Application of Advanced Multimodality Care to Pseudomyxoma Peritonei Patient: Report of First Patient Treated at a Tertiary Center

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Abstract Pseudomyxoma peritonei following dissemination of appendiceal mucinous neoplasms is slowly progressive but inevitably a lethal condition. It is locally invasive and does not lead to lymph node or distant metastasis making it amenable for more radical procedures. We present a case of pseudomyxoma peritonei treated by Cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) with Mitomycin C (12.5mg/m^2) at 41.50°C . This was followed by five cycles of early postoperative intraperitoneal chemotherapy (EPIC) with 5FU (650mg/m^2) over 5 days. Patient underwent standard Peritonectomy procedure combined with resection of gallbladder, Spleen, subtotal colectomy and resection of part of small bowel. Blood loss during the procedure was 4000ml. Histopathology revealed Pseudomyxoma peritonei (hybrid type). The patient recuperated well and was discharged and now is living a productive life. Peritonectomy with perioperative intraperitoneal chemotherapy is the current standard of treatment for appendiceal tumors with

peritoneal dissemination which offers a hope of disease free long survival in such patients.

Keywords Appendix · Mucinous tumors · Peritoneal dissemination · Pseudomyxoma peritonei · Peritonectomy · Intraperitoneal · Hyperthermic chemotherapy

Introduction

Pseudomyxoma peritonei (PMP) is an uncommon slowly progressive condition that usually arises from perforation of appendix due to an enlarging appendiceal adenoma, allowing mucin producing neoplastic cells to gain access to peritoneal cavity. PMP syndrome rarely metastasizes outside the abdominal cavity but remains a fatal illness as the space in the abdomen and pelvis required for normal function of the gastrointestinal tract becomes filled with copious amounts of the mucinous tumor [1]. Eventually patients develop terminal starvation because of abdominal distension and increased tumor volume [2]. The appendiceal malignancies causing PMP are characterized by unique features that facilitate successful treatment of these tumors [3]. They are of low biological aggressiveness and do not metastasize to lymph nodes and liver. The tumor accumulates in dependent portions of peritoneal cavity and the sites where peritoneal fluid is absorbed. The small bowel with active peristalsis all the time is spared of tumor deposits which makes near possible removal of cancer from peritoneal cavity a possibility [4]. Mucinous nature of this tumor allows greater penetration by chemotherapy than most solid tumors, and as it spreads only intraperitoneally all the tumor is in regional chemotherapy field. Very few patients with PMP survive past 10 years and if they are treated by cytoreductive surgery (CRS) plus heated intra-

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peritoneal chemotherapy (HIPEC) median survival may exceed 10 years and many of these patients are tumor free [5]. We are presenting this case here as a first case of PMP treated by CRS and HIPEC marking the initiation of peritonectomy program at our centre.

Case Report

A 48-y old male, who had received a diagnosis of Pseudomyxoma peritonei 9 months ago was referred to our hospital for further management. 9 months ago he had presented to a peripheral hospital with severe abdominal pain and tenderness and USG had revealed massive loculated ascitis. Because of peritoneal signs he underwent a limited laparotomy which had revealed jelly like granulations filling the peritoneal cavity, which was subsequently proved to be PMP histopathologically. The patient was referred to a central hospital for further care where he was managed conservatively and the definitive care was delayed because of non availability of expertise to cure such cases.

Examination revealed an alert patient with stable vital signs, wasted look and unremarkable systemic exams except abdomen was distended with non shifting ascites and few irregular masses but no organomegaly. CBC revealed Hb of 11.3 g/dl. Serum chemistry revealed low albumin (32 g/L) and very high levels of CA19-9 (4165 Ku/L) and CEA (215.5 µg/L). Colonoscopy was unremarkable except hemorrhoids. CT scan showed scalloping of liver surface, omental caking and ascitis (Fig. 1). Preoperative workup did not show loco regional or distant metastasis. He was planned for peritonectomy with hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC). Intraoperatively Peritoneal carcinomatosis index (PCI) score was estimated to be 34. Standard Peritonectomy procedure was performed with the addition of resection of a portion of jejunum, extended right hemicolectomy, Splenectomy and cholecystectomy because of heavy bulk of disease. Rest of the small intestine and colon was cleaned off the tumour granulations (Fig. 2a, b). Complete Cytoreduction was achieved (CC=0). HIPEC with mitomycin C (12.5 mg/m²) at 41.5°C was administered by means of a perfusion pump for 90 min. This was followed by restoration of bowel continuity and construction of diversion ileostomy. Histopathology showed borderline mucinous adenoma of appendix with intermediate PMP. Post operatively the patient was managed in ICU. 5 cycles of cold EPIC with 5FU were given. The hospital course was complicated by central line sepsis due to pseudomonas, Klebsiella pneumonia and intraabdominal collection which was percutaneously drained. He was discharged on 30th postoperative day. On

Fig. 1 Cross-sectional CT of the abdomen showing dense ascitis and scalloping of liver surface

follow up at one and a half year, the patient has no systemic complaints and he has gained weight. There is no biochemical or radiological evidence of disease recurrence. More over he has started to live a productive life.

