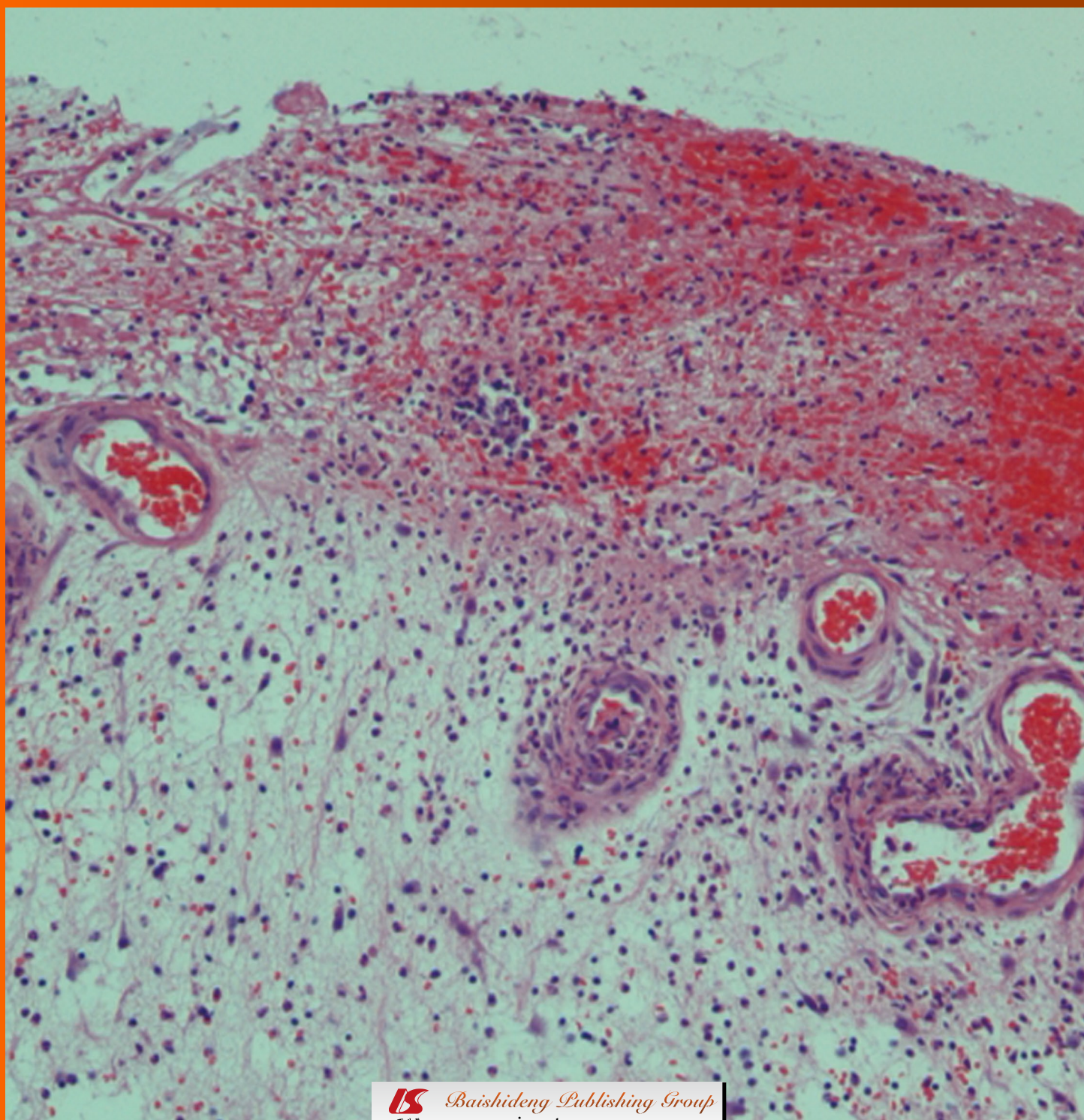


World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2012 June 27; 4(6): 135-162





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World J Gastrointest Surg 2012; 4(6): 157-162
<http://www.wjgnet.com/1948-9366/full/v4/i6/157.htm>

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NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

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PUBLISHER
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Fax: +852-31158812
Telephone: +852-58042046

E-mail: bpg@baishideng.com
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PUBLICATION DATE
June 27, 2012

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Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion: The University of Arizona early experience

Ioannis T Konstantinidis, Christine Young, Vassiliki L Tsikitis, Ellyn Lee, Tun Jie, Evan S Ong

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Received: December 18, 2011 Revised: June 22, 2012

Accepted: June 24, 2012

Published online: June 27, 2012

cancer index (PCI) of 25. The eight patients that underwent curative CRS/HIPEC had an average PCI of 10 and a completeness of cytoreduction score of 0 (87.5%) or 1 (12.5%). Postoperative morbidity was 36%; the worst adverse event was Grade 3 ileus. Mortality rate was 0%.

CONCLUSION: CRS with HIPEC is safe and feasible at tertiary institutions with fledgling programs. PCI is an accurate predictor of surgical outcomes.

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Key words: Cytoreductive surgery; Hyperthermic intraperitoneal chemoperfusion; Peritoneal carcinomatosis; Early outcomes

Peer reviewer: Lberto Zaniboni, MD, UO di Oncologia, Fondazione Poliambulanza, Via Bissolati 57, Brescia 25124, Italy

Konstantinidis IT, Young C, Tsikitis VL, Lee E, Jie T, Ong ES. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion: The University of Arizona early experience. *World J Gastrointest Surg* 2012; 4(6): 135-140 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v4/i6/135.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v4.i6.135>

Abstract

AIM: To evaluate the safety and effectiveness of our new cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC) program.

METHODS: Retrospective review of patients with gastrointestinal malignancies who were suitable candidates for CRS and HIPEC between 12/1/2009 and 10/1/2010. All clinicopathologic data were reviewed with a special focus on the surgical outcome and the postoperative morbidity and mortality.

RESULTS: Fourteen patients were identified. Median age was 64 years; seven were female. The primary tumors were: colonic (29%), appendiceal (36%), peritoneal mesothelioma (14%), gastric (7%), adenocarcinoma of unknown primary (7%), and gastrointestinal stromal tumor (7%). Eleven patients (79%) received CRS/HIPEC, three for palliation. Three patients that did not undergo CRS/HIPEC had an average peritoneal

INTRODUCTION

Peritoneal carcinomatosis (PC) arising from intra-peritoneal seeding of cancer cells is a relatively frequent phenomenon for a variety of gastrointestinal malignancies. The two main mechanisms that are believed to contribute to the intra-abdominal spread of cancer cells is either preoperatively as a result of full thickness invasion of an organ by the cancer or intraoperatively as a result of surgical manipulations^[1].

The presence of peritoneal disease has been associated with a grave prognosis and a survival of less than

6 mo^[2]. The traditional approach for many decades was palliative chemotherapy with surgery reserved only for complications such as intestinal obstruction. An aggressive surgical approach using cytoreduction for PC and, correlation of residual disease with survival was initially recognized in the treatment of ovarian cancer^[3,4]. The combination of cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemoperfusion (HIPEC) is a treatment that has gained increasing popularity amongst surgical oncologists in the last two decades^[5-8]. It is now established that patient survival after CRS and HIPEC directly correlates with the extent of the achieved cytoreduction^[9-15] and a randomized controlled trial has shown a survival benefit of CRS with HIPEC for colorectal cancer in comparison to palliative chemotherapy^[12]. CRS with HIPEC is slowly growing to become the standard of care in the setting of PC for certain malignancies^[7,16-23].

The recognition of the survival benefit after CRS and HIPEC has contributed in this technique gaining popularity. Many institutions have published their experience on series of more than 100 patients^[10-13,15,24,25]. Therefore, the existing knowledge in the literature mainly reflects the long-standing experience of those tertiary centers. CRS and HIPEC is associated with a significant morbidity and mortality; even in high volume institutions, the mortality rate is reported between 0.9%-5.8% and the reported rate of major or grade III/IV morbidity is between 12%-52%^[8,10-13,15,18,24-28]. Some authors have emphasized the importance of a learning curve in performing this technique safely and effectively^[29]. While it is necessary to provide this treatment modality to larger numbers of patients in a safe way there is limited knowledge on the experience of newly-started programs. Our aim was to review our experience with CRS and HIPEC in our newly established peritoneal surface malignancy program with an emphasis on the safety and effectiveness of this technique.

MATERIALS AND METHODS

From 12/1/2009 to 10/1/2010 we reviewed the clinicopathologic data of fourteen patients with gastrointestinal malignancies who were considered suitable candidates for CRS and HIPEC. All patients had a histologic diagnosis of a peritoneal surface malignancy with no evidence of extra-abdominal metastasis at the time of surgery based on preoperative imaging. Clinicopathologic characteristics, operative data and 30-d morbidity and mortality were evaluated. All procedures were performed by a surgical oncologist trained in CRS and HIPEC (Ong ES) with the assistance of a colorectal surgeon (Tsikitis VL) and a hepatobiliary surgeon (Jie T) when needed.

The extent of peritoneal disease was recorded using the peritoneal cancer index (PCI) and the presence of residual disease was reported postoperatively using the completeness of cytoreduction score (CCR)^[30]. The PCI combines assessment of the thickness of the lesion size (LS: 0 for no macroscopic tumor, 1 if tumor < 0.5 cm, 2

Table 1 Clinicopathologic characteristics of 14 patients with attempted cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion *n* (%)

| | |
|--|------------|
| Age (yr), median (range) | 64 (43-77) |
| Female gender | 7 (50) |
| Preoperative imaging | |
| Computerized tomography | 14 (100) |
| Positron emission tomography | 5 (36) |
| Type of cancer | |
| Appendiceal | 5 (36) |
| Colonic | 4 (29) |
| Mesothelioma | 2 (14) |
| Gastric | 1 (7) |
| GIST | 1 (7) |
| Unknown | 1 (7) |
| Successful CRS and HIPEC | 11 (79) |
| Curative intent CRS and HIPEC | 8 (57) |
| PCI for curative CRS/HIPEC, median (range) | 5 (3-26) |
| CCR for curative CRS/HIPEC, median (range) | 0 (0-1) |

GIST: Gastrointestinal stromal tumor; PCI: Peritoneal carcinomatosis index; CCR: Completeness of cytoreduction score; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemoperfusion.

if tumor 0.5-5 cm and 3 if tumor > 5 cm) and tumor distribution (abdominopelvic region 0-12) and quantifies the disease as a numerical score 0-39. The CCR equals 1 if no nodule > 2.5 mm remained, 2 if nodules 2.5 mm-2.5 cm remained and 3 if nodules > 2.5 cm remained. Following surgical cytoreduction, HIPEC was performed with the instillation of mitomycin (40 mg) into the abdomen using the closed coliseum technique at approximately 42 degrees celcius for 90 min. Morbidity was evaluated using the common terminology criteria for adverse events version 3.0 of the National Institute of Health criteria^[31].

RESULTS

Clinicopathologic characteristics

Fourteen patients with attempted CRS with HIPEC were identified. The median age was 64 years (range 43-77 years) and seven (50%) were females. Clinicopathologic factors are listed in Table 1. All patients underwent preoperative computed tomography (CT) scans and five of them underwent also positron emission tomography scans. Appendiceal adenocarcinoma and colonic adenocarcinoma comprised 65% of the primary tumors (Figure 1). The rest of the pathologies were peritoneal mesothelioma (14%), gastric adenocarcinoma (7%), gastrointestinal stromal tumor (7%) and adenocarcinoma of unknown primary (7%). Of these 14 patients, 11 (79%) eventually received CRS and HIPEC for curative intent. For the other three patients the procedure was abandoned secondary to the extent of the intra-abdominal disease which precluded a safe cytoreduction.

