Original Article

Postoperative Peritonitis Without An Underlying Digestive Fistula After Complete Cytoreductive Surgery Plus HIPEC

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ABSTRACT

Background/Aim: Peritoneal carcinomatosis (PC) is a pernicious event associated with a dismal prognosis. Complete cytoreductive surgery (CCRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is able to yield an important survival benefit but at the price of a risky procedure inducing potentially severe complications. Postoperative peritonitis after abdominal surgery occurs mostly when the digestive lumen and the peritoneum communicate but in rare situation, no underlying digestive fistula can be found. The aim of this study was to report this situation after CCRS plus HIPEC, which has not been described yet and for which the treatment is not yet well defined. **Patients and Methods:** Between 1994 and 2012, 607 patients underwent CCRS plus HIPEC in our tertiary care center and were retrospectively analyzed. **Results:** Among 52 patients (9%) reoperated for postoperative peritonitis, no digestive fistula was found in seven (1%). All had a malignant peritoneal pseudomyxoma with an extensive disease (median Peritoneal Cancer Index: 27). The median interval between surgery and reoperation was 8 days [range: 3-25]. Postoperative mortality was 14%. Five different bacteriological species were identified in intraoperative samples, most frequently *Escherichia coli* (71%). The infection was monobacterial in 71%, with multidrug resistant germs in 78%. **Conclusions:** Postoperative peritonitis without underlying fistula after CCRS plus HIPEC is a rare entity probably related to bacterial translocation, which occurs in patients with extensive peritoneal disease requiring aggressive surgeries. The principles of treatment do not differ from that of other types of postoperative peritonitis.

Key Words: Digestive fistula, hyperthermic intraperitoneal chemotherapy, peritoneal carcinomatosis, postoperative peritonitis, spontaneous bacterial peritonitis

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The development of peritoneal carcinomatosis (PC) during cancer progression is a pernicious event associated with a dismal prognosis.[1-3] Although often considered a terminal condition, if disease is limited to the peritoneum, complete cytoreductive surgery (CCRS) combined with heated intraperitoneal chemotherapy (HIPEC) is able to yield an important survival benefit with 5-year overall survival attained in 80% patients, depending on the tumor origin.[4-7]

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The price to pay is a long and risky surgical procedure. Even in highly specialized centers, morbidity ranges from 30% to 68% and mortality from 3% to 8%.[4-7] The occurrence of complications is closely related to the extent of the peritoneal disease.[4,6] Postoperative peritonitis is one of the most severe complications encountered in all types of abdominal surgical procedures with mortality ranging from 36% to 44% in the literature.[8-13] In 15% of the cases, the cause of the peritonitis (i.e., underlying perforation) cannot be found.[14] We wondered whether the peritoneal trauma resulting from the direct toxic effect of HIPEC added to extensive surgery and occasionally combined with the severe neutropenia induced by chemotherapy, could generate such postoperative peritonitis without an evident cause.[15,16] The aim of this study was to report and analyze all cases of postoperative peritonitis without an underlying digestive perforation or fistula after HIPEC, in our tertiary care center.

PATIENTS AND METHODS

Patient selection and variables studied

Between 1994 and 2012, 607 patients underwent CCRS plus HIPEC in our tertiary care center and were included in a dedicated prospective database. Among them, a retrospective analysis was performed to identify patients who had experienced a severe postoperative intra-abdominal complication of any kind (Dindo–Clavien grade 3-4[17]). Patients with secondary peritonitis, as defined by the Hamburg classification[18] [Table 1], were subsequently selected and analyzed to identify patients having developed peritonitis without an underlying digestive perforation. Variables studied in this population were preoperative and operative parameters, histologic tumor characteristics, and the postoperative course.