Discussion

PMP also popularly known as jelly belly, a syndrome first described by Karl F. Rokitsky in 1842, is often fatal intra-abdominal disease characterized by dissecting gelatinous ascites and multifocal peritoneal epithelial implants secreting copious globules of extracellular mucin. The most common site is a low grade mucinous tumor of the appendix. Other sites include ovary and pancreas. Most cases of cystic ovarian mucinous tumors associated with pseudomyxoma peritonei are associated with metastases from an appendiceal tumor [6]. In women, cells become entrapped within the corpus hemorrhagicum and consequently, it is the detection of an ovarian cyst that often brings about the diagnosis of pseudomyxoma peritonei.

PMP syndrome has been histologically classified into three categories: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and PMCA with intermediate or discordant features (PMCA-I/D) which predominantly have features of DPAM but also have focal areas of carcinoma [6]. There is a significant survival difference between DPAM and the intermediate type or mucinous adenocarcinomas and thus for the greatest benefit

Fig. 2 **a** Large mucinous tumor and tumor granulations filling the entire abdominal cavity **b** Tumor free abdominal cavity at the end of debulking and before the start of HIPEC. A plastic sheet is being stitched to abdominal wall for instilling chemotherapy by open technique

of treatment the noninvasive histology is the most important thing [4]. Our case had pseudomyxoma peritonei of hybrid type that was treated by peritonectomy and perioperative intraperitoneal chemotherapy.

PMP is three times more common in women than men with median age at diagnosis of 53 years [7]. Symptoms are dependent upon the location of disease. Preoperative imaging is useful and provides information necessary for planning of operation and evaluating for disease recurrence. Computed tomography (CT) of the pelvis and abdomen is used most often to diagnose and determine the extent of PMP syndrome. Magnetic resonance imaging (MRI) provides information similar to that obtained with a CT scan. Cytology has not proven to be clinically valuable and frozen section analysis is not very helpful [8]. The measurement of the tumour marker, CA19.9 is useful in evaluating therapy in patients with PMP treated with CRS and HIPEC. Elevated tumor markers are believed to be indicative of advanced and

invasive disease, which would make complete cytoreduction difficult. High tumor markers in post-operative period indicate that recurrence is imminent [9].

The traditional surgical approach for PMP syndrome has been debulking to resect all gross disease to reduce the build-up of mucus. Because of residual disease, progression is likely and repeated debulking surgery makes the procedure more difficult because of adhesions and small bowel involvement, increasing the potential for complications such as fistulae and malabsorption [10]. Patients may survive for several years with repeated debulking procedures, but eventually no further surgical options are available and patients die from intestinal obstruction and cachexia.

Sugarbaker introduced a more aggressive approach including extensive CRS with HIPEC. The surgical approach is based on extra peritoneal dissection which allows removal of all visible peritoneal masses while dissecting in a tumor free plane. CRS entails peritonectomy procedures along with visceral resections in order to reduce the tumor volume to the smallest, which is apparently a departure from palliative approaches used earlier for peritoneal carcinomatosis [11]. Patient selection for treatment protocol requires clinical assessment on four fronts viz histopathology, preoperative CT scan of chest abdomen and pelvis, peritoneal cancer index (PCI) and completeness of cytoreduction score (CC) [12].

Peritoneal surface malignancy if treated by surgery alone, inevitably progresses because of free intraperitoneal tumor emboli, fibrin entrapment of intraabdominal tumor emboli on denuded peritoneal surfaces and progression of entrapped tumor cells through growth factors involved in wound healing process [13]. Perioperative chemotherapy given by intraperitoneal route reduces the chances of progression of disease by killing the residual microscopic disease. The timing of chemotherapy is critical as it is instilled before the wound healing and formation of interloop adhesions because once the fibrinous deposits become organized the chemotherapy will be unable to reach the cancerous cells and local recurrence could occur [14]. Effects of this regional chemotherapy varies from deleterious effects on local wound healing to more systemic effects as manifested by hematological toxicity [15].

Prognosis in this disease is closely related to the bulk of the disease, completeness of tumor removal by cytoreductive surgery, microscopic degree of differentiation of the neoplastic epithelium and pre-operative tumour marker levels [3, 9]. In a group of patients with minimally aggressive disease who received this treatment, the survival rate at 20 years approached 80%, and was 60% for patients with more aggressive mucinous carcinoma [16].

Conclusion

We have described a case of hybrid form of PMP who was treated by CRS and perioperative intraperitoneal chemotherapy. Awareness of this indolent and rare condition is an important prerequisite for early diagnosis and appropriate management. Further as it can present years later one should be vigilant enough to recognize and treat it early as good prognosis could be achieved by starting the treatment early, when the bulk of tumor is still small as increased tumor bulk increases the chances of morbidity and mortality.

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