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Pseudomyxoma peritonei: Role of cytoreduction and intraperitoneal chemotherapy

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In the past, pseudomyxoma peritonei was considered as an incurable disease and often no active treatment was given. With the advent of cytoreductive surgery, including peritonectomy procedures and intraperitoneal chemotherapy, long-term survival of these patients is actually possible. A 61-year-old patient with adenocarcinoma of the appendix who presented with a clinical picture of pseudomyxoma peritonei is described in the present report. The patient achieved independent activity of daily living and improved quality of life after aggressive surgical approach and intraperitoneal chemotherapy.

在过去，腹膜假性粘液瘤被视作不治之症，并且通常没有积极的治疗手段可运用，随着细胞去负荷手术的出现，包括腹膜切除术和腹腔内化疗，这类病人得以长期存活确有可能。

我们报道一位患有阑尾腺癌的病人，他在临床上还表现为腹膜假性粘液瘤。在积极的外科手术和腹腔内化疗的治疗下，病人能够进行独立的日常生活活动，并提高了生活质量。

关键词：阑尾癌、腹腔内化疗、腹膜切除术、膜假性粘液瘤。

Key words: appendiceal carcinoma, intraperitoneal chemotherapy, peritonectomy, pseudomyxoma peritonei.

Introduction

Pseudomyxoma peritonei (literally means 'false mucinous tumour of the peritoneum') is described as a slowly progressive disease process characterized by copious amounts of mucoid fluid and tumour that, over time, fills the peritoneal cavity.

There are a variety of pathological conditions that result in extensive mucus accumulation within the abdomen and pelvis, including tumour originated from: (i) a mucinous adenoma of the appendix; (ii) a mucus-producing gastrointestinal adenocarcinoma; (iii) a primary ovarian mucinous tumour; or (iv) mucinous peritoneal carcinomatosis of an unknown primary tumour. Using the above definition, diseases with different biological behaviours were grouped as one clinical entity. As a result the treatment outcome of pseudomyxoma peritonei varies widely.

Sugarbaker *et al.* limited the term 'pseudomyxoma peritonei' to include only those benign peritoneal tumours that are frequently associated with an appendiceal mucinous adenoma and have an indolent course.[1] This means that it does not invade or metastasize and should be distinguished from aggressive tumours of gastrointestinal and ovarian origin. The 'redistribution phenomenon'[2] was proposed to describe the spread of tumour to predictable anatomic sites in the abdomen. The peritoneal surfaces of small bowel are never extensively involved because of peristalsis. With this new concept, a dose-intensive approach (i.e., to concentrate the treatment effect to the target pathology) that combines maximal surgery and regional intraperitoneal chemotherapy has evolved.

Cytoreductive surgery is a combination of peritoneal stripping procedure and resections that remove all macroscopic tumour from the peritoneal cavity.[3] It consists of six different procedures:

1 omentectomy-splenectomy
2 left subdiaphragmatic peritonectomy
3 right subdiaphragmatic peritonectomy
4 pelvic peritonectomy-sigmoidectomy
5 cholecystectomy-lesser omentectomy
6 antrectomy.

This is followed by intraoperative hyperthermic intraperitoneal chemotherapy with Mitomycin C for 1 h. Immediate postoperative intraperitoneal 5-fluorouracil is then given for 5 days.

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The rationale for combining cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are as follows:[4] (i) to destroy residual cancer cells in the tumour bed or free cancer cells before postoperative changes in tumour cell kinetics occur and while the tumour burden is minimal; (ii) to ensure favourable drug access to all surfaces at risk for recurrence before cancer cells are entrapped by wound healing or covered by surgical reconstruction; (iii) to provide dose-intensive, timely regional chemotherapy; (iv) to minimize the possibility of toxicity by close monitoring of physiologic parameters; and (v) to administer a reasonable adjuvant treatment at minimal extra cost and without additional hospitalization.

In October 2000, we operated on a lady having 'pseudomyxoma peritonei' at United Christian Hospital.

WCY, a 61-year-old woman, had a history of uterine fibroid with total hysterectomy and bilateral salpingo-oophorectomy carried out 10 years ago. She suffered from progressive abdominal distension for 2 months. A computed tomography (CT) scan of the abdomen (Fig. 1) showed omental enhancement, dense ascites with septations. Blood carcinoembryonic antigen (CEA) was raised to 656. Provisional diagnosis of pseudomyxoma peritonei was made. Initially she preferred conservative treatment.

Two years past and at this stage the ascites became so tense that she was dyspneic and could barely walk. Ultrasound guided peritoneal tapping was carried out with 3 L of jelly-like fluid drained out for symptomatic relief. The peritoneal fluid cytology showed no malignant cells. She finally agreed for operative treatment.