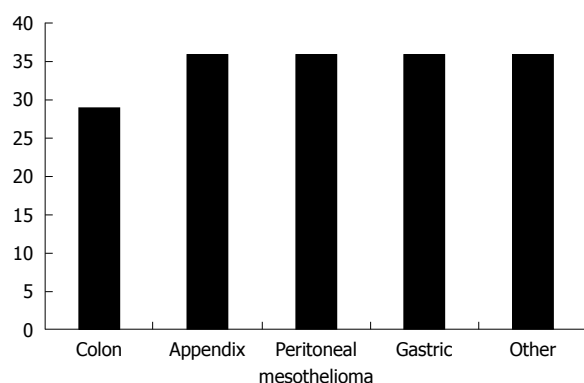
Procedures performed

CRS with HIPEC was performed in 11 patients. For eight patients the procedure had curative intent (mean

Table 2 Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion organ resections according to tumor type

| Curative-intent procedures (<i>n</i> = 11) | Colon (<i>n</i> = 2) | Appendix (<i>n</i> = 4) | Mesothelioma (<i>n</i> = 2) | Gastric (<i>n</i> = 1) | Other ¹ (<i>n</i> = 2) |
|---|--------------------------|-----------------------------|---------------------------------|----------------------------|---------------------------------------|
| Gastrectomy | 0 | 1 | 0 | 1 | 0 |
| Total | | 0 | | 1 | |
| Wedge | | 1 | | 0 | |
| Colectomy | 2 | 4 | 0 | 1 | 0 |
| Total colectomy | 0 | 1 | | 0 | |
| Right hemicolectomy | 1 | 2 | | 0 | |
| Left hemicolectomy | 0 | 0 | | 1 | |
| Sigmoidectomy/LAR | 1 | 1 | | | |
| Small bowel resection | 1 | 0 | 0 | 2 | 0 |
| Salpingo-oophorectomy | 1 | 1 | 0 | 0 | 0 |
| Pancreatectomy (distal) | 0 | 1 | 0 | 0 | 0 |
| Splenectomy | 1 | 1 | 1 | 1 | 0 |
| Cholecystectomy | 2 | 2 | 1 | 1 | 0 |
| Liver resection | 1 | 1 | 0 | 0 | 0 |
| Left lateral segmentectomy | 1 | 0 | | | |
| Wedge resection | 0 | 1 | | | |
| Palliative procedures (<i>n</i> = 3) | | | | | |
| Laparoscopic HIPEC | 0 | 0 | 0 | 0 | 2 |
| Limited debulking and HIPEC | 0 | 1 | 0 | 0 | 0 |

¹Gastrointestinal stromal tumor (*n* = 1) and adenocarcinoma of unknown origin (*n* = 1).

**Figure 1** Relevant frequency of primary cancers for 14 patients.

PCI: 8) whereas for three of them the procedure had a palliative intent (mean PCI: 25). The indication for operation in the latter group was palliation of malignant ascites in two patients and the HIPEC was performed laparoscopically, whereas the third patient could not undergo curative operation due to the extent of the disease. The organs which were resected in addition to the peritonectomies are demonstrated in Table 2. Patients operated with curative intent (*n* = 8) underwent two gastrectomies, seven colectomies, three small bowel resections, two salpingo-oophorectomies, four splenectomies, one distal pancreatectomy, two liver resections and six cholecystectomies. Patients operated with curative intent underwent an optimal cytoreduction with CCR of 0 (87.5%) or 1 (12.5%).

No patient was re-operated for a complication. One patient underwent a takedown of a loop ileostomy 2 mo after the initial CRS. Another one had repeat of CRS and HIPEC 10 mo after the first surgery for recurrence.

Table 3 Postoperative course in 11 patients who underwent cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion

| Complication | <i>n</i> (%) |
|--------------------------------------|--------------|
| 30-d mortality | 0 |
| 30-d morbidity | 4 (36) |
| Ileus grade 3 | 3 (27) |
| Hypertension grade 3 | 1 (9) |
| In-hospital stay (d), median (range) | 9 (5-18) |

Postoperative course

There was no difference in the mean length of hospital stay between those patients who underwent CRS with HIPEC *vs* those who did not (9 d for both groups). The postoperative course for patients who underwent CRS and HIPEC is summarized in Table 3. Overall, the postoperative morbidity was 36% with the worst adverse event being grade 3 ileus in three patients and 30-d mortality rate being 0%.

Two of the three patients who underwent palliative CRS and HIPEC died of disease after 1 and 6 mo whereas the third is alive with disease 5 mo postoperatively.

DISCUSSION

Peritoneal dissemination of gynecological and gastrointestinal malignancies has been traditionally regarded as a terminal condition amenable only to palliative chemotherapy until the introduction of CRS followed by HIPEC two decades ago^[5,6]. There is an increasing enthusiasm about CRS and HIPEC due to the survival benefits in selected patients^[7-9] however, most of the available literature still consists of the experience from a selected

small number of high volume tertiary centers^[10-13,24]. In this report, we reviewed the results of the first year of our newly established peritoneal surface malignancy program focusing mainly on procedure safety and initial effectiveness at an early program.

CRS combined with intra-peritoneal chemotherapy can be used either with therapeutic or palliative intent. It is considered by many as the standard of care for peritoneal mesothelioma and appendiceal mucinous neoplasms^[16-20,23,32] whereas its use for colon cancer with low volume peritoneal disease is supported by a consensus statement of experts^[7]. Moreover, for rare peritoneal processes such as sarcomatosis it appears as the only promising treatment^[21,22]. Data are conflicting for gastric cancer, however the greatest benefit appears to be derived for stage III serosa invading gastric cancer with limited, resectable peritoneal dissemination^[33-35]. More studies are needed before conclusions can be drawn. The integration of CRS and HIPEC in the setting of systemic chemotherapy has not been well studied yet. The most common regimen used is neoadjuvant FOLFOX before CRS and HIPEC. One should keep in mind that delay in the use of CRS and HIPEC can waste the opportunity of benefit due to disease progression on systemic chemotherapy and can also be associated with increased postoperative morbidity. Interestingly, recent reports emphasize that even failure of the neoadjuvant chemotherapy is not a contra-indication to CRS in the setting of absence of extraperitoneal metastases^[36,37]. More research and multi-institutional efforts are needed in order to define the best multi-modality treatments.

In our cohort, the majority (65%) of patients were operated for peritoneal dissemination of cancers that originated from the appendix and colon. This is similar to large series reported by tertiary high volume centers around the world where these two malignancies represent the main bulk of the patient population^[11,13,25-27,38]. Most of the patients underwent CRS and HIPEC with curative intent (87.5%) and had a median CCR of 0. Three patients could not undergo CRS and HIPEC due to the extent of intra-abdominal disease. All three patients underwent preoperative CT imaging. Unfortunately, CT imaging has been previously demonstrated to have limitations in detecting the location and extent of peritoneal disease^[39]. Three other patients underwent palliative laparoscopic HIPEC for recurrent malignant ascites requiring frequent paracentesis, among which a patient with GIST and another with adenocarcinoma of unknown origin. Although there are only anecdotal reports about the use of CRS and HIPEC for tumors like GIST and there is no proven benefit compared to systemic chemotherapy however, HIPEC is an effective procedure for the prevention of recurrent malignant ascites^[40].

CRS and HIPEC is associated with significant morbidity and mortality^[26,28,31]. In centers with long-term experience with this technique the reported mortality rate appears to be around 3% and the reported incidence of grade III-IV complications between 31%-43%^[8-13,15,18,24-28].

In our cohort of eleven patients we did not experience any mortality whereas the overall morbidity was 36%. The most serious morbidity was grade 3 ileus in three of our patients. We did not experience other surgical complications which are frequent after this procedure such as abdominal abscesses, perforations, fistulas or anastomotic leaks^[28]. We believe that prior training on CRS and HIPEC technique, through fellowship training, is important for good surgical outcomes as well as the additional cooperation of experienced colorectal and hepatobiliary surgeons to make multi-organ resections safe. Although the small number of patients introduces selection bias in our study, we believe that CRS and HIPEC can be initiated safely in a new peritoneal surface malignancy program when the prior conditions are met.

The short follow-up period of our patients precludes meaningful survival analyses. However, in our study the PCI was a useful exclusionary measure for determining cases that could be operated for curative *vs* palliative intent. Procedures performed with palliative intent were associated with poor survival outcome. Many studies have previously shown that the PCI is a strong prognostic indicator after CRS and HIPEC^[10-14,41]. Some authors believe that a PCI over 20 should be considered a relative contraindication for this technique^[8]. Other studies have addressed issues like quality of life and cost-effectiveness. Although initially impaired as in any large operation, the quality of life is expected to closely return to the previous baseline as early as 4 mo postoperatively^[42]. There is even evidence to show that a portion of long term survivors experience an improved quality of life^[43]. CRS and HIPEC results in parallel increases in both health costs and survival and, it can be considered a cost-effective technique in the appropriate setting^[44].

In conclusion, our early experience with CRS followed by HIPEC was performed with no mortality and acceptable morbidity during the first year of the establishment of a new peritoneal surface malignancy program. The PCI score predicts the surgical outcomes. Improvements in the preoperative imaging will allow for better patient selection which hopefully translates into better outcomes.

COMMENTS

Background

The use of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemoperfusion (HIPEC) for peritoneal carcinomatosis (PC) has been increasing and is now considered standard of care for certain malignancies. There is need of expanding the use of this technique in more institutions.

Research frontiers

The existing literature on CRS and HIPEC reflects mainly the experience of a relatively limited number of tertiary centers with long standing experience with this technique. More data on the expected outcomes of peritoneal surface malignancy programs in their birth are needed. In this study the authors demonstrate that CRS and HIPEC can be performed safely and effectively in newly established programs from appropriately trained surgeons and carefully selected patients.

Innovations and breakthroughs

In centers of excellence and significant experience with CRS and HIPEC, these extensive operations can be performed with low mortality and acceptable morbidity. In this study the authors report that in our cohort of fourteen patients we

experienced no mortality whereas the morbidity parallels that reported in the literature. They emphasize on the factors of careful patient selection, appropriate training with the technique and multi-modality surgical teams when needed in order to perform those operations successfully from the establishment of a new peritoneal surface malignancy program.

Applications

The description of the experience of newly established peritoneal malignancy programs will aid in the safe spread of this continuously growing technique.

Terminology

PC is the intra-peritoneal seeding of cancer cells and is a frequent mode of cancer spread for a variety of neoplasms. CRS aims to eliminate the presence of macroscopic peritoneal disease and Hyperthermic Intraperitoneal Chemotherapy aims in the delivering of the chemotherapeutic agents directly to the cancer cells in the peritoneal surfaces.

Peer review

This is a well-written clinical experience of HIPEC procedure in a limited number of pts describing the learning curve of this innovative treatment. Authors should expand the Discussion by performing a more in-depth analysis of the current indication and strategic position of the procedure concerning its integration with systemic therapies.

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S- Editor Wang JL L- Editor A E- Editor Zheng XM

Virtual modeling of robot-assisted manipulations in abdominal surgery

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Received: June 16, 2011 Revised: June 22, 2012

Accepted: June 24, 2012

Published online: June 27, 2012

Abstract

AIM: To determine the effectiveness of using multidetector computed tomography (MDCT) data in preoperative planning of robot-assisted surgery.

METHODS: Fourteen patients indicated for surgery underwent MDCT using 64 and 256-slice MDCT. Before the examination, a specially constructed navigation net was placed on the patient's anterior abdominal wall. Processing of MDCT data was performed on a Brilliance Workspace 4 (Philips). Virtual vectors that imitate robotic and assistant ports were placed on the anterior abdominal wall of the 3D model of the patient, considering the individual anatomy of the patient and the technical capabilities of robotic arms. Sites for location of the ports were directed by projection on the roentgen-positive tags of the navigation net.

RESULTS: There were no complications observed during surgery or in the post-operative period. We were able to reduce robotic arm interference during surgery.

The surgical area was optimal for robotic and assistant manipulators without any need for reinstallation of the trocars.

CONCLUSION: This method allows modeling of the main steps in robot-assisted intervention, optimizing operation of the manipulator and lowering the risk of injuries to internal organs.

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Key words: Virtual modeling; Robotic surgery; Multidetector computed tomography; Abdominal surgery; Virtual surgery

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INTRODUCTION

Robotic techniques in modern surgery have undergone a number of stages from their initial introduction to their application in daily practice. Today, there are several surgery clinics where robotic complexes are used and applied in a range of fields. Urological applications of robotic technology have ranged from robot-assisted prostatectomy for prostate cancer to laparoscopic donor nephrectomy and cystectomy, renal transplant, and recently, robotic vasovasostomy^[1-5]. Gynecology is one of the fastest growing fields of robotic surgery. Applications

include the use of the da Vinci surgical system (Intuitive Surgical, USA) in benign gynecology and gynecologic oncology. Robotic surgery can be used to treat fibroids, abnormal periods, endometriosis, ovarian tumors, pelvic prolapse, and female cancers^[6-13]. The role of this technology is now clearly established as it allows minimally invasive surgery with the benefits of traditional open surgical techniques.

Nonetheless, the published literature on robotic surgery reveals that the application of robotic technology in abdominal surgery is, as yet, quite limited. In our opinion the infrequent use of robot-assisted interventions on the peritoneum and retroperitoneal space is due to the limited instrument dexterity and the necessity to constantly manipulate in different regions of the abdomen during surgery. For example, transposition of the intestinal tract from one floor of the peritoneal cavity to another is difficult to perform using robotic manipulators.