Preoperative preparation

The standard procedure for colonic preparation in our surgical oncology department was applied to all patients preoperatively: A 5-day low-residue food diet, sennosides started 2 days before surgery and 1-3 colonic enemas the day before surgery. Since 2008, all patients receive a 7-day course of preoperative immunonutrition as recommended by the French Society of Digestive Surgery.[19] No oral antibiotics were administered preoperatively. All patients received 2 g of amoxicillin/clavulanic acid 30 min before the initial incision and 1 g was renewed every 2 h during surgery. Antibiotics were discontinued immediately after surgery. All patients scheduled for CCRS plus HIPEC had a triple vaccination (against meningococcus C, *Haemophilus influenzae* and pneumococcus) at least 3 weeks before surgery in case an intraoperative splenectomy was required. Skin preparation for surgery included body hair removal by clipping, the day before surgery. In the operating room, the surgical site was cleaned with an iodine-based antiseptic soap before two consecutive applications of aqueous povidone–iodine solution.

Table 1: Hamburg classification of peritonitis

Primary peritonitis
Spontaneous peritonitis of the child
Spontaneous peritonitis of the adult
Peritonitis in patients with CAPD
Tuberculous peritonitis
Secondary peritonitis
Non-iatrogenous digestive tract perforation
Postoperative peritonitis
Post-traumatic peritonitis
Peritonitis after blunt abdominal trauma
Peritonitis after penetrating abdominal trauma
Tertiary peritonitis
Peritonitis without pathogen
Peritonitis with fungi
Peritonitis with low-grade pathogenic bacteria
Intra-abdominal abscess
Intra-abdominal abscess after primary peritonitis
Intra-abdominal abscess after secondary peritonitis
Intra-abdominal abscess after tertiary peritonitis

CAPD: Continuous ambulatory peritoneal dialysis

Surgical technique

Through a median xypho-pubic incision, all postoperative adhesions were liberated to ensure a complete intraperitoneal exploration [including calculation of the Peritoneal Cancer Index (PCI)].[20] The principles of the curative treatment of peritoneal carcinomatosis and primary peritoneal disease applied were to remove all the visible tumor disease with a complete surgical resection (requiring either direct destruction or removal of an organ) associated with treatment of the residual invisible peritoneal disease with heated intraperitoneal chemotherapy.[21] A complete resection of the omentum, an appendectomy, and a cholecystectomy were systematically associated even when there was no sign of direct tumor invasion. HIPEC was performed using an open "coliseum" technique, as previously described.[22]

Postoperative outcome and microbiological sampling

All complications occurring up to 3 months after surgery were prospectively recorded in a dedicated database and graded according to the Dindo–Clavien classification.[17] Every patient diagnosed with postoperative peritonitis underwent an emergency relaparotomy. A meticulous search for the origin of the peritonitis was always carried out with a systematic exploration of the entire abdominal cavity and systematic testing applying manual pressure to all digestive sutures made during primary surgery. During this procedure, samples were systematically collected for microbiological analysis, including a culture with an antibiogram. Multidrug resistant (MDR) microorganisms were defined as resistant to two or more classes of antibiotics (usually adequate for their bacteriological species).

Statistical analysis

Quantitative data are expressed as median values with ranges, unless expressed otherwise. The statistical analysis was performed using the Word Excel software, Microsoft®.

RESULTS

Among the 607 patients submitted to CCRS plus HIPEC between January 1994 and May 2012 in our tertiary care center, 123 (20%) developed an intra-abdominal complication as listed in Figure 1. Eighty-one patients (13%) required emergency surgery and 52 (9%) were operated on for acute postoperative peritonitis. Among them, no underlying digestive fistula was found in 7 (1%).

Patient demographics and surgery

All the seven identified patients (two males and five females) had a malignant peritoneal pseudomyxoma (MPM) [Table 2]. Their median age was 51 years (range: 39-68). Like all patients scheduled for CCRS plus HIPEC, their general status was good (28% were ASA2 and 100% had a WHO PS of 0 or 1). The median body mass index was 23.8 kg/m^2 (range: 15.4-30.8). Two were preoperatively malnourished (both operated on before 2002, when preoperative nutrition was not systematically prescribed). All patients had received preoperative chemotherapy. The type of surgery required to achieve complete removal of malignant lesions and the type of HIPEC associated are reported in Table 3. In all patients, the peritoneal disease was very extensive as reflected by the median PCI of 27 (range: 15-35). Surgeries, even in the setting of peritoneal carcinomatosis, were considered extensive with a median duration of 11 h and blood loss ranging from 200 to 4000 mL.