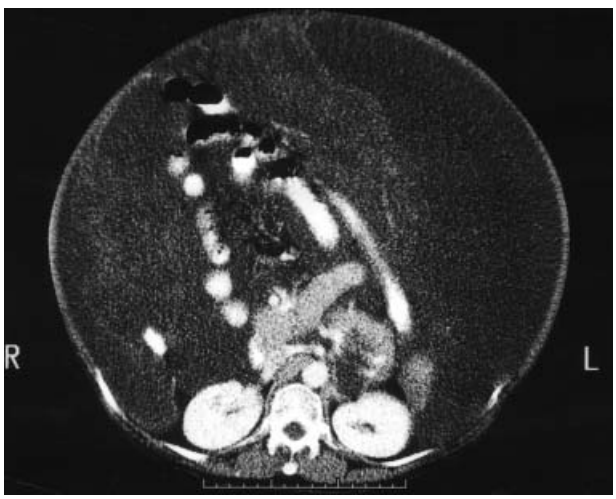

Fig. 1. Preoperative computed tomography abdomen showing deposits of pseudomyxoma peritonei and gross ascites.

She was grossly malnourished because of the abdominal distention associated with poor feeding. Preoperative parenteral nutrition was given to build up her nutritional status. As her abdomen was so tense, it became impossible to assume supine posture during induction of anaesthesia, the anaesthetist requested for preoperative abdominal drainage. A Tenchoff catheter was inserted 9 days preoperatively for daily drainage of ascitic fluid.

She then underwent an operation which confirmed the preoperative CT scan findings. Tumour deposits were observed over the subdiaphragmatic region, the pelvis, the greater omentum and the lesser sac. The tumour also encased the whole colon and the spleen. There was relative sparing of the stomach, the duodenum and the small intestine. Total colectomy, splenectomy and peritonectomy were carried out. An intraperitoneal catheter was inserted and 10 mg/m^2 heated Mitomycin C at 41°C was infused for 1 h with vigorous agitation. Closed suction catheters were placed beneath the right and left hemidiaphragms and within the pelvis to serve as drainage lines. The operative time was 12 h and total intraoperative blood loss was 10 L. Blood transfusion was given.

Postoperatively, she received 5 days of intraperitoneal 5-Fluorouracil (5-FU) (600 mg/m^2). Each dose of 5-FU is prepared in 1.5% dextrose peritoneal dialysis solution, infused at a full rate, allowed to dwell for 23 h and finally drained out 1 h prior to the next infusion.

Parenteral nutrition was given during the early postoperative period as a nutritional supplement. She gradually resumed a normal diet. Ileostomy functioned from day 4.

Pathological examination revealed well-differentiated adenocarcinoma of appendix and pseudomyxoma peritoneum with multilocular spaces containing mucin and floating neoplastic cells. She was thus referred to an oncologist for systemic chemotherapy. However, she was reluctant to undergo systemic chemotherapy because of the side-effects.

She recovered uneventfully and was discharged to an old age home after 1 month of hospitalization. A review CT abdomen scan 1 month later and pelvis scan 8 months later showed negligible ascitic fluid and no evidence of tumour recurrence.

At the recent follow-up in the outpatient clinic (2 years postoperatively), she achieved independent daily activity. She was able to take care of her ileostomy on her own.

Discussion

There is increasing evidence that pseudomyxoma peritonei is a neoplastic condition which usually arises

from a primary adenoma or adenocarcinoma of the appendix.[5] When the appendix is examined histologically, mucoceles, adenomas or carcinomas are found in nearly all cases. Simultanous disease in the ovary might be explained either on the basis of spread from the appendix to the ovary or on the basis of two independent primary disease processes. This broad definition and the rarity of the condition limit the conclusions that can be drawn regarding its treatment and prognosis. Sugarbaker tried to define pseudomyxoma peritonei to include only those with benign pathology, and this serves as a sensible way to select the group of patients that would benefit from aggressive surgery.[1]

Pseudomyxoma peritonei presents with an insidious onset of symptoms and is characterized by long-term survival with good general health and absence of visceral invasion or distant metastasis.[6] Death is usually the result of extrinsic intestinal obstruction by tumour mass. There is no sex preponderance. The mean age of presentation is approximately 53 years.[7] The most common presenting symptom is a gradually increasing abdominal pain and distension, as illustrated in the present case. Other symptoms include inguinal hernia, ovarian masses, appendicitis, right femoral neuropathy, and bladder tumour.