However, in abdominal surgery there are many operations that require highly precise movements of the kind which can be achieved with the help of robotics, providing three-dimensional vision, tremor filtration, and motion scaling.

Therefore, it is important to find a compromise solution that includes the advantages of both methods and provides maximum utility, thereby achieving widespread acceptance of robot-assisted technologies in the treatment of various lesions in abdominal surgery.

One of the current advantages in robotic assisted abdominal surgery, which is driving its continued development and expansion, is precise computer-assisted precise of the laparoscopic and manipulation ports on the anterior abdominal wall in relation with the operation field. Reviewing the literature, we were unable to find any publications related to this problem.

Our goal was to determine possible intervention strategies and the capabilities of robot-assisted intervention in patients with surgical diseases of the peritoneum and retroperitoneal space.

MATERIALS AND METHODS

From March 2009 to June 2010, forty three robot-assisted operations were performed in the department of abdominal surgery at the Vishnevsky Institute of Surgery (Russia, Moscow). Table 1 summarizes the range of diseases and the operations performed.

Given the wide spectrum of diseases, we faced the problem of the adequate installation of ports on the anterior abdominal wall. In contrast with gynecological and urological surgery, we had to operate in various anatomic regions of the abdominal cavity. There were, therefore, some technical problems with the correct installation of the trocars that lead to the narrowing of the surgical field, interference of the robotic arms and complications for the surgical team's work.

The aim of our study was to create a method that would allow preoperative planning of the optimal loca-

tion of the laparoscopic and manipulation ports on the anterior abdominal wall in relation to the required surgical area in a range of operations.

We added computer modeling of the upcoming surgical procedure to the treatment algorithm of every patient in our study. Preoperative 3-D modeling was performed for 14 patients (age range 26 to 72 years). Three patients underwent splenectomy (non-parasitic splenic cysts), 3 patients had pancreas resections and one patient underwent a combined cholecystectomy and gastric tumor resection. Seven patients were operated for non-parasitic cysts of the liver (segments VII, VIII). This location is considered one of the most hard-to-reach for conventional laparoscopic surgery, but with preoperative 3-D modeling and the advantages of robot-assisted surgery (increased dexterity, 3-D visualization, seven degrees of freedom, physiological tremor elimination and the ability to scale motions) these operations became much more precise and safe.

All patients underwent a preoperative contrast enhanced triphasic 64-slice and 256-slice multi-detector computed tomography (Phillips Brilliance). About 500 mL of water was routinely administrated 5-10 min before the examination to demarcate the duodenum and delineate the pancreatic head region. Each patient received 100 mL of non-ionic contrast material containing 370 mg iodine/mL (omnipaque 350, ultravist 370, optiray 350) *via* intravenous injection at the rate of 3-5 mL/s using automatic power injectors [OptiVantage DH (Mallinckrodt; Inc.)] through a 18-gauge or 20-gauge intravenous catheter in a antecubital vein. Unenhanced and triphasic (arterial phase, portal venous phase) enhanced scans were performed. Unenhanced and enhanced scan images were obtained from the top of the diaphragm through the pelvis. Monitoring of contrast media bolus was performed on the level of the aortic arch in all cases. The trigger threshold of density was set at 150 HU for the aortic ROI placed at the center of the vessel lumen. Delay after the start of injection was 10 s for arterial phase, and 35 s for portal venous phase. The levels of the tracker and starting position were the same in both cases.

Virtual modeling of robot-assisted operations was performed with the Brilliance iCT workstation (Workstation Brilliance iCT 4.0). We used the Liver segmentation program with RFA planning section (virtual radiofrequency ablation). The examination of the portal phase was carried out semi-automatically with manual correction in different reconstructions, including 3-D visualization. Modeling started with "vector 1" that imitated the robotic laparoscopic camera. The first laparoscopic port was then installed virtually, taking into consideration features of the abdominal cavity, the anterior abdominal wall and bone structures. The internal part of the "vector 1" was directed to the surgical area. Usually, the installation point was the umbilical zone. The next two or three robotic ports were located in the optimal locations, considering all individual anatomical features (the distance between all the ports was not less than 10-12 cm). The

Table 1 Surgical diseases and types of interventions

| Robot-assisted operations | Quantity | Surgical illnesses |
|--|----------|--|
| Atypical liver resection | 16 | Non-parasitic liver cysts, FNH, cystadenoma |
| Pancreatic resection | 5 | Solid pseudopapillary tumor, cystadenocarcinoma, cystic lymphangioma, cystic adenocarcinoma and neuroendocrine tumor |
| Cholecystectomy | 2 | Polyps, adenomyosis of the gall bladder |
| Spleenectomy | 1 | Cystic lymphangioma of the spleen |
| Spleen resection | 2 | Spleen cysts, lymphangioma |
| Wedge gastric resection | 2 | Gastrointestinal stromal tumor |
| Adrenalectomy | 2 | Endothelial adenoma of the adrenal cortex |
| Phrenum plastic | 1 | Relaxation of the left cupola of the diaphragm |
| Adnexectomy | 1 | Luteal cyst of the left oophoron |
| Resection of gastric cysts | 1 | Duplication gastric cyst |
| Left colon resection | 1 | Cancer of the colon |
| Duodenojejunal passage resection | 2 | Gastrointestinal stromal tumor, teratoma |
| Anterior resection of the rectum | 1 | Rectal cancer |
| Erasion of the extra-organ retroperitoneal tumor | 1 | Lipoma |
| Cholecystectomy, resection of the gastric tumor | 1 | Submucous gastric tumor; BSD: chronic acalculous cholecystitis |
| Cholecystectomy, liver resection | 1 | Liver cysts, gall bladder polyps |
| Cholecystectomy, spleen resection | 1 | Non-parasitic spleen cyst. BSD |
| Left-sided lobectomy of the liver | 1 | FNH |
| PDR | 1 | Adenocarcinoma |
| Total | 43 | |

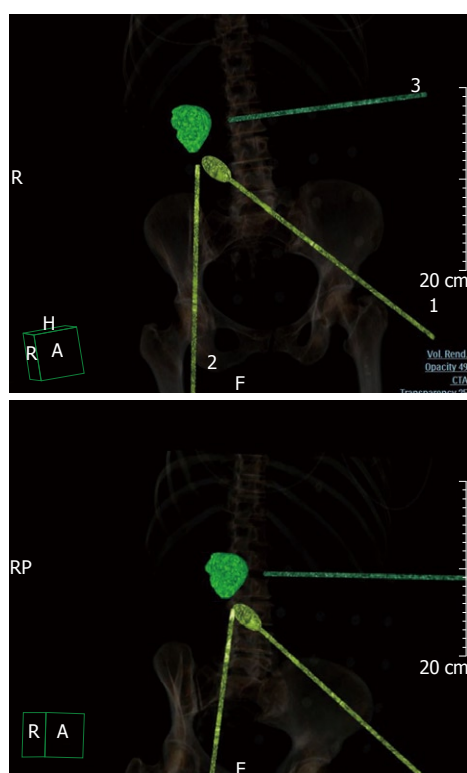


Figure 1 Virtual modeling of robot-assisted operations was performed. 1: Virtual robotic laparoscopic camera; 2: First virtual laparoscopic port; 3: Second Virtual robotic ports.

internal parts of the ports were focused on the lesion (Figure 1). The assistant trocar location was selected after the robotic ports were placed (vectors 1, 2 and 3). The assistant port was situated on the opposite side of the surgical area in the largest interval between the robotic ports. Finally, the image of the virtually installed instruments (regarding the body surface) was saved and sent to the surgery department.

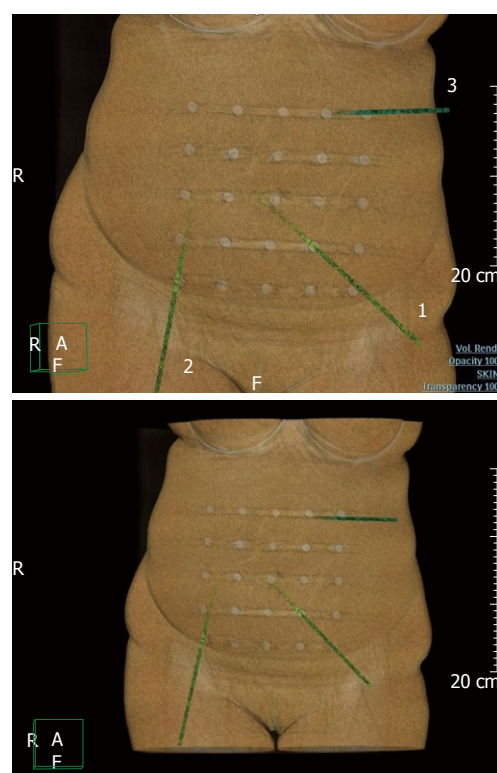


Figure 2 3-D volume rendering with net application. Each trocar is navigated to a roentgen positive tag. 1: Virtual robotic laparoscopic camera; 2: First virtual laparoscopic port; 3: Second Virtual robotic ports.

We used a self-constructed navigation net (Figure 2) for more accurate projection of the virtually installed trocar location points on the anterior abdominal wall of the patients. The net cells are 5 cm × 5 cm wide, and roentgen positive tags are installed at the corners of each square. Before starting the unenhanced phase of the multidetector computed tomography (MDCT) examination, we placed the net on the patient's anterior abdominal



Figure 3 Intra-operative view. Trocars are located as during 3-D virtual multi-detector computed tomography modeling.

wall; the central roentgen positive tag of the net was located on the umbilical area. After adequate virtual installation of the “vectors” on the navigation net background, we achieved the exact overlay of the robotic and assistant ports points onto the roentgen positive tags of the net.

Just before the operation, the navigation net was placed on the anterior abdominal wall (centralized on the umbilical area, as previously described). Having full information about the location of the “virtual” trocar points, relative to the roentgen positive tags of the net, the places for the robotic ports injection were marked (Figure 3).

RESULTS

This method helps to model the main steps of the robot-assisted intervention, to optimize the manipulators’ work and to lower the risk of injury to internal organs. When compared to the open approach, robotic surgery has been shown to have comparable times with the additional benefits of minimally invasive surgery. It becomes possible to analyze the choice of necessary instruments and their arrangement in the robotic manipulators. The properly selected trocar injection sites, virtually planned before surgery, give the opportunity to avoid additional injury of the anterior abdominal wall associated with trocar disposition.

There were no complications registered during surgery or in the post-operative period. All of the interventions occurred without serious blood loss. Comparing two groups of patients with similar operations (Atypical liver resection for non-parasitic liver cysts). The mean duration of the operations completed with 3-D modeling shortened to 90 ± 15 min in comparison with those conducted without the 3-D method at 130 ± 15 min. We were able to reduce robotic arms interference during surgery. The surgical area was optimal for robotic and assistant manipulators without any need for reinstallation of the trocars. The mean duration of the postoperative period was 7 d.

A clinical case

A 56-year-old woman was admitted to the Vishnevsky

Institute of Surgery in May 2010 for further examination of a liver cyst (VII-VIII segments) detected during a routine ultrasonographic examination in 2006. The cyst showed an increase in size (up to 8 cm) on a subsequent ultrasound examination. Vital signs were normal and physical examination showed no abnormalities. A laboratory screening including complete blood count, renal function and liver function tests, was normal. We did not observe any tenderness, discomfort or pain during palpation of the abdominal cavity.

Conventional ultrasound revealed a thin-wall fluid structure in the VIII segment of the liver, of irregular round form, with homogenous anechogenic content, 74 mm × 58 mm.

MDCT of the abdominal cavity showed a 8 cm lesion (7 HU), in the VII-VIII segments of the liver, with a homogenous structure and no contrast enhancement; no cyst capsule was observed. We performed preoperative 3-D computed modeling of the robot-assisted intervention. A robot-assisted atypical resection of the VII-VIII liver segments and drainage of the abdominal cavity was carried out during the robotic laparoscopic fenestration of the cyst. The duration of the surgery was 80 min. According to the urgent histological examination, the lesion was a non-parasitic cyst of the liver. In 3-4 h after the intervention the patient could walk unassisted and after 5-6 h water and soft foods were allowed. On the second day the patient was completely mobile, without any food limitations. On the 5th day the sutures were removed, and after the control ultrasound on the 7th day, the patient was discharged from hospital. Thus, the postoperative period was uncomplicated, so there was no need for administration of narcotic analgesics.

DISCUSSION

The introduction of a virtual modeling procedure into the diagnostic algorithm is a significant contribution to standard robot-assisted interventions, and a new step for its application in intra-abdominal surgery. This method helps to define the optimal location of the robotic ports, taking into consideration anatomical and technical features of individual cases.

