CASE REPORT

Critical Role of Hyperthermic Intraperitoneal Chemoperfusion in the Treatment of a Patient With Pseudomyxoma peritonei

KARIN L. COLE, MD,1* HAROON A. CHOUDRY, MD,2 HEATHER L. JONES, PA-C,2 PAMELA P. GOODELL, MD,3 AND DAVID L. BARTLETT, MD2

1Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
2Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
3Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

The role of hyperthermic intraperitoneal chemoperfusion (HIPEC) in the treatment of Pseudomyxoma peritonei is debated by clinicians. We report the case of a patient who had multiple episodes of short-interval disease recurrence following debulking surgery, and only achieved long-term remission with the addition of HIPEC. A review of the relevant literature is presented.


INTRODUCTION

Pseudomyxoma peritonei (PMP)—the accumulation of mucinous ascites and mucin-secreting epithelial nodules within the peritoneal cavity—most commonly results from the intra-abdominal spread of invasive or non-invasive appendiceal tumors. The clinical course of this disease is dictated by the volume of extra-cellular mucin accumulation and the degree of epithelial cellular atypia [1]. Mucinous peritoneal carcinomatosis in the setting of mucocoeles, non-invasive mucinous cystadenomas, and invasive low-grade mucinous adenocarcinomas—considered “classic” P. peritonei—demonstrates bland cellular architecture and has a good long-term prognosis. This is in stark contrast to carcinomatosis in the setting of invasive, high-grade mucinous adenocarcinomas that demonstrates severe cellular atypia and has a poor prognosis [2].

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC), as described by Sugarbaker [3], has emerged as the preferred treatment for PMP in many centres. However, controversy still exists. Miner et al. [4] describe a “palliative” approach, involving less aggressive surgery with selective intra-peritoneal chemotherapy, primarily for symptom management. Sugarbaker [3] have promulgated a more aggressive upfront “curative” approach, involving maximum cytoreduction to clear all disease at the initial surgery, in combination with intra-peritoneal dwell chemotherapy. The additional benefit of peri-operative intra-peritoneal chemotherapy after cytoreduction is still debated by clinicians, given the absence of clinical trials and potential for added morbidity.

We report the case of a patient who underwent aggressive surgical cytoreduction for advanced PMP by an experienced surgeon at a busy peritoneal surface malignancy center, but refused HIPEC. After rapid recurrence, she had a second aggressive cytoreduction by the same surgeon, but this time agreed to HIPEC therapy with mitomycin C. This patient effectively serves as her own internal control for comparison of the effect of HIPEC on this disease.

CASE REPORT

A 44-year-old woman presented in January of 1998 with 3 months of right lower quadrant pain. CT scan demonstrated ascites and a “fullness” in the right pelvis; paracentesis yielded mucinous material but no malignant-appearing cells. In March of 1998, the patient underwent appendectomy, supracervical hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and cytoreductive surgery. Findings included P. peritonei with tumor deposits throughout the peritoneal cavity, as well as a 4 cm mass at the base of the appendix. Pathology demonstrated well-differentiated mucinous adenocarcinoma. The patient’s tumor recurred intra-abdominally, and she underwent additional cytoreductive surgeries in February of 1999 (distal gastrectomy, sigmoid colecetomy, cholecystectomy, and portal lymph node dissection) and March of 2000 (partial liver resection and distal pancreatectomy/splenectomy). From 2002 to 2004 she was treated medically with Xeloda and Celebrex.

She presented to our institution at the beginning of 2004 complaining of 6 months of increasing shortness of breath and abdominal pain. On CT she was found to have increasing mucinous ascites and intra-abdominal mucinous masses (Fig. 1). At this time, repeat cytoreduction with HIPEC was discussed; however, the patient would consent only to cytoreduction and not to HIPEC. Intraoperatively, she was found to have extensive fused mucinous tumor in all regions of her abdominal cavity. Her fourth cytoreductive surgery included a low anterior resection, small bowel resection, and diverting loop ileostomy. After cytoreduction she had minimal residual disease.

In November of 2005, the patient once again complained of shortness of breath and abdominal pain. A CT scan revealed significant re-accumulation of mucinous peritoneal carcinomatosis (Fig. 2). At this point, she was recommended to have cytoreduction with HIPEC, and she agreed. This was performed in January of 2006 by the same surgeon as the previous case, with a similar extent of disease documented intraoperatively. She underwent extensive lysis of adhesions with tumor cytoreduction followed by HIPEC with mitomycin C

*Correspondence to: Karin L. Cole, MD, Portland Surgical Associates, 195 Fore River Parkway, Suite 420, Portland, ME 04102. Fax: 207-553-6520. E-mail: coleka@mercyme.com

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(30 mg for 60 min plus 10 mg for an additional 40 min, at 42°C). Once again, minimal residual disease was achieved.

