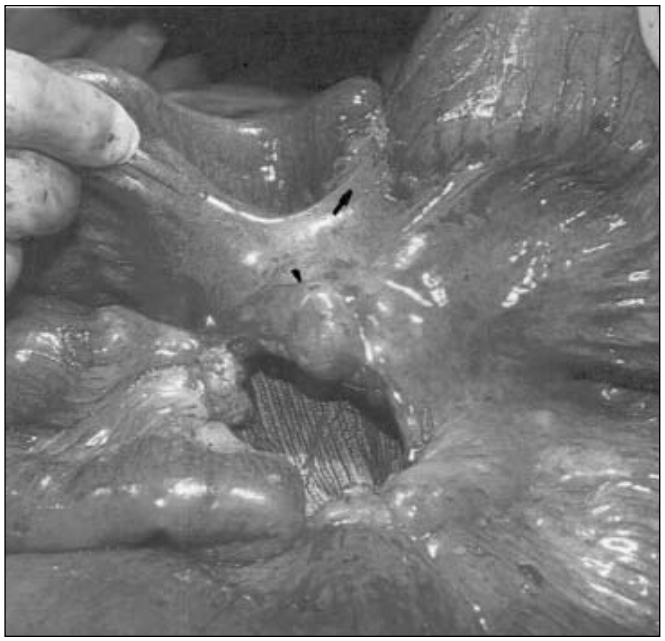

Fig. 2: Operative slide of the jejunal napkin-ring tumour (arrow) with extensive regional lymphadenopathy. (arrowhead)

neoplastic deposits including tumour nodules involving the right hemidiaphragm, pelvic peritoneum, pouch of Douglas, right and left kidneys (Gerota's fascia), bladder dome, left paracolic gutter, greater curvature of the gastric wall and the right ureter (Fig. 3). The primary tumour was excised with

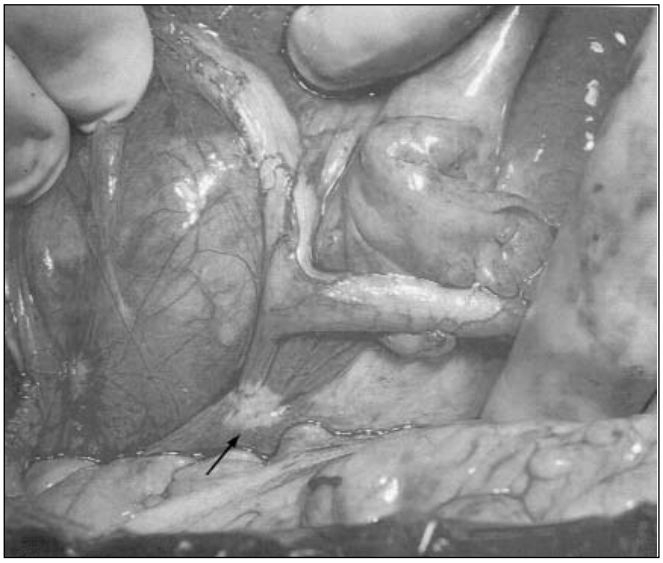

Fig. 3: One example of an intraperitoneal metastasis near the appendix. (arrow)

10 cm proximal and distal margins and primary anastomosis (side-to side because of luminal disparity) and all intraperitoneal deposits were removed. Frozen section histology confirmed a 2 cm x 2 cm infiltrating non-mucinous adenocarcinoma with small- and medium-sized neoplastic glands and cell nests arranged in a cribriform pattern associated with marked stromal desmoplasia. A Tenchkoff peritoneal dialysis catheter was inserted into the right iliac fossa for intraperitoneal chemotherapy. No intraperitoneal drains were used.

Following visible macroscopic cytoreduction, the catheters were immediately flushed in the postoperative period with 1000mL of 1.5% dextrose peritoneal dialysis solution warmed to body temperature with one-hour clamping, with this schedule repeated 8-hourly in accordance with the recommendations of Sugarbaker (Washington Cancer Institute, Washington DC) (15). Following water-soluble contrast peritoneography at 48 hours to show free flow of contrast. IPC was commenced using 5-fluorouracil (15 mg/kg) in 2.0 litre aliquots of 2.5% dextrose dialysate at room temperature infused over one hour with a 23-hour period of catheter occlusion and release. Intraperitoneal chemotherapy was continued for five days with daily blood-count monitoring and perioperative total parenteral nutrition. Systemic chemotherapy was commenced five weeks following an uneventful postoperative course with 5-fluorouracil (425 mg/m^2) and leukovorin (20 mg/m^2) between days one to five for six cycles of therapy with no initial or delayed clinical or laboratory manifestation of toxicity.

Paraffin histology confirmed the frozen section findings with transmural infiltration to the serosa, clear resection margins and 3/11 lymph nodes displaying metastatic carcinoma (nodal size ranging from 1.5 cm to 4 cm in maximal diameter). Seventeen of the 19 additional intraperitoneal deposits were confirmed as containing deposits of the same tumour (all with clear resection margins) with one negative deposit (one pelvic nodule) and the gastric wall lesion representing a small leiomyoma. Immunohistochemistry to demonstrate neurosecretory granules (chromogranin A) was negative. Follow-up to 36 months has shown no sign of recurrence, the patient gaining 70 lbs in weight. CT scan and tumour marker levels were normal. In view of the normal preoperative CEA, a second-look laparotomy was offered at 12 months but the patient declined.