With experience, will come standardized schemes for locating robotic and assistant ports on the anterior abdominal wall appropriate to the type of surgical manipulation.

In addition, unlike robot-assisted operations, virtual modeling can be easily provided and does not depend on the localization and the difficulty of surgery. The modeling stage helps to predict and evaluate potential difficulties of the robotic operation in an individual case and gives the opportunity to choose between robot-assistant surgery or another type of intervention.

Robotic surgery is an evolution of conventional laparoscopy potentially offering the surgeon increased dexterity and better vision. With accumulated experience, more and more interventions will be performed robotically,

resulting in significant benefit to our patients. The combination of two high-tech methods such as MDCT with 3-D modeling and robot-assisted surgery can increase the safety of mini-invasive surgery and provide maximum use and widespread acceptance of robotics in abdominal surgery.

COMMENTS

Background

Robotic techniques are considered "gold standard" in many fields of surgery, including urology, nephrology, gynecology, oncology, etc. However, the application of robotic technology in abdominal surgery is limited. The infrequent use of robot-assisted interventions on the peritoneum and retroperitoneal space is due to limited instrument dexterity and the necessity to constantly manipulate in different regions of the abdomen during surgery; it is difficult to transpose the intestinal tract from one floor of the peritoneal cavity to using robotic manipulators. At the same time in abdominal surgery many operations require highly precise movements which can be achieved with the help of robotics, providing three-dimensional vision, tremor filtration, and motion scaling. Therefore, it is important to find a solution that includes the advantages of both methods and provides maximum use and acceptance of robot-assisted technologies in the surgical treatment of various abdominal lesions. The purpose of this study was to determine the effectiveness of using multidetector computed tomography (MDCT) data in the preoperative planning of robot-assisted surgery.

Research frontiers

The introduction of a virtual modeling procedure into the diagnostic algorithm is a significant contribution to standard robot-assisted interventions, and a new step for its application in intra-abdominal surgery. This method helps to define the optimal location of the robotic ports, taking into consideration anatomical and technical features of individual cases.

Innovations and breakthroughs

Unlike robot-assisted operations, virtual modeling can be easily provided and does not depend on the localization and the difficulty of surgery. The modeling stage helps to predict and evaluate potential difficulties of the robotic operation in the individual case and provides the opportunity to choose in favor of robot-assistant surgery or any other type of intervention.

Applications

With experience standard schemes will be developed for locating robotic and assistant ports on the anterior abdominal wall appropriate to the type of surgery.

Peer review

The paper describes the usage of MDCT with 3-D modeling to plan port placement for robotic surgery in complex cases. The authors define two groups,

with and with out preoperative 3-D modelling and state that operating time was shorter in one group.

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S- Editor Wang JL L- Editor Hughes D E- Editor Zheng XM

Pentoxifylline improves liver regeneration through down-regulation of TNF- α synthesis and TGF- β 1 gene expression

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Received: September 20, 2011 Revised: June 20, 2012
Accepted: June 23, 2012
Published online: June 27, 2012

Abstract

AIM: To investigate the mechanism of pentoxifylline (PTX) improvement in liver regeneration.

RESULTS: Rats were randomized into 4 groups: Control rats; Sham - sham-operation rats; Saline - 70% hepatectomy plus saline solution; PTX - 70% hepatectomy plus PTX. At 2 and 6 h after hepatectomy, aspartate aminotransferase, alanine aminotransferase, tumor necrosis factor (TNF)- α and interleukin-6 (IL-6) serum and hepatic tissue levels were determined. Tumor growth factor (TGF)- β 1 gene expression in liver tissue was evaluated 24 h after hepatectomy by quantitative reverse transcriptase polymerase chain reaction analy-

sis. Proliferation was analyzed by mitotic index and proliferating cell nuclear antigen (PCNA) staining 48 h after hepatectomy.

RESULTS: TNF- α and IL-6 serum levels increased at 2 and 6 h after hepatectomy. At 2 h after hepatectomy serum PTX was reduced but not hepatic levels of TNF- α and IL-6. A decrease in liver TGF- β 1 gene expression and an increase in mitotic index and PCNA after hepatectomy were observed in the PTX treatment group in comparison to the saline group.

CONCLUSION: PTX improves liver regeneration by a mechanism related to down regulation of TNF- α production and TGF- β 1 gene expression.

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Key words: Liver regeneration; Hepatectomy; Pentoxifylline; Tumor necrosis factor α ; Tumor growth factor β 1

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INTRODUCTION

Liver regeneration in small-for-size liver grafts and in subtotal hepatectomies may be suppressed, thereby increas-

ing the morbidity and mortality in these situations^[1,2].

The regenerative capacity of the liver has been known for a long time although the mechanisms of this complex physiological process are not completely understood. This process has been reported to be regulated by cytokines [interleukin-6 (IL-6) and tumor necrosis factor (TNF)] and growth factors^[3,4]. TNF- α and IL-6 blood levels increase after partial hepatectomy and are strong promoters of hepatic regeneration after hepatectomy^[2,5]. Indeed, inhibition of TNF- α production retards liver regeneration after partial hepatectomy^[6].

TNF- α regulates the initial phase of liver regeneration after partial hepatectomy by enhancing the mitogenic effects of hepatic growth factor (HGF) *in vivo* and *in vitro* and through the release of IL-6 which activates Stat 3^[7,8]. However, TNF- α and IL-6 are recognized as initial phase cytokines in inflammatory response to systemic infection or injury, and play a pivotal role in liver damage following hepatectomy or ischemia/reperfusion injury^[9,10]. Its excessive production after 90% hepatectomy has been associated with adverse effects on the hepatic microcirculation and liver regeneration^[11]. It has also been recently demonstrated that pentoxifylline (PTX), an inhibitor of TNF- α production^[12], reduces liver injury and improves liver regeneration in a model of small-for-size liver transplantation through a mechanism thought to be related to interruption of TNF- α signaling^[13]. Indeed a recent randomized controlled trial demonstrated the beneficial effects of PTX in major liver resections^[14]. However the mechanisms of the effect of PTX on hepatic regeneration have not been completely evaluated.

Tumor growth factor (TGF)- β 1 is an anti-inflammatory cytokine and also a potent growth inhibitor that suppresses the production of HGF and, when administered in high doses, reduces the peak of DNA synthesis at 24 h after partial hepatectomy^[15-17]. TGF- β 1 is produced during hepatic regeneration and released in the peripheral circulation after partial hepatectomy^[18]. There are several pieces of evidence suggesting that TNF- α induces TGF- β 1 expression in many cell types^[19-22].

The aim of the present study was to test the hypothesis that PTX could improve liver regeneration through inhibition of TNF- α synthesis and reduction of liver TGF- β 1 gene expression

MATERIALS AND METHODS

Animals

One hundred and twelve adult male Wistar rats weighing 230-270 g were housed in individual cages and kept under standard conditions (12 h of light-dark cycle and temperature between 22 °C and 28 °C) with free access to a standard rat chow and water *ad libitum*. The experimental protocol was approved by the Ethics Commission of the Hospital das Clínicas: São Paulo University.

Surgical procedure

The partial hepatectomy was carried out under general anesthesia with intraperitoneal ketamine chloride (Ketalar,

Parke Davis, São Paulo, Brazil) (100 mg/kg) through an upper abdominal midline incision. A 70% hepatectomy was performed using the technique described by Higgins and Andersen^[23]. No mortality was observed in this model.

Experimental design

Animals were randomized into the four experimental groups: Group control - twenty four animals were not submitted to hepatectomy; Group sham - twenty four sham-operated rats underwent laparotomy and liver manipulation; Group saline - thirty two animals submitted to 70% hepatectomy and saline administration; Group PTX - thirty two animals with 70% hepatectomy and PTX administration.

PTX and saline administration

Intraperitoneal administration of PTX, at 25 mg/kg of animal weight (1.25 mL/kg) (Trental™, Sanofi Aventis Pharma, São Paulo, Brazil), was performed immediately after the operation and the same dose was repeated after 12 h.

Intraperitoneal administration of saline solution, at 1.25 mL/kg of animal weight, was performed immediately after the operation and was repeated after 12 h.

Sample preparation

At 2 and 6 h after hepatectomy animals were anesthetized for blood sampling through cardiac puncture and killed by exsanguination. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), as well as TNF- α and IL-6 serum and hepatic tissue levels were determined. TGF- β 1 gene expression was evaluated 24 h after hepatectomy in remnant liver tissue. Proliferation was analyzed in remnant regenerating liver by mitotic index and proliferating cell nuclear antigen (PCNA) staining 48 h after hepatectomy.

AST and ALT

Serum levels of AST and ALT were assayed by using optimized ultraviolet kit from Roche (Rotkreuz, Switzerland).

TNF- α and IL-6

Serum and liver tissue levels of TNF- α and IL-6 were determined using an enzyme-linked immunosorbent assay kit from Biosource International Cytoscreen (Camarillo, California - USA).

TGF- β 1

Livers were rapidly removed and were immediately frozen in liquid nitrogen. All tissues were stored at -70° C until use. Total RNA was isolated from fresh-frozen liver tissues from the two groups using Trizol reagent (Invitrogen, Life Technologies, USA) according the manufacturer's protocol. RNA quality was analyzed with an aliquot of 500 ng on a 1% agarose gel. Samples were kept at -80 °C until processing by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). qRT-

PCR analysis for TGF- β 1 gene was performed in the Rotor-Gene RG-3000 (Corbett Research, Sidney, Australia) using a SuperScriptTM III Platinum SYBR Green One-Step qRT-PCR kit (Invitrogen, Life Technologies) with 100 ng of total RNA and 0.2 mmol/L sense/anti-sense primer per reaction, according to the manufacturer's recommendations. The reaction was carried out under the following cycling conditions: 10 min at 50 °C, 5 min at 95 °C, followed by 35 cycles of 15 s at 95 °C, 30 s at 55 °C, and 30 s at 72 °C. To verify amplification reaction specificity, melting curves were determined using the following conditions: 72 °C ramping to 99 °C at 0.2 °C/s. A primer set was designed to amplify two separate intron-spanning regions, enabling us to assess the possible genomic DNA contamination: TGF- β 1 sense 5'-CG-GCAGCTGTACATTGACTT-3' and antisense 5'-AGC-GCACGATCATGTTGGAC-3' β -actin sense 5'-TGT-CACCAACTGGGACGATA-3' and β -actin antisense 5'-GGGGTGTGAAGGTCTCAAA-3'. Primers were designed using primer 3_www.cgi v 0.2 program.13. RNA template concentrations (500, 100, 20, 4 and 0.8 ng/ μ L) were used to generate a standard curve to evaluate the amplification efficiency of the TGF- β 1 gene in comparison to β -actin. The content of TGF- β 1 RNA was determined as the number of transcripts relative to those of β -actin and additionally normalized to the mean value of control liver tissue. Quantification was obtained according to the $\Delta\Delta$ CT method.

PCNA and mitotic index

Hepatocyte proliferation was assessed by PCNA and by mitotic index staining. Liver specimens were fixed in 2% formalin solution and stained with hematoxylin-eosin for histological analysis. The PCNA-labeling index was obtained by measuring the number of PCNA-positive hepatocytes in 20 consecutive high power fields (HPF: 400 \times). For mitotic index evaluation mitotic hepatocytes were counted in 20 consecutive high power fields (HPF: 400 \times).

Statistical analysis

Results were expressed as a mean \pm SD. Statistical analysis was conducted with one-way ANOVA and post hoc testing with Tukey-Kramer multiple comparison test. Mann-Whitney's test was performed for histological data. *P* values less than 0.05 were considered significant. Graph pad prism 4.0 Software was used for statistical data analysis.

RESULTS

PTX effect on AST and ALT after hepatectomy

Transaminase levels were not significantly reduced in rats treated by PTX (data not shown).