Postoperative course

The median interval between surgery and reoperation for peritonitis was 8 days (range: 3-25). Postoperative mortality was 14%. One patient who rapidly developed multiorgan failure died 6 days after reoperation. Among the six remaining patients, five required either subsequent laparotomies or percutaneous drainage for recurrent intra-abdominal infection. In total, five patients also developed medical complications listed in Table 2. The median intensive care unit and hospital stay were, 33 and 54 days, respectively.

Bacteriological findings

Nine germs of five different bacteriological species were identified in the seven intraoperative samples. The germs most frequently found were *Escherichia coli* in five (71%)

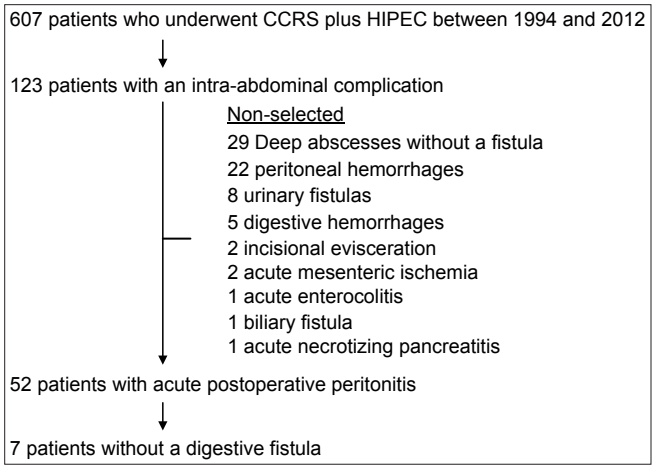

Figure 1: Flowchart of the selection of patients with acute postoperative peritonitis after complete cytoreductive surgery (CCRS) plus HIPEC without an underlying digestive fistula

Table 2: Preoperative and intraoperative variables

Patient	Gender	PC origin	Age (years)	BMI (kg/m^2)	Preoperative malnutrition	WHO performance status	ASA score	PCI	Number of digestive sutures	Operative time (min)	Intraoperative blood loss (mL)	Postoperative morbidity (Dindo-Clavien classification)	Interval before reoperation	Associated medical complication
1	F	MPM	42	18	1	1	2	25	2	720	1500	5	16	Multiorgan failure neutropenia
2	M	MPM	40	15	1	1	2	35	3	870	4000	4	18	-
3	F	MPM	56	20	0	0	2	28	2	660	1500	4	3	Lung failure
4	F	MPM	46	29	0	0	3	15	2	450	200	3	4	-
5	F	MPM	52	24	0	1	2	15	0	500	500	4	25	Lung failure
6	M	MPM	68	31	0	0	2	32	1	720	1500	4	7	Pneumonia Upper GI bleeding neutropenia
7	F	MPM	60	28	0	1	2	27	1	540	400	4	8	Upper GI bleeding
Median			51.5	23.8				27		660	1500			
Range			40-68	15-31				15-35		450-870	200-4000			

PC: Peritoneal carcinomatosis, MPM: Malignant peritoneal pseudomyxoma, BMI: Body mass index, PCI: Peritoneal cancer index, ASA : American Society of Anesthesiologists, GI : Gastrointestinal

samples and *Enterobacter* species in two (29%). The infection was mono-bacterial in five (71%) patients with MDR germs in seven (78%) of the nine identified bacteriological species [Table 4].

DISCUSSION

Postoperative peritonitis without an underlying digestive fistula occurred after CCRS plus HIPEC in 1% of cases in our series of 607 patients. It was diagnosed between the 3rd and the 25th postoperative days after surgery and was associated with a 14% mortality rate.