The CT scan is now widely employed to establish the diagnosis and extent of pseudomyxoma peritonei. It helps to differentiate between pseudomyxoma peritonei and peritoneal carcinomatosis. In pseudomyxoma peritonei, there is the relative sparing of the small bowel and its mesentery, which are clearly separated from a large volume of mucinous tumour. The small bowel and normal mesenteric fat are compartmentalized in the centre of the abdominal cavity. The small bowel lumen is of normal caliber and its configuration does not show obstructed segments. In contrary, peritoneal carcinomatosis can affect any part within the abdomen. Sugarbaker *et al*. uses two features of the CT scan to predict completeness of cytoreduction.[1] The presence of a tumour greater than 5 cm on the small bowel or the small bowel mesentery, and focal narrowing of small bowel loops with segmental obstruction signify the invasive nature of the tumour and high chance of incomplete cytoreduction. Nonetheless, despite the absence of these features, the present case was malignant.

Tumour markers are sometimes helpful. Carcinoembryonic antigen is non-specifically raised in tumour of gastrointestinal and ovarian origin. Some anecdotal data indicate that CEA are not infrequently raised in patients with pseudomyxoma peritonei and may rise in association with recurrent disease.

The value of aspiration cytology and frozen section in clinical practice remains uncertain.[5] Flow cytometric analysis of the histological specimen for DNA has been used as an indicator for some neoplasms. In recent published reports, DNA ploidy was suggested to be a marker of metastatic potential, however, it was not correlated with patient survival, disease-free interval or histological grade.

Traditional treatment of pseudomyxoma peritonei involved repeated operative procedure to evacuate the mucus and wipe the peritoneal surfaces. It was for symptomatic relief only, and the long-term result was poor. In recent times, the modern treatment aims at cure rather than palliation. Selection factors that correlate with long-term benefit are: (i) low grade of malignancy; (ii) lack of lymph node or liver metastasis; and (iii) treatment of low volume disease.[8] Most authorities agree that a thorough surgical debulking plus intraperitoneal chemotherapy should be done. Pestieau *et al.* concluded that patients with peritoneal seedling at the time of resection of primary malignancy, peritonectomy procedures plus intraoperative intraperitoneal chemotherapy achieved more complete cytoreduction and better survival than peritonectomy plus delayed chemotherapy.[9]

The 5-year survival rate ranges from 53 to 75%,[7] but outcomes vary widely between relatively benign and malignant subgroups. Sugarbaker *et al*. reported 87% 5-year disease free survival in patients within the benign spectrum.[1]

Nevertheless, aggressive cytoreduction and intraperitoneal chemotherapy is being criticized for its high morbidity and mortality. Complications observed included: small bowel or gastric fistula (13.6%), anastomotic leak (4.5%), peripancreatitis (4.5%), postoperative bleeding (4.5%) and haematological toxicity (4%).[4] Morbidity was statistically associated with: (i) duration of surgery; (ii) the number of peritonectomy procedures and resections; and (iii) the number of suture lines. Major morbidity was 27% and treatment-related mortality was 1.5%. Yet the technique has shown an acceptable frequency of adverse events to be tested in phase III adjuvant trials.

The majority of patients will eventually suffer recurrence, one-third of whom will need reoperation. Recurrences were most frequent in the left subhepatic/lesser omentum area (28%), while the right subdiaphragmatic area (3%) was least involved. Pseudomyxoma peritonei recurrence in the laparotomy scar was found in 52% of cases and in 60% of cases pseudomyxoma peritonei recurrence were found at the suture lines. Differences in the completeness of cytoreduction, inadequate distribution of intraperitoneal chemotherapy to upper abdominal and small bowel surfaces and entrapment of tumour within suture lines were thought to be causal factors consis-

tent with this pattern of recurrence.[10] It was reported that, with intraperitoneal chemotherapy, the residual disease is relatively minimal and adhesion is less. However, studies concerning reoperation are scarce.

In order to decrease disturbance of the anterior abdominal wall, thus minimizing future adhesions, as well as possible tumour-cell sites, Raj *et al.* advocated laparoscopic exploration as an alternative to radical peritoneal dissection.[11] Laparoscopic approach allows thorough exploration of the abdomen, appendicectomy ± right hemicolectomy, as well as irrigation and aspiration of the thick mucinous material and instillation of mucolytic/chemotherapeutic agents. However, its deficiency in peritonectomy and cytoreduction is not addressed.

Conclusion

Pseudomyxoma peritonei is a treatable condition that may result in long-term disease-free survival. Careful patient selection is crucial in determining the result of aggressive treatment.

Up until now, few definitive conclusions may be drawn owing to the small number of patients and the casemix in the published trials.

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