PTX effect on serum and liver tissue levels of TNF- α after hepatectomy

Serum levels of TNF- α were undetectable in control and sham operated groups but increased at 2 and 6 h after partial hepatectomy. Administration of PTX significantly

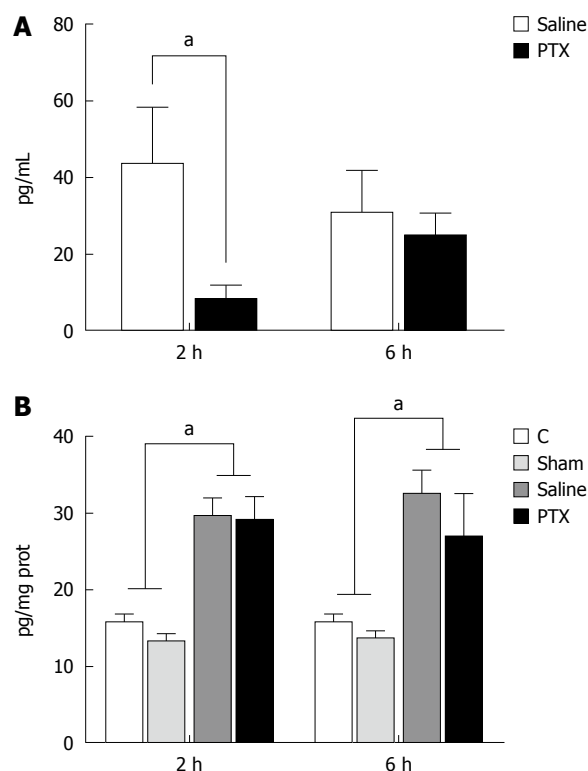


Figure 1 Serum (A) and liver tissue (B) levels of tumor necrosis factor- α after partial hepatectomy at 2 and 6 h. Group saline and Group pentoxifylline (PTX). Data are presented as mean \pm SD of 10 animals per group. ^a*P* < 0.05.

decreased serum levels of TNF- α at 2 h but not at 6 h after hepatectomy, when compared to non-treated animals (Figure 1A).

Liver tissue levels of TNF- α increased after hepatectomy when compared to Control and Sham operation groups. However no difference was observed between Saline and PTX groups at 2 and 6 h after liver resection (Figure 1B).

PTX effect on serum and liver tissue levels of IL-6 after hepatectomy

Serum levels of IL-6 were undetectable in Control and Sham operated groups and increased at 2 and 6 h after liver resection in group saline. Administration of PTX significantly decreases serum levels of IL-6 at 2 and 6 h after hepatectomy (Figure 2A).

Compared to control group, liver tissue levels of IL-6 increased in laparotomy and liver resection groups. However no differences were observed among these three groups (Figure 2B).

PTX effect on gene expression of liver TGF- β 1 after hepatectomy

A significant reduction in TGF- β 1 mRNA liver tissue levels was observed in group PTX when compared to group Saline (Figure 3).

PTX effect on hepatocyte proliferation after hepatectomy

The pathological results obtained 48 h after the hepatec-

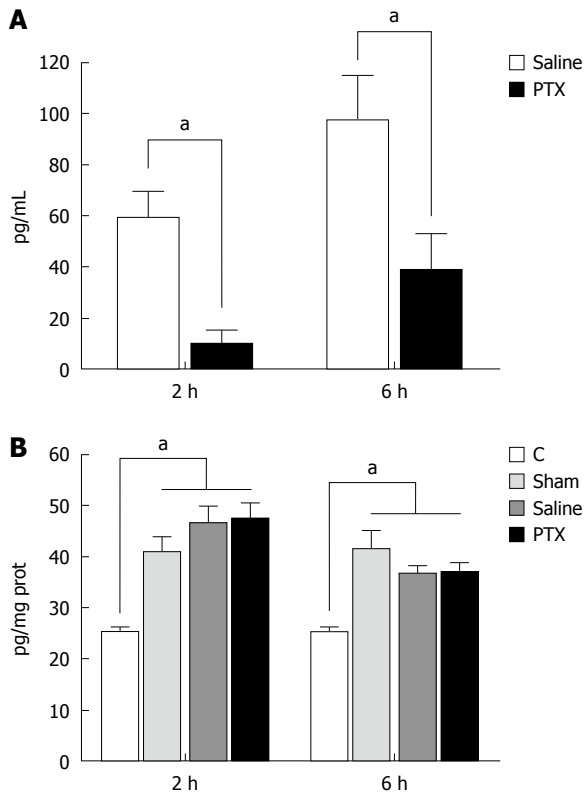


Figure 2 Serum (A) and liver tissue (B) levels of interleukin-6 after partial hepatectomy at 2 and 6 h. Group saline and Group pentoxifylline (PTX). Data are presented as mean \pm SD of 10 animals per group. $^aP < 0.05$.

tomy showed an increased PCNA labeling index (12.1 ± 3.8 core/20 HPF) and mitotic index (2.9 ± 1.2 core/20 HPF) in animals treated with PTX compared to saline treated rats (PCNA: 6.1 ± 2.2 core/20 HPF; mitotic index: 1.7 ± 0.5 core/20 HPF) (Figure 4).

DISCUSSION

In the present study, PCNA expression was used as an indicator of hepatic cell proliferation since there is a perfect correlation between this method, liver weight and 5-bromo-2-deoxyuridine incorporation^[24].

After resection or injury the remaining hepatocytes enter into the G₁ phase. Several previous studies demonstrated that cytokines, mainly TNF- α and IL-6, are involved in liver regeneration after partial hepatectomy^[1,6,10,25].

TNF- α is recognized as a regulator of the initial phase of hepatic regeneration after liver resection and injury, given that it is able to increase the activity of DNA polymerase- α and the incorporation of [H3] thymidine into DNA in the liver cells of intact adult rats^[26].

TNF- α also induces IL-6 production through NF- κ B activation^[27]. IL-6 is a strong promoter of liver regeneration in rats after 70% hepatectomy^[28]. Antibody against TNF- α inhibits IL-6 production and liver regeneration, and the administration of suppressive agents against TNF- α also inhibits hepatic regeneration^[6,26].

However, TNF- α and IL-6 are recognized as initial

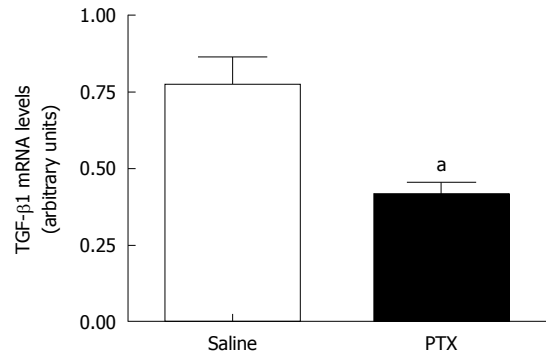


Figure 3 Liver tissue levels of tumor growth factor- β 1 mRNA after partial hepatectomy at 2 h. Group saline and Group pentoxifylline (PTX). Data are presented as mean \pm SD of 6 animals per group. $^aP < 0.05$.

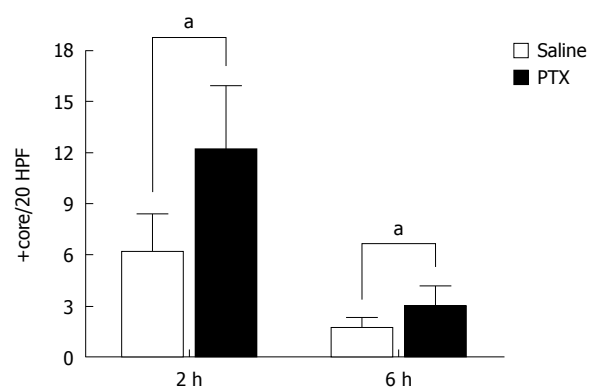


Figure 4 Liver tissue proliferating cell nuclear antigen and mitotic index after partial hepatectomy at 48 h. Group saline and Group pentoxifylline. Data are presented as mean \pm SD of 6 animals per group. $^aP < 0.05$.

phase cytokines in the inflammatory response following systemic injury, stimulating the expression of chemoattractants which induce neutrophil accumulations and tissue injury^[9]. Indeed TNF- α is involved in liver injury due to galactosamin, and endotoxin^[11,29].

It has been demonstrated that excessive production of IL-6 in 90% hepatectomized rats is associated with adverse effects on liver regeneration. Indeed reduction of initial cytokine response in extensive hepatic resection in rats improves liver regeneration^[11].

In the present study we demonstrated that the administration of PTX reduces TNF- α and IL-6 serum levels but not liver tissue levels (Figures 1 and 2). It has also been demonstrated that PTX administration increases the production of anti-inflammatory and growth promoting factors (IL-6 and IL-10) in a small-for-size liver transplantation in mice^[13]. It was concluded that these effects were related to inhibition of the TNF- α signaling pathway^[13]. However, in the present study we did not find a reduction in TNF- α levels in liver tissue following the administration of PTX, suggesting that the production of TNF- α in the liver tissue follows a different signaling pathway from that of macrophages. Indeed it has been demonstrated that the bile duct and the portal and central veins are major producers of TNF- α in regenerating livers^[30]. Depletion of Kupffer cells by gadolinium chloride does not reduce

liver TNF- α and actually enhances liver regeneration after partial hepatectomy^[31]. This complex relationship between hepatocytes and non parenchymal cells was also underscored by findings that blocking nuclear factor (NF)- κ B activation in hepatocytes increases NF- κ B activation and TNF- α production in non parenchymal cells, augmenting proliferative response following partial hepatectomy^[32]. It is, therefore, possible that PTX blocks TNF- α production specifically in Kupffer cells, thereby increasing the production of TNF- α by parenchymal cells.

TGF- β 1 is a strong inhibitor of hepatocyte regeneration. It inhibits proliferation of hepatocytes in culture and suppresses the production of HGF^[16,33]. TGF- β expression increases in liver tissue after hepatectomy in response to the regenerative process^[34]. It has been also demonstrated that TNF- α influences TGF- β 1 expression in many cell types^[19-21]. There is also a correlation between TNF- α mRNA expression and TGF- β 1 mRNA expression *in vivo*^[22]. Therefore, suppression of TNF- α may also suppress TGF- β 1 production, thereby enhancing liver regeneration. Indeed, in the present study we demonstrated that PTX administration reduces TGF- β 1 expression in liver tissue and also improves liver regeneration. Recently it was demonstrated that liver regeneration is inhibited in small-for-size liver grafts and that this effect is prevented by over-expression of smad 7 which blocks TGF- β 1 induced activation of smad 2/3^[24]. Suppression of TGF- β 1 expression may be one of the mechanisms related to the beneficial effect of PTX in liver regeneration.

After extensive hepatectomy, gut-derived endotoxins cause increase production of TNF- α and IL-1, stimulating the production of other cytokines, and further amplifying the inflammatory response, thereby possibly contributing to hepatic injury^[35]. Therefore reduction of cytokine serum levels could also be beneficial for liver regeneration, particularly in extended hepatectomy or small-for-size liver transplantation.

As demonstrated in the present study (Figure 4), the decrease of TNF- α and IL-6 serum levels without changing TNF- α and IL-6 liver tissue levels (Figures 1 and 2), and the reduction of liver TGF- β 1 expression (Figure 3) may explain some of the beneficial effects of PTX in liver regeneration. Reduction of serum levels of cytokines seems to be crucial for the improvement of liver regeneration. Indeed, in rats that had undergone subtotal hepatectomy, serum cytokines levels were persistently elevated and associated with decrease in liver regeneration^[11].

We can speculate that suppression of TNF- α liver tissue levels is deleterious for liver regeneration. However, reduction of cytokine serum levels without change in liver tissue levels, as observed both in the present study and by others, enhances liver regeneration^[6,26,36].

In conclusion, our results demonstrate that PTX decreases the systemic inflammatory response and reduces liver TGF- β 1 mRNA expression, thereby enhancing liver regeneration. This may be useful to improve the function of small liver remnants in extended resection and in small-for-size liver grafts.

COMMENTS

Background

Liver regeneration in small-for-size liver grafts and following hepatectomy may be suppressed, thereby increasing mortality. The complex physiological processes of liver regeneration are not completely understood. Cytokines, such as tumor necrosis factor (TNF)- α , play a pivotal role in this process and in liver damage following hepatectomy or ischemia/ reperfusion injury.

Research frontiers

Pentoxifylline (PTX), an inhibitor of TNF- α production, reduces liver injury and improves liver regeneration. However the mechanisms of this have not been completely evaluated. Tumor growth factor (TGF)- β 1 is an anti-inflammatory cytokine and also a potent growth inhibitor. Given that TNF- α induces TGF- β 1 expression, the authors demonstrated that PTX could improve liver regeneration through inhibition of TNF- α synthesis and reduction of liver TGF- β 1 gene expression

Innovations and breakthroughs

Previous publications have stated that PTX improves liver regeneration by the inhibition of the liver TNF- α signaling pathway. However, in this study the authors did not find a reduction in TNF- α levels in liver tissue. The authors found a down-regulation of TGF- β 1 gene expression in liver tissue and reduction in serum levels of TNF- α . The authors concluded that the effect of PTX on liver regeneration is related to down-regulation of systemic TNF- α production and liver tissue TGF- β 1 gene expression.

Applications

PTX may be useful for improving the function of small liver remnant in extended resection and in small-for-size liver grafts.

Peer review

This is a nicely written preclinical study on liver regeneration which investigate surrogate of inflammation and their anti-inflammatory cytochine as promoter and treatment of liver regeneration after large hepatectomy.