Table 3: Type of surgery and HIPEC

	Number of patients	%
Type of surgery		
Splenectomy	6	86
Cholecystectomy	5	74
Omentum resection	4	57
Hysterectomy	3	43
Complete colectomy	3	43
Partial colectomy	3	43
Rectal resection	3	43
Partial gastrectomy	2	29
Annexial resection	2	29
Douglassectomy	2	29
Small bowel resection	1	14
Appendectomy	1	14
Type of HIPEC		
Oxaliplatin+irinotecan	5	74
Oxaliplatin	1	14
Mitomycin	1	14

HIPEC: Hyperthermic intraperitoneal chemotherapy

Postoperative peritonitis without any underlying digestive perforation or anastomotic leakage is an intermediate entity because it cannot be classified as primary (in which there is no rupture of the anatomical barrier) nor as secondary (in which there is a digestive perforation). Postoperative peritonitis without an underlying digestive perforation represented 13% of all postoperative cases of peritonitis after CCRS plus HIPEC. This rate was comparable to those found after other types of digestive surgeries.[14]

The physiopathology of this postoperative peritonitis without an underlying fistula is still obscure and probably not explained by simple intraoperative peritoneal bacterial contamination or misdiagnosed secondary peritonitis. The most likely explanation is postoperative bacterial translocation (BT), comparable to that responsible for spontaneous peritonitis in the cirrhotic patient.[23] When we analyzed our results, we found a high rate of mono-bacterial infections (71%), *E. coli* being the germ most frequently found. This is strongly in favor of our hypothesis because in postoperative secondary peritonitis, the infection is most commonly poly-bacterial, with an average of four germs per patient.[14,24,25] The most frequently encountered combination is *E. coli* and *Bacteroides fragilis*.[24,25] Most studies on BT were conducted in cirrhotic patients. They reported that mesenteric lymph node BT was a physiological phenomenon, implicated in the normal immune response to digestive bacteria but could become pathological in three specific circumstances: changes in gut microbiota, an increase in intestinal wall permeability and impaired immunity.[26] To date, we have no evidence-based data, either clinical or experimental, to corroborate the hypothesis that BT may be at the origin of primary peritonitis after CCRS plus HIPEC but the three specific circumstances mentioned

Table 4: Bacteriological findings

Patient	Germ	Antibiotic susceptibility							
		Amoxicillin	Amoxicillin+ Clavulanic acid	Piperacillin+ Tazobactam	Imipenem/ Cilastatin	Cefotaxime	Gentamicin	Amikacin	Ciprofloxacin
1	*Streptococcus faecium*	I		R		R	S		
2	*Enterobacter cloacae*	R	R	I		R	S	S	S
	Escherichia coli	R	R	I	S	S	S	S	S
3	*E. coli*	R	I	S	S	S	S	S	S
4	*E. coli*	R	R	I	S	I	S	S	S
5	*E. coli*	R	R	I	S	S	S	S	S
6	*Enterobacter aerogenes*	R	R	S	S	I	S	S	S
	Enterococcus faecium	S	S	S	S	R	S		
7	*E. coli*	S	S	S	S	S	S	S	R