DISCUSSION

Primary small bowel carcinomas are relatively rare and their definitive treatment is ill defined. They often present comparatively late with extensive intraperitoneal metastases. It is suggested that an aggressive surgical approach to eradicate all macroscopic disease is required, where necessary, incorporating formal peritonectomy. This principle of cytoreductive surgery is based on the finding that invasion into intra-abdominal organs or metastases to other viscera are often not evident so that wide resection margins may not necessarily be required in order to achieve prolonged disease-free status. Such a view has garnered support for the use of IPC in intra-abdominal epithelial cancers with extensive peritoneal surface spread only. This case report shows the benefit of such an approach in one patient.

Although there are no randomized trials assessing the use of IPC, case cohort studies have shown long-term benefit in appendiceal, colonic and gastric cancer presenting with intraperitoneal carcinomatosis (16) as well as in abdominopelvic sarcoma, mesothelioma and pseudomyxoma peritonei. Intraperitoneal chemotherapy has the advantage of peritoneal dissemination permitting high local drug concentrations (17, 18). It must be initiated either intraoperatively or immediately postoperatively since cytotoxic agents only superficially penetrate residual tumour nodules to a limited depth, (19) where viable tumour cells will rapidly colonize injured peritoneal surfaces (20) and because these viable cells quickly become entrapped and isolated from IPC by adhesions during the healing phase where they are believed to be relatively inaccessible to systemic chemotherapy during the period prior to tumour angiogenesis (21). This theory of 'tumour cell entrapment' has been advanced by Sugarbaker and colleagues where malignant cells are thought to implant as free intraperitoneal tumour emboli when primary tumours infiltrate the bowel serosa, by leakage of neoplastic cells from transected lymphatics, dissemination of cells during tumour handling and as part of fibrinous entrapment within healing peritonealized surfaces. Each of these phenomena may account for the high incidence of treatment failure in such patients (22).

In order to maintain maximal distribution of the chemotherapeutic agents to all surfaces, the regime must be started during the very early postoperative period before commencement of the natural adhesion process with abdominal lavage using 1.5% dextrose dialysate to remove blood clot and post-surgical debris. The use of standard IPC in the past has only met with limited success particularly when it has been used for established tumour residua (either with limited or no cytoreduction) and because of non-uniform drug distribution. Such IPC has been shown to be potentiated by hyperthermia (with temperatures of at least 43°C) (23, 24) although a heat exchanger and heater/cooler unit required for this purpose (25) were not available at the Queen Elizabeth Hospital. Here, following cytoreductive surgery, a watertight seal is made with the skin using plastic drapes with recording of the wound temperature and perfusion by a roller-pump of heated chemotherapy solution into the sealed peritoneal space with the surgeon manipulating the chemotherapy solution around the viscera *via* a slit in the seal, (Coliseum Technique). It is recognized that further advantages of intraoperative, intraperitoneal chemohyperthermia include a direct anti-tumour effect of the heated solution, the ability to manually distribute the heated drug with some uniformity to all parts of the abdomen and pelvis, the achievement of acceptable pharmacokinetics and drug bioavailability (22) and avoidance of potential nephrotoxicity. A range of chemotherapeutic agents has been used with acceptable toxicity and pharmacokinetics (dependent upon the tumour histology) including mitomycin C (pseudomyxoma, gastrointestinal adenocarcinoma) cisplatin or doxorubicin (gastric and ovarian cancer) (26, 27) and intraperitoneal taxanes (28), camptothecin (CPT-11) (29) and mitoxantrone (30). The heated intraoperative IPC technique has been shown to result in a higher morbidity when compared with postoperative IPC dependent upon the absolute temperature used and the duration of exposure, particularly when cytoreduction is carried out in association with a bowel anastomosis (31, 32).

Traditionally, the intra-abdominal distribution of peritoneal surface disease has been categorized into different regions with varying lesional size for the creation of a peritoneal cancer index (PCI) (5), although the extent of peritoneal involvement may also be ascertained by preoperative CT scanning and the determination of a completeness of cytoreduction (CC) score; the latter based on the residual presence of macroscopic tumour nodules following aggressive cytoreduction. The PCI may be of limited benefit in low-grade tumours such as grade 1 sarcoma, mesothelioma and pseudomyxoma or in critical anatomical sites with low volume disease where resection is contraindicated (33). It is equally recognized that CT scanning is inaccurate in both the detection and quantification of peritoneal carcinomatosis

(34), however, greater accuracy has been reported when the tumour is of mucinous histology (35). In non-mucinous tumours, particularly as in the index case where preoperative tumour markers were not elevated, it is recommended that patients undergo timed second-look procedures (4, 36).

This case illustrates the value of an aggressive surgical approach towards cytoreductive surgery with the use of intraperitoneal chemotherapy in a patient with advanced intraperitoneal disease from small bowel adenocarcinoma. As far as the authors are aware, there is only one other report of its use in this setting for a cohort of six patients where the median survival was 12 months and where two out of the six cases showed progressive disease (14). This technique should be considered in patients with high performance status without hepatic (or systemic) metastatic disease and where the primary and its draining lymph node bed can be completely resected. It would appear that the more complete the cytoreduction, the more effective the long-term control of the disease (37).

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