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S- Editor Wang JL L- Editor Hughes D E- Editor Zheng XM

Postoperative pneumoperitoneum after colorectal surgery: Expectant vs surgical management

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Author contributions: Spinelli N and Frattini JC contributed equally to this work; Spinelli N and Frattini JC performed the research; Nfonam V, Marcet J and Velanovich V analyzed the data; Spinelli N and Frattini JC wrote the paper.

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Received: June 19, 2011 Revised: June 18, 2012

Accepted: June 23, 2012

Published online: June 27, 2012

Abstract

Postoperative pneumoperitoneum poses a clinical dilemma. Depending on the cause, its management includes a spectrum from simple observation and supportive care to surgical exploration. The aim of this paper is to present four clinical cases and propose an algorithm for the management of postoperative pneumoperitoneum based on available literature. The causes, diagnosis and possible complications arising from pneumoperitoneum will also be discussed. Three of the four cases presented were successfully managed conservatively and one had an exploratory laparotomy with negative findings. In such scenarios, it is important to consider the non-surgical causes of pneumoperitoneum, which include pseudopneumoperitoneum, thoracic, abdominal, gynecological and idiopathic. These causes do not always require emergent exploratory laparotomy. The surgical team needs to consider the history, physical exam and diagnostic workup of the patient. If a patient presents with peritoneal signs, then exploratory laparotomy is a must. Since 10% of the cases of pneumoperitoneum are caused by nonsurgical entities, managed expectant-

ly, a negative exploratory laparotomy and its associated risks are avoided.

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Key words: Postoperative pneumoperitoneum; Free air under diaphragm; Colorectal surgery; Benign pneumoperitoneum; Spontaneous pneumoperitoneum

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Spinelli N, Nfonam V, Marcet J, Velanovich V, Frattini JC. Postoperative pneumoperitoneum after colorectal surgery: Expectant vs surgical management. *World J Gastrointest Surg* 2012; 4(6): 152-156 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v4/i6/152.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v4.i6.152>

INTRODUCTION

Postoperative pneumoperitoneum, or free air in the peritoneal cavity after surgery, can be seen as a radiolucency on radiographs. It localizes under the diaphragm, where the pressure is negative compared to the rest of the peritoneal cavity, and can be found there regardless of position of patient^[1]. Free air after a major abdominal procedure poses a clinical dilemma. Is the retained free air from the operation or does this indicate a perforated viscus or possible postoperative complication? Clearly, these have different forms of management; the former one is observation while the latter requires re-exploration. It is well established that pneumoperitoneum with fever, abdominal tenderness or distension, leukocytosis or signs of peritoneal irritation is a surgical emergency^[2-4]. Free air postoperatively can indicate visceral perforation, anastomotic leak or a ruptured pericolic abscess^[1]. In the majority of cases of pneumoperitoneum there is visceral

perforation. Only 5% to 15% of the time, the cause of free air is something other than a perforation and does not require surgery^[5-7]. This is called “nonsurgical^[4,8,9]”, “spontaneous^[2,10-13]” or “misleading^[14]” pneumoperitoneum. This is a condition in which imaging shows free air in the peritoneal cavity that can either be managed with observation and supportive care alone or results in a negative laparotomy^[4,12].

The aim of this paper is to present four clinical cases seen in our colorectal practice and discuss the causes, diagnosis, management and possible complications of pneumoperitoneum.

CASE REPORT

Case 1

The patient, a 63-year-old male, with a height of 177.8 cm, weight of 77.6 kg and BMI 24.6, underwent an ileostomy reversal status post restorative proctocolectomy with creation of ileoanal J-pouch and diverting ileostomy secondary to rectal and colonic polyps. On postoperative day 6, he began having episodes of emesis. His abdominal exam was unremarkable, without signs of an acute abdomen. The next day, the emesis continued and an acute abdominal series was obtained, showing free air. Patient was made NPO, intravenous fluids were given and a nasogastric tube was placed. He remained afebrile without leukocytosis and a normal abdominal exam. The patient was monitored clinically with serial abdominal exams. Eventually, his ileus resolved, his diet was slowly advanced and he was discharged from the hospital without requiring re-exploration.

Case 2

The patient, a 45-year-old female, with a height of 172.7 cm, weight of 63.1 kg and BMI 21.2, status post laparoscopic subtotal colectomy with end-to-side ileorectal anastomosis, sacrocolpopexy and rectopexy for colonic inertia and pelvic floor dysfunction, presented to the emergency department on postoperative day 7 with progressively worsening abdominal pain, nausea, vomiting and an inability to urinate. On clinical exam, she had incisional tenderness and an X-ray showed free air. She had no leukocytosis and was afebrile. She was taken to the operating room for exploratory laparotomy, which resulted in negative findings. She eventually was discharged home after tolerating a diet.

Case 3

The patient, a 66-year-old male, with a height of 170.2 cm, weight of 65.1 kg and BMI 22.5, had ulcerative colitis status post laparoscopic restorative proctocolectomy with ileoanal J-pouch and diverting loop ileostomy, developed nausea and emesis on postoperative day 3 without peritoneal signs. He had a leukocytosis but remained afebrile. Abdominal series showed free air and continued distended loops of bowel with mucosal thickening. A nasogastric tube was placed, he was made NPO, given IV

fluids and started on antibiotics. He was followed clinically and on postoperative day 6, he continued to have nausea and a high nasogastric tube output. A computed tomography (CT) of abdomen and pelvis was obtained and demonstrated a moderate amount of free intraperitoneal air, as well as diffuse dilation of the small bowel without transition point likely to represent ileus. In the following days, the patient's clinical symptoms improved, white blood cell count trended down to a normal value and the nasogastric tube was removed, he tolerated a diet and was discharged home.

Case 4

The patient, a 44-year-old male, with a height of 172.7 cm, weight of 75.8 kg and BMI 25.4, underwent the creation of an end ileostomy to palliate an enterovesicular fistula that developed after undergoing an ileal pouch anal anastomosis for ulcerative colitis. He presented 8 d postoperatively with a wound infection. The abdominal X-ray demonstrated no free air but the CT scan performed 3 h later did. The white blood cell count was 11.5 and he was without peritoneal signs. He was discharged home 2 d later, without exploration, tolerating a diet.

DISCUSSION

These vignettes serve as examples of the management of postoperative pneumoperitoneum in relationship to the clinical history, physical exam and diagnostic workup. Two of our patients had ulcerative colitis, a form of inflammatory bowel disease. Could these patients be at a higher risk of developing postoperative pneumoperitoneum? No study answers this question directly; however, it has been shown that patients with inflammatory bowel disease are at a higher risk of postoperative complications^[15,16]. One of the possible complications is anastomotic leaks, which in turn, has been shown to be a cause of postoperative pneumoperitoneum^[1,15,16]. These patients are at a higher risk for leaks due to their immunosuppressed state and overall inflammatory disease process causing tissue friability and dense adhesions^[16]. In the year 2000, Hamel *et al.*^[16] compared ileocolic vs. subtotal colectomy for inflammatory bowel disease and found that the overall postoperative complication rate was not significantly different between the two groups. However, their study had a small sample size of 109 patients^[16]. In 2011, Cotte *et al.*^[15] compared inflammatory bowel disease to other indications of total colectomy and found significantly more anastomotic leaks in the former patients. In addition, in patients receiving total colectomy for other indications other than inflammatory bowel disease, such as colon cancer, slow transit constipation or diverticular disease, the anastomotic leak rate was equivalent to segmental colectomy^[15,17]. Thus, because the rate of leaks between total and segmental colectomy for conditions other than inflammatory bowel disease is similar, it can be inferred that the rate of postoperative pneumoperitoneum is not increased because of the procedure but is related

Table 1 Pathophysiological mechanisms for some of the causes of nonsurgical pneumoperitoneum^[2,4,19,20,22,23]

| Nonsurgical causes | Pathophysiological mechanism |
|------------------------|---|
| Pseudopneumoperitoneum | Adventitial air shadows Overdistension of hollow viscera Undulant configuration of the diaphragm Gas trapped in established wounds Basal pulmonary atelectasis Subdiaphragmatic extraperitoneal fat Interposition of the hepatic flexure of colon between right lobe of liver and diaphragm |
| Thoracic | Mechanical ventilation High airway pressures Large tidal volumes Noncompliant lungs Preexistent pulmonary disease Cardiopulmonary resuscitation Pneumothorax Pneumomediastinum Rapid decompression (diving accidents) Tracheal rupture Median sternotomy Blast injury |
| Abdominal | Postoperative retained air after abdominal surgery Peritoneal dialysis Percutaneous endoscopic gastrostomy Endoscopic procedures Pneumatosis cystoides intestinalis Blunt abdominal trauma |
| Gynecological | Vaginal insufflations Pelvic inflammatory disease Post partum knee chest exercises Coitus Gynecological exams Vaginal douching |
| Idiopathic | |

to the underlying disease process. Interestingly, the two patients in this series with ulcerative colitis did not have an anastomotic leak and were managed conservatively.

The causes of pneumoperitoneum can be surgical or nonsurgical. There are five main nonsurgical causes of free air in the peritoneal cavity. These are categorized as follow: pseudopneumoperitoneum, thoracic, abdominal, gynecological and idiopathic^[3,8,18-22]. Table 1 lists the pathophysiological mechanisms for causes of nonsurgical pneumoperitoneum^[2,4,19,20,22,23].

Pseudopneumoperitoneum is described as the simulated roentgenographic appearance of free intraperitoneal air^[18,20]. Features that can be used to discriminate this from true free peritoneal air include failure of air to shift location with different radiographic positioning and failure of radiolucency to collect in the most superior possible position^[14]. Some causes of pseudopneumoperitoneum can occur with adventitial air shadows, overdistension of hollow viscera and basal pulmonary atelectasis simulating subphrenic air^[14,24]. In the year 2000, Mularski *et al*^[20] performed a systematic review of the literature from 1970 to 1999, using MEDLINE Medical Literature Database, to find the prevalence of nonsurgical causes of pneumoperitoneum. Few thoracic causes exist and in adults the most frequent are mechanical ventilation, cardiopulmonary resuscitation and pneumothorax. For abdominal causes, the most frequently encountered are

abdominal surgery, peritoneal dialysis and endoscopic procedures^[20]. Free air after an abdominal procedure is common; it occurs in 60% of laparotomies and 25% of laparoscopic procedures. Reabsorption of free air is expected with time^[20]. Two-thirds of cases resolve within 2 d and 97% of cases resolve within 5 d^[25]. Lean adults have a more prolonged postoperative pneumoperitoneum than overweight patients because the bulky panniculus in obese adults restricts the distension of the peritoneal space and thus limits the volume of air collected initially^[24]. The most common abdominal cause that is not procedure related is pneumatosis cystoides intestinalis; a condition where multiple intramural gas-filled cysts are found in any portion of the gastrointestinal tract. If these cysts rupture, then pneumoperitoneum can result. The cause can be idiopathic or can be associated with other diseases such as bone marrow transplantation, collagen vascular disease, malignancy, inflammatory bowel disease and others. It resolves spontaneously with conservative management^[2,4,20,26]. The gynecological causes occur anytime air is introduced *via* the genital tract into the peritoneal cavity; most common causes include pelvic manipulation or insufflation^[20]. For idiopathic causes, it has been suggested that there could be a subclinical perforation that resolves without surgery or other unidentified processes^[20].