R: Resistant, I: Intermediate, S: Susceptible

above are found after this specific surgery. Intestinal wall edema is responsible for loosening of the intercellular tight junctions and for internalization of bacteria by stressed enterocytes, which could increase bacterial permeability via either paracellular or transcellular translocation.[27] This generalized visceral edema is clinically obvious at the end of HIPEC. In addition to this increased permeability, two other factors were implicated in the development of pathological BT in patients with liver cirrhosis: Changes in gut microbiota and impaired immunity.[26,28] All major surgeries induce transient postoperative impaired immunity. Although the phenomenon is not well understood, a plausible explanation could be an excessive inflammatory response leading to the suppression of cell-mediated immunity that is directly proportional to the aggressiveness and duration of the procedure.[29-31] CCRS plus HIPEC are considered as aggressive procedures but, in our experience, treatment of MPM required the longest and most difficult surgeries because of the tumor burden. All seven patients in our series had extensive MPM with a median PCI of 27, which required a median duration of surgery of 11 h. Combining this major surgical trauma with the systemic toxic effect of the chemotherapy sustained during HIPEC could have exacerbated the impaired immunity in the patients (in this short series, two patients developed grade 3 postoperative neutropenia). Finally, changes in the gut microbiota, could also be easily induced by multiple factors surrounding the CCRS plus HIPEC: preoperative bowel preparation, perioperative antibiotherapy, and the prolonged postoperative ileus-lowering intestinal clearance. These last factors could explain the high rate of MDR germs found in our series.[32,33]

From a therapeutic point of view, we never opted for medical treatment and a systematic emergency relaparotomy was performed as soon as the diagnosis was made. The surgical management was based on three fundamental principles as in any patient with postoperative peritonitis: eliminating the source of infection (which was not found in these cases), reducing bacterial contamination (with extensive peritoneal lavage) and preventing persistent or recurrent intra-abdominal infection (with adequate postoperative peritoneal drainage).[25] In addition to this mandatory surgical management, a wide spectrum of empirical antibiotherapy was started to achieve a probabilistic coverage of the most likely pathogens, until bacterial identification was achieved from adequate intraoperative samples. In 2010, the Surgical Infection Society and the Infectious Diseases Society of America issued guidelines for empirical antimicrobial therapy in health-care-associated complicated intra-abdominal infection, which recommended a multidrug regimen that included meropenem, imipenem/cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. The association with aminoglycosides or colistin could also be discussed.[34] At the same time, the French Society of Anesthesiology and Intensive Care (SFAR) recommended a multidrug regimen, which either combined piperacillin-tazobactam or imipenem/cilastatin with amikacin as empirical antibiotherapy for postoperative peritonitis. The association with fluconazole was not systematically recommended but could be discussed.[35] When we consider the germs identified in our series, they were MDR in 78% of the cases, although mostly mono-microbial, but the empirical treatment started according to the latest French recommendations, piperacillin-tazobactam (n = 4) or imipenem/cilastatin (n = 2) combined with amikacin (n = 6), was effective against 100% of the bacterial specimens identified (one patient had received a combination of cefepim plus metronidazole but this had occurred before the SFAR recommendations). Interestingly, no patient had fungi found in the bacteriological specimens sampled at the time of the reoperation. Therefore, systematic empirical antifungal treatment might not be indicated. As in the case of postoperative peritonitis with an underlying digestive fistula, the subsequent course was complicated in most patients.[36] Three of the seven patients required further surgery after their initial reoperation and as many as four times in one patient. Five patients also developed severe medical complications [Table 2]. Nevertheless, mortality remained low compared with the 10-47% reported in the latest series of postoperative peritonitis after colorectal surgery in the literature.[37-39] This can probably be explained by the good general status of the patients selected for CCRS plus HIPEC, but also by our expertise and the rapidity of the surgical treatment, as attested by our 11% mortality rate in patients developing postoperative peritonitis with an underlying digestive fistula after CCRS plus HIPEC (unpublished data).

To our knowledge, this is the first study on this rare postoperative complication. Although it is retrospective, these data were extracted from a dedicated prospective database of CCRS plus HIPEC, which is one of the largest in the world. Nevertheless, these data collected in a single European center may be influenced by the local bacterial ecology and the local perioperative antibiotic policies, which could limit their external validity.

In conclusion, postoperative peritonitis without an underlying fistula after CCRS plus HIPEC is a rare entity, which can occur in patients with extensive peritoneal disease requiring aggressive surgeries. It is probably related to a bacterial translocation. The principles of its treatment do not differ from that of other types of postoperative peritonitis neither in terms of surgical techniques nor in terms of the recommended empirical antibiotherapy.

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