Subjectively, she felt that the addition of HIPEC contributed to prolonged post-operative fatigue and inanition. Currently, 5 years after the cytoreductive surgery plus HIPEC, she remains asymptomatic and as of her last CT scan on June 3, 2010 she has no imaging evidence of disease progression (Fig. 3).

DISCUSSION

P. peritonei is characterized by accumulation of mucinous ascites within the peritoneal cavity, typically due to dissemination of mucin-producing cells originating from an appendiceal neoplasm. Ronnett et al. [5] analyzed 109 cases of the so-called P. peritonei and divided them into three categories based on histology. Disseminated peritoneal adenomucinosis (DPAM) cases were those with “peritoneal lesions composed of abundant extracellular mucin containing scant simple to focally proliferative mucinous epithelium with little cytologic atypia or mitotic activity, with or without an associated appendiceal mucinous adenoma.” Peritoneal mucinous carcinomatosis (PMCA) was characterized by “peritoneal lesions composed of more abundant mucinous epithelium with architectural and cytologic features of carcinoma, with or without an associated primary mucinous adenocarcinoma.” A third category was also identified, which consisted of patients with intermediate or discordant features. Based on an abundance of acellular mucin and relatively indolent disease course in the setting of an established appendiceal adenocarcinoma, we would place our patient in this intermediate category (PMCA-I/D) with low-grade features (Fig. 4). Despite several attempts at standardization, ongoing inconsistency in the nomenclature of this disease, in particular the persistence of the nonspecific term “P. peritonei,” makes a review of the relevant literature somewhat challenging [6–8].

The use of cytoreductive surgery combined with intraperitoneal chemotherapy to treat “P. peritonei” was first described by Sugarbaker et al. [9]. Since then, multiple retrospective and prospective reports have documented the effectiveness of this approach in managing PMP. In 2006, Yan et al. [10] summarized these studies in a systematic review of the literature specific to P. peritonei. Ten observational studies, without control groups, were included in the review, totaling 863 patients, with the majority having appendiceal primaries. Nine of the 10 studies described outcomes of cytoreduction and
Use of HIPEC in Pseudomyxoma peritonei

Although the combination of complete cytoreduction and HIPEC has been embraced by many centers as the optimal treatment strategy for PMP, others have questioned the role of aggressive surgery and intraperitoneal chemotherapy. In 2005, Miner et al. reported the Memorial Sloan-Kettering Cancer Center experience with PMP [3]. In their series of 97 patients (some with multiple cytoreductive surgeries), only four underwent HIPEC and 30 underwent EPIC. Median survival of the whole population was 9.8 years. Median survival was 12.8 years in patients with low-grade mucinous adenocarcinoma and only 4 years in patients with high-grade. With their approach of non-aggressive serial cytoreduction with selective use of intra-peritoneal chemotherapy, the authors documented a 21% 10-year survival and a median of 2.2 operations per patient. The authors point out that overall survival was equivalent to that reported by proponents of more aggressive surgery with HIPEC. However, analysis of a similar subgroup of patients by Sugarbaker and colleagues, undergoing aggressive upfront cytoreductive surgery in combination with peri-operative intra-peritoneal chemotherapy, required on average 1.3 operations and demonstrated a 20-year survival of 70%. This comparison lends credence to the potential for long-term disease control with an aggressive up-front approach [12].

The rationale for a combined approach is based on the eradication of macroscopic disease via aggressive cytoreductive surgery, followed by treatment of residual microscopic disease via intra-peritoneal chemotherapy. Early upfront radical cytoreduction allows complete disease clearance that may not be possible after less radical “palliative” surgery due to progressive scarring that occurs with each successive operative intervention. The low-grade, relatively acellular DPAM histologic phenotype seen in our patient is an ideal target for HIPEC since the direct non-cell-cycle dependent toxic effects of hyperthermia impairs DNA repair, denatures proteins, induces heat-shock proteins and promotes apoptosis in residual microscopic malignant cells [13].

There is no definitive evidence for increased morbidity and mortality from the addition of intra-peritoneal perfusion; in fact multiple studies have correlated intestinal leaks and perforations with the extent of cytoreductive surgery, number of peritonectomy procedures and operative time but not with the administration of intra-peritoneal chemotherapy [14].

Randomized trials have proven difficult for this rare disease and a protocol at the NIH intramural program randomizing PMP patients to surgery alone versus surgery plus HIPEC closed prematurely due to an inability to accrue patients (Personal communication 2011; Pingpank). There is no question that the use of standardized and specific terminology, prospective data collection and multi-institutional collaboration would be invaluable in determining which PMP patients benefit from which treatments, specifically HIPEC. Our case, viewed as a single-patient crossover trial, supports the conclusion that HIPEC is an essential component of the treatment strategy in some patients.

CONCLUSION

Until additional prospective data becomes available, all patients presenting with P. peritonei should be considered for HIPEC.

REFERENCES