Pneumoperitoneum can be detected during clinical exam by abdominal percussion or by imaging. CT scan is

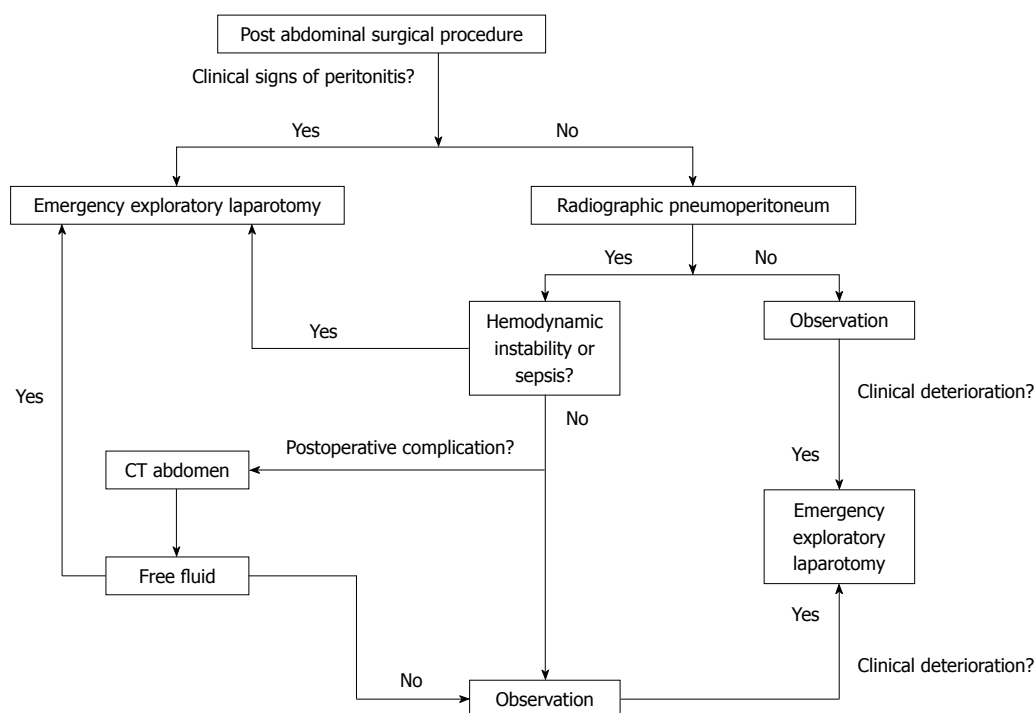


Figure 1 Proposed management of postoperative pneumoperitoneum^[3,4,9,18,20-23,29,31]. CT: Computed tomography.

more sensitive than plain radiographs, both upright chest and lateral decubitus position, in detecting free air; in addition, CT scans showed no correlation between body habitus and the amount of free air^[27,28]. If patients are suspected of having a ruptured viscus, a water-soluble contrast should be used. After the iodinated contrast material is given by mouth, nasogastric tube or enema, a CT scan or a right anterior oblique film of the abdomen should be obtained^[22,24].

The literature shows that nonsurgical pneumoperitoneum should be managed conservatively when no signs of peritonitis are encountered^[2,4,8,9,12,19-21,29,30]. Unfortunately, there has not been a guideline or algorithm developed based on a clinical trial for postoperative pneumoperitoneum. With regards to management of free air postoperatively, we propose the following: if after an abdominal procedure, a patient develops signs of peritonitis, this patient needs emergent re-exploration^[2-4,9,12,20,21,23]. Cues aiding the decision to explore include abdominal tenderness or distension, leukocytosis, fever or peritoneal irritation. If no signs of peritonitis are seen but there is radiographic evidence of pneumoperitoneum and hemodynamic instability or sepsis, the patient needs surgical exploration. If there is radiographic evidence of pneumoperitoneum but no peritonitis and no hemodynamic instability or sepsis, the patient can be observed with repetitive clinical exams and supportive care^[9,18]. In this case, nonsurgical causes of pneumoperitoneum should be considered^[2-4,7-9,18-22]. Failure of conservative management should prompt exploration^[9]. In the case where there is radiographic pneumoperitoneum and no hemodynamic instability or sepsis but a postoperative complication is suspected, then abdominal computed tomography is sug-

gested. If this abdominal CT shows free fluid, then the patient should be considered for exploration based on clinical judgment. It has been suggested that if the assessment for peritonitis is equivocal, then a peritoneal tap and lavage can be useful; if the fluid recovered is normal then continue clinical observation^[3,9,18,19,23,29-31]. Figure 1 shows management of postoperative pneumoperitoneum as a flowchart based on the literature^[3,4,9,18,20-23,29,31].

In 1961, Bevan^[1] listed the complications arising from postoperative pneumoperitoneum as: (1) postoperative pain in same shoulder of unilateral pneumoperitoneum, presumably due to diaphragmatic stretching by air below; (2) basal pulmonary collapse; (3) dehiscence of the surgical incision; (4) subphrenic abscess due to air opening up spaces where intra-abdominal infection can spread; (5) phlebotrombosis and pulmonary embolism due to increased abdominal pressure preventing venous return to heart leading to lower extremity venous stasis; and (6) delayed restoration in gastro-intestinal function.

It is of uttermost importance to raise awareness of management of postoperative pneumoperitoneum, along with its clinical and medicolegal implications. Further research should focus on prospective studies for the management of free air and should include a multidisciplinary team composed of surgeons and radiologists. Without a doubt, if a clinical exam suggests peritoneal irritation with laboratory and imaging supporting pneumoperitoneum, surgical exploration is a must. It is important to recognize nonsurgical pneumoperitoneum and remember its association with pseudopneumoperitoneum, intrathoracic, intra-abdominal, gynecological and idiopathic causes. If the clinical history suggests postoperative retained air or nonsurgical causes, then conservative management

with frequent clinical evaluations should be considered to avoid the risks and financial burden of a negative exploratory laparotomy.

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S- Editor Wang JL L- Editor Roemmele A E- Editor Zheng XM

Solitary rectal cap polyp: Case report and review of the literature

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Received: June 23, 2011 Revised: December 23, 2011

Accepted: December 28, 2011

Published online: June 27, 2012

Key words: Cap polyposis; Inflammatory polyp; Rectal mass

Peer reviewer: Tsukasa Hotta, MD, PhD, Department of Surgery, Wakayama Medical University, School of Medicine, 811-1, Kimiidera, Wakayama 641-8510, Japan

Papaconstantinou I, Karakatsanis A, Benia X, Polymeneas G, Kostopoulou E. Solitary rectal cap polyp: Case report and review of the literature. *World J Gastrointest Surg* 2012; 4(6): 157-162 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v4/i6/157.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v4.i6.157>

INTRODUCTION

Cap polyposis was initially described by Williams *et al*^[1] in 1985. From that initial report and before a review of the literature by Ng *et al*^[2] in 2004, sporadic cases emerged in the literature in which constipation seemed to be closely associated with it, thus postulating colonic dysmotility and mucosal prolapse as the etiological factor. Diagnosis was usually set by exclusion of ulcerative colitis, after poor response to mesalamine and steroids, and surgical resection was considered the optimal treatment^[3]. However, new cases of cap polyposis reported in the literature modified the initial belief concerning the pathogenesis and treatment of this entity. We herein present the case of a patient diagnosed with cap polyposis and review the literature, summarizing and analyzing the available data from cases reported in the past and proposing an algorithm for the treatment of cap polyposis.

CASE REPORT

A 21-year-old Caucasian male presented in our clinic with intermittent rectal bleeding that had lasted for 10 mo. His past medical history was unremarkable. At admission, digital examination revealed a lobular mass located at

Abstract

Rectal bleeding combined with the presence of a rectal mass has been traditionally associated with the presence of malignant disease. Cap polyposis is a relatively young and still undefined rare entity which mainly involves the rectosigmoid. It is characterized by the presence of inflammatory polyps. In this case report, we present a patient who was diagnosed with a solitary cap polyp of the rectum during the investigation of a bleeding rectal mass. The patient's age and the absence of family history were not in favor of malignancy, despite the strong initial clinical impression. After confirmation of the diagnosis, the patient underwent a snare excision and remains asymptomatic. Cap polyposis, although rare, should be suspected and, when diagnosed, should be treated according to location, number of polyps and severity of symptoms.

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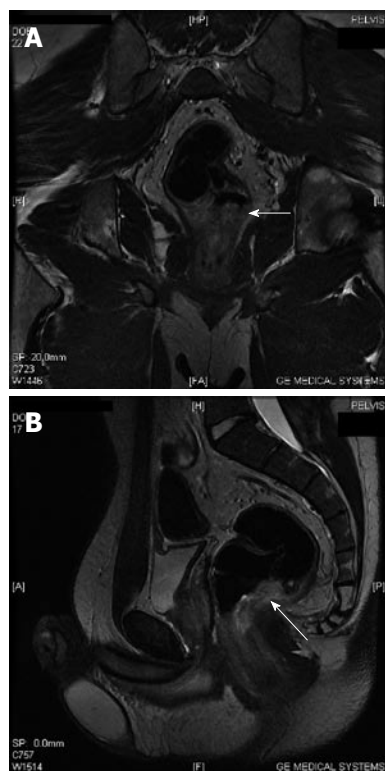


Figure 1 Coronal (A) and sagittal (B) T2 sequence MRI demonstrating the polyp (arrows).

the posterior wall of the rectum, 2 cm above the dentate line. Laboratory tests were unremarkable, with the exception of mild hypoproteinemia (protein: 5.7 g/dL, normal range 6-8 g/dL) and hypoalbuminemia (alb: 3.2 g/dL). CEA was within normal range (1.0 ng/mL). Colonoscopy revealed the presence of a large, lobular polyp, with fibrinopurulent exudate on its apical surface. The lesion was approximately 6 cm in diameter and occupied more than 50% of the lumen. Bioptic material was obtained and malignancy was excluded. The patient underwent Magnetic Resonance Imaging of the pelvis (Figure 1). The lesion present in the rectum was confined to the mucosa and did not breach the muscularis mucosa. Therefore, snare excision in piecemeal fashion was performed. The specimen consisted of multiple tissue fragments, 0.3-2.5 cm at maximum diameter, some with polypoid morphology, often with a reddish eroded surface, covered in areas by white mucus or purulent exudate. On a cut section, the tissue fragments were tan-brown or reddish in color and of soft, rubbery consistency, with small mucin-filled areas. Their total dimensions were estimated at 6 cm × 6 cm × 1 cm.

Histopathological examination showed polypoid tissue fragments exhibiting elongated, dilated or tortuous hyperplastic colonic crypts in their central parts and covered in most superficial regions by a “cap” of inflamed and ulcerated granulation tissue, fibrin and inflammatory exudate (Figures 2 and 3). The intervening lamina propria contained increased numbers of inflammatory cells. Mucin lakes of different sizes were present and areas of fibrosis were common in the central part of several fragments. Hemosiderin deposits were observed in places. A

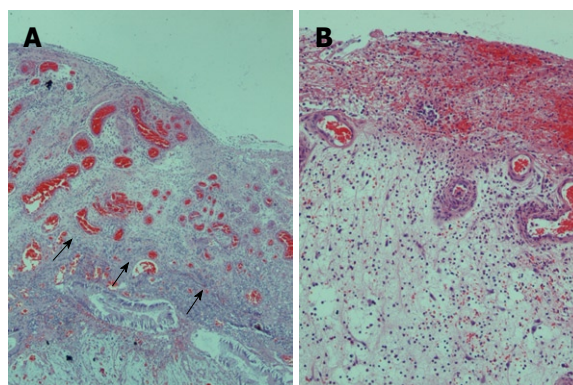


Figure 2 A cap of inflamed and ulcerated granulation tissue was observed in most superficial regions (arrows) (A), covered by fibrin and inflammatory exudate, as presented in higher magnification in (B).

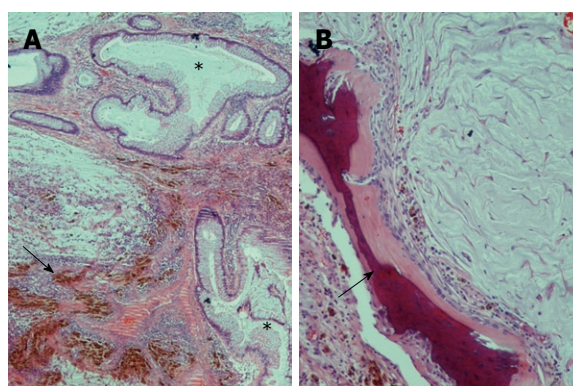


Figure 3 Dilated or tortuous colonic crypts (asterisks) were observed in central parts, alternating with lakes of mucin and hemosiderin deposits (arrow) in fibrotic or inflammatory areas (A), and heterotopic bone formation (arrow) was observed focally, adjacent to mucin lakes (B).

few small foci of osseous metaplasia were observed in the proximity of mucin lakes. The findings were considered consistent with the diagnosis of inflammatory cap polyp.

The patient was investigated for *Helicobacter pylori* (*H. pylori*) infection but gastroscopy and Campylobacter-like organism test were negative. The patient was readmitted 1 mo later for follow-up control, being asymptomatic. Serum albumin was within reference values (alb: 4.4 g/dL). Lower gastrointestinal endoscopy was repeated. At the site of polypectomy, a large ulcer with adenomatous tissue in its center was depicted. Subsequently, the patient was examined under anesthesia and the pathological tissue was removed and sent for histopathological examination, which was negative for recurrence. One year later, the patient remains asymptomatic.

DISCUSSION

A PUBMED search using the key words “cap polyp” and “cap polyposis” was performed from 1993 to the present day (2011). The search retrieved 23 articles with 29 cases. The articles were reviewed, analyzing patient data concerning sex, age, clinical presentation, endoscopic findings, treatment and clinical outcome (Table 1).

Table 1 Cases of cap polyposis reviewed

| No. | Case | Age (yr) | Gender | Clinical presentation | Location | Solitary vs multiple lesions | Presumed or Initial diagnosis | Treatment | Outcome |
|-----|--|----------|--------|--|----------------------------|------------------------------|---|--|----------|
| 1 | Campbell <i>et al</i> ^[3] , 1993 | 68 | M | Weight loss, diarrhea | Sigmoid | Multiple | UC | Total colectomy | Resolved |
| 2 | Campbell <i>et al</i> ^[3] , 1993 | 65 | F | Diarrhea | Rectum | Multiple | Solitary rectal ulcer <i>vs</i> infection | Sigmoid diverting colostomy/ cleversal enema | Improved |
| 3 | Géhénot <i>et al</i> ^[4] , 1994 | 42 | F | Bloody diarrhea | Recto sigmoid | Multiple | Non-specific colitis | Sigmoid colostomy | Resolved |
| 4 | Oshitani <i>et al</i> ^[5] , 1998 | 54 | F | Hypoproteinemia, diarrhea | Desc. colon | Multiple | UC | Left hemicolectomy | Resolved |
| 5 | Peny <i>et al</i> ^[6] , 1998 | 72 | M | Diarrhea, tenesmus | Rectum to ascending colon | Multiple | UC | Proctocolectomy | Resolved |
| 6 | Oriuchi <i>et al</i> ^[7] , 2000 | 20 | F | Hypoproteinemia, mucousy diarrhea | Recto sigmoid | Multiple | | Avoidance of straining | Resolved |
| 7 | Oriuchi <i>et al</i> ^[7] , 2000 | 52 | F | Hypoproteinemia, mucousy diarrhea | Rectum | Multiple | | Diversion transverse double barrel colostomy | Resolved |
| 8 | Kajihara <i>et al</i> ^[8] , 2000 | 38 | F | Bloody diarrhea | Recto sigmoid | Multiple | CP | Metronidazole | Resolved |
| 9 | Isomoto <i>et al</i> ^[9] , 2001 | 51 | F | Mucousy bloody diarrhea | Recto sigmoid | Multiple | Non-specific colitis | APR | Resolved |
| 10 | Esaki <i>et al</i> ^[10] , 2001 | 21 | M | Weight loss, diarrhea | Recto sigmoid | Multiple | | Metronidazole | Resolved |
| 11 | Esaki <i>et al</i> ^[10] , 2001 | 67 | F | Abdominal pain, mucousy diarrhea | Recto sigmoid | Multiple | | Anterior resection | Resolved |
| 12 | Esaki <i>et al</i> ^[10] , 2001 | 21 | M | Abdominal pain | Rectum | Multiple | | Patient refused | |
| 13 | Esaki <i>et al</i> ^[10] , 2001 | 76 | F | Diarrhea, tenesmus | Recto sigmoid | Multiple | | Patient refused | Resolved |
| 14 | Sadamoto <i>et al</i> ^[11] , 2001 | 73 | M | Asymptomatic | Sigmoid to cecum | Multiple | CP | Observation | Resolved |
| 15 | Oiya <i>et al</i> ^[12] , 2002 | 63 | M | Mucousy diarrhea | Rectum to ascending colon | Multiple | | <i>H. pylori</i> eradication therapy | Resolved |
| 16 | Shimizu <i>et al</i> ^[13] , 2002 | 12 | F | Mucousy bloody diarrhea | Recto sigmoid | Multiple | UC | Metronidazole | Resolved |
| 17 | Park <i>et al</i> ^[14] , 2002 | 60 | F | Tenesmus | Rectum | | | Low anterior resection | Resolved |
| 18 | Ohkawara <i>et al</i> ^[15] , 2003 | 67 | F | Mucousy bloody diarrhea | Recto sigmoid | Multiple | Non-specific colitis | Patient refused | Resolved |
| 19 | Akamatsu <i>et al</i> ^[16] , 2004 | 33 | F | Hypoproteinemia, mucousy bloody diarrhea | Rectum | Multiple | UC | <i>H. pylori</i> eradication therapy | Resolved |
| 20 | Akamatsu <i>et al</i> ^[16] , 2004 | 50 | F | Weight loss, diarrhea | Recto sigmoid | Multiple | CP | <i>H. pylori</i> eradication therapy | Resolved |
| 21 | Akamatsu <i>et al</i> ^[16] , 2004 | 53 | F | Mucousy bloody diarrhea | Recto sigmoid | Multiple | CP | <i>H. pylori</i> eradication therapy | Resolved |
| 22 | Bookman <i>et al</i> ^[17] , 2004 | 36 | F | Mucousy bloody diarrhea | Recto sigmoid | Multiple | CP | Infliximab | Resolved |
| 23 | Maunoury <i>et al</i> ^[18] , 2005 | 52 | F | Mucousy diarrhea | Rectum | Multiple | CP (recurrence) | Infliximab | Failed |
| 24 | Konishi <i>et al</i> ^[19] , 2005 | 76 | F | Hypoproteinemia, Mucousy bloody diarrhea | Through out the colon | Multiple | CP | Sigmoidectomy for villous adenoma | Resolved |
| 25 | Ryu <i>et al</i> ^[20] , 2006 | 64 | M | Weight loss, diarrhea | Recto sigmoid | Multiple | CP | Observation | Resolved |
| 26 | Nakagawa <i>et al</i> ^[21] , 2009 | 52 | F | Weight loss, mucousy bloody diarrhea | Rectum to transverse colon | Multiple | CP | <i>H. pylori</i> eradication therapy | Resolved |
| 27 | Kim <i>et al</i> ^[22] , 2009 | 53 | F | Mucousy bloody diarrhea, tenesmus | Recto sigmoid | Multiple | Pseudomembranous colitis | Infliximab | Resolved |
| 28 | Obusez <i>et al</i> ^[23] , 2010 | 70 | F | Diarrhea | Ileal pouch | Solitary | CP | Piecemeal snare polypectomy | Resolved |
| 29 | Yang <i>et al</i> ^[24] , 2010 | 67 | F | Epigastric pain, nausea | Stomach | Multiple | | <i>H. pylori</i> eradication therapy | Resolved |
| 30 | Present case | 21 | M | Blood loss p.a. | Lower rectum | Solitary | Rectal cancer | Piecemeal snare polypectomy | Resolved |

CP: Cap polyposis; UC: Ulcerative colitis; *H. pylori*: *Helicobacter pylori*.

Table 2 Symptoms of cap polyposis

| Symptoms | % |
|------------------|------|
| Mucousy diarrhea | 86.7 |
| Bloody stool | 33.3 |
| Weight loss | 10 |
| Abdominal pain | 10 |
| Tenesmus | 10 |

Twenty-nine cases of histopathologically confirmed cap polyposis were reported from 1993 to 2010, with our patient being the 30th case. Twenty-two out of 30 patients (73.4%) were female, whereas the age of afflicted patients ranged from 12 to 76 years of age (mean age 51.6 years).

The main symptom at presentation was mucousy diarrhea (86.7%), followed by the presence of bloody stool (33.3%), abdominal pain, weight loss and tenesmus (10%). One patient was asymptomatic, 1 patient presented with epigastric pain and nausea and 1 (our patient) presented with rectal bleeding (Table 2). Clinical impression and, in some cases, initial diagnosis, included ulcerative colitis^[3,5,6,13,14], pseudomembranous colitis^[19], non-specific colitis^[4,9], diverticular disease, solitary rectal ulcer, infection and rectal carcinoma.

Hypoproteinemia was present in most patients, probably as a result of protein-losing enteropathy, and was accompanied by edema of the lower extremities in some cases^[5,11].

All patients underwent endoscopy. The rectosigmoid was most commonly affected (22 patients, 73.4%), whereas extension of cap polyposis to the proximal colon was found in 6 patients (20%). One of the aforementioned patients exhibited concurrent lesions in the stomach^[12]. One was diagnosed with cap polyposis of the stomach solely during gastroscopy and finally, 1, who had been submitted to restorative proctocolectomy with ileal pouch anal anastomosis for ulcerative colitis, was diagnosed with a cap polyp in the ileal pouch^[23].

Until the diagnosis of cap polyposis was established, several patients had been treated as patients suffering from ulcerative colitis or non specific colitis. Aminosalicates, broad-spectrum antibiotics and steroids had been administered without clinical response. Nine patients (30%) were treated with surgical resection, after which the problem resolved. In 3 patients, recurrence occurred and 2 were re-operated on, whereas one improved with cleversal enemas^[3,5]. One patient was treated solely by the avoidance of straining at defecation. In 4 patients^[10,11,15,20], the problem resolved spontaneously. Three patients were treated successfully with the administration of metronidazole^[8,10,13]. Infliximab was administered in 3 patients^[17,18,22], but in the case reported by Maunoury *et al.*^[18], the treatment was unsuccessful. After the first report of cap polyposis resolution after *H. pylori* eradication therapy by Oiya *et al.*^[12], 4 more cases^[16,21] were treated accordingly, with complete remission of the symptoms and reversal of the endoscopic features.

In 1985, Williams *et al.*^[1] described 15 cases of what was a distinct endoscopic and pathological entity: inflammatory cap polyps of the large intestine. Therefore, the term cap polyposis was introduced to describe this new and rare entity. From the cases reviewed, cap polyposis seems to affect patients of any age (range 12-76 years of age, median age 51.6 years old), with a female predominance (22 out of 30, 73.4%). The main symptom of these patients at presentation was mucousy diarrhea, followed by bloody stool, weight loss, abdominal pain, tenesmus and bleeding per rectum. Constipation and straining at defecation were also reported^[2].

Laboratory tests commonly included hypoproteinemia and hypoalbuminemia, as a result of protein-losing enteropathy. Oshitani *et al.*^[5] utilized scintigraphy with Tc-99m-labeled DTPA complexed with human serum albumin that showed protein loss from the descending colon in the case of a 54-year-old female patient. After cap polyposis is effectively treated, protein loss ceases and serum albumin returns to normal levels. Usually, there are no other remarkable findings in the laboratory tests performed.

At endoscopy, cap polyps are typically small, sessile and are covered by a "cap" of fibrinopurulent exudate, thus resembling pseudopolyps typically encountered in ulcerative colitis and pseudomembranous colitis^[2,22]. They are usually located on the apical surface of transverse mucosal folds. A characteristic finding discriminating cap polyposis from ulcerative colitis is the presence of normal mucosa among the lesions. Magnifying colonoscopy with indigo carmine dye staining will reveal a type III crypt pattern^[8]. The polyps are multiple. In fact, only 2 cases of cap polyposis from those reviewed involved a solitary lesion, our patient and the patient reported by Obusez *et al.*^[23] in which the polyp was located in the ileal J-pouch. The size of these solitary polyps was also considerable compared to the small polyps usually encountered in cap polyposis. The polyp in our case was approximately 6 cm in diameter and 7 cm in the patient presented by Obusez *et al.*^[23]. The sites most commonly afflicted are the rectum and sigmoid colon. However, cap polyposis seems to extend to the proximal colon as well as the stomach, as reported by Oiya *et al.*^[12] and Yang *et al.*^[22].

Osseous metaplasia (heterotopic bone formation) is uncommonly observed in the gastrointestinal tract and occurs in association with benign or, in the majority of cases, malignant lesions. A recent review of the literature by Oono *et al.*^[25], who described a case of osseous metaplasia in a rectal inflammatory polyp, revealed only nine cases of osseous metaplasia reported in association with benign colorectal polyps, inflammatory, juvenile or adenomatous. Histologically, heterotopic bone formation is often associated with inflammation and/or ulceration, or with the presence of mucin production and extravasation. Repeated local trauma, factors released from adenoma cells or peculiar characteristics of the rectal mucosa were also considered as possible factors in the pathogenesis^[25,26]. In our case, mucin lakes and inflammatory infiltrates were both in close proximity to the osse-

We propose the following algorithm: Once the diagnosis is set, patients should be evaluated according to the severity of symptoms, the number and location of the polyps. Endoscopic snare excision in piecemeal fashion is indicated in cases of solitary polyps, such as our patient, or when the total number of polyps renders snare excision feasible. In cases of multiple polyps, asymptomatic patients

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S- Editor Wang JL L- Editor Roemmele A E- Editor Zheng XM



ACKNOWLEDGMENTS

Acknowledgments to reviewers of *World Journal of Gastrointestinal Surgery*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Gastrointestinal Surgery*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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July 1-5, 2012

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September 15-16, 2012

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November 4-7, 2012

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November 14-16, 2012

Pancreatic Society of Great Britain
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World Journal of Gastrointestinal Surgery

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ISSN 1948-9366 (online)

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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean \pm SD or mean \pm SE.

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