European Review for Medical and Pharmacological Sciences 2021; 25: 362-365

Hyperthermic intrathoracic chemotherapy combined to iterative cytoreductive surgery to treat a pleural carcinosis from psudomixoma peritonei. A case report

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Abstract. – Pseudomyxoma peritonei (PMP) is an uncommon disease with locally-invasive attitude. Intrathoracic spread is rarely reported and its management extremely challenging. A 51-year-old Caucasian female presented with left pleural carcinosis 9-months after two sequential abdominal surgical procedures combined with HIPEC for low-grade PMP. Cytoreductive surgery (pleurectomy/decortication) was followed by 60-minutes hyperthermic intrathoracic chemotherapy mitomycin-C (215 mg/m2) infusing at same temperature (42°C) and intrapleural pression (2-4 $mm^{H}2O$). No intra-operative complication occurred, the post-op stay was uneventful and no sign of recurrence was observed 9-months after surgery. Cytoreductive thoracic surgery and hyperthermic chemotherapy (HITHOC) could be a feasible therapeutic option in very selected cases.

Key Words:
Chemotherapy, Hyperthermic, Psedomixoma, Intrathoracic chemotherapy.

Introduction

Pseudomyxoma peritonei (PMP) is a rare disease that is caused by the dissemination of a mucin-producing tumor (usually appendicular tumor) in the peritoneal cavity, thereby leading to mucinous ascites. There is body of evidence[1] suggesting that an aggressive strategy of care including cytoreductive surgery with intraperitoneal chemotherapy could prolong survival in these patients. The rationale of such policy is based on the biological behaviour of PMP that usually presented with a locally spread with very low metastatic ability. Thus, long-term survival could be expected after aggressive loco-regional therapy.

When the extension of PMP occurred into the thoracic cavity (an extremely rare scenario) a very poor prognosis is predictable[2]. Since clear evidence on the best treatment to be adopted is not available, systemic palliative chemotherapy remains the usual treatment option. However, on the basis of the same rationale reported above, few authors have reported the resection of intrathoracic lesions, and surgery[3] with or without hyperthermic intrathoracic chemotherapy (HITHOC) in specialized centers[4]. We herein report a multimodal aggressive treatment consisting in iterative hyperthermic intraperitoneal chemotherapy (HIPEC) for PMP with peritoneal spread followed by HITHOC 9 months later for a left pleural recurrence of disease.

Case Report

A 51-year-old Caucasian female presented with significantly high CEA levels, ascites and suspicion of peritoneal carcinomatosis. The patient underwent exploratory laparoscopy, which revealed massive gelatinous ascites, peritoneal metastases ("omental cake") from an appendicular pseudomyxoma peritonei. Extensive cytoreductive surgery (peritonectomy, omentectomy, hepatic Glisson's capsule, splenectomy, hysterectomy) was performed following by HIPEC with Oxaliplatin 360 mg/m^2 and intravenous administration of 5FU 400 mg/m^2 + Leucovorin 20 mg/m^2. One year later the patient presented with recurrent ascites and she underwent a 2nd abdominal cytoreductive surgery (right hemicolectomy and resection of multiple carcinosis lesions in the pelvis) followed by a further HIPEC-procedure (mi-

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tomycin-C 35 mg/mq). Clinical, CEA levels and radiological surveillance did not show any relapse at 3 and 6 months after second surgery.

About 9 months after surgery left pleural thickenings were observed at CT-scan (Figure 1A-B) and the levels of CEA was high (78.50 ng/ml) with no signs of abdominal recurrence.

A multidisciplinary tumor board planned an "off-label loco-regional procedure" after patient's informed consent.

A lateral muscle-sparing thoracotomy was performed at left 6th intercostal space. At exploration, several neoplastic implants on the visceral and (above all) parietal pleura were observed (Figure 1C-D). Cytoreductive surgery consisted of a macroscopic left complete pleurectomy including parietal, mediastinal and diaphragmatic pleura (Figure 2A-B-C). In detail, the diaphragm and pericardium were spared because the resection of the pleura at these levels was judged macroscopically complete while the visceral pleura was involved and partially resected (operation time: 190 minutes).

Two 28Fr drains for inflow and two drains for outflow were adopted during HITHOC (Figure 2D) and temperature sensors were put with the inflow and outflow catheters.

An infusing pump (RAND-Performer®, HT) filled the pleural cavity with 3L Ringer's lactate solution at 42°C. Afterward, mitomycin-C (215 mg/m^2) was added, and the perfusion was continued for 90 minutes at a rate of 1,000 mL/min (Figure 2D-E). Finally, a "wash out" of the chest cavity with 2L of Ringer's lactate solution at room temperature was performed. The duration of the whole procedure was 390 minutes and no intra-operative complication occurred. The patient stayed in the intensive care unit for 1 day. Considering the low risk of renal disfunction associated to mitomycin-C, a nefroprotection protocol consisted of 2L of saline solution for the first 3 days only. Blood lab tests were performed in 1st-2nd-4th-7th post-op day with no evidence of toxicity related to HITHOC. The post-op was substantially uneventful and the histopathology examinations revealed low-grade PMP.

CT-scans performed at 3 and 6 months after surgery showed no sign of recurrent disease at the level of both thorax and abdomen and CEA levels supported the absence of recurrent disease.

Discussion

PMP is a very rare neoplasm (annual incidence: 2/1,000.000 individuals[4]), usually secondary to mucinous tumor (non-adenocarcinoma) of the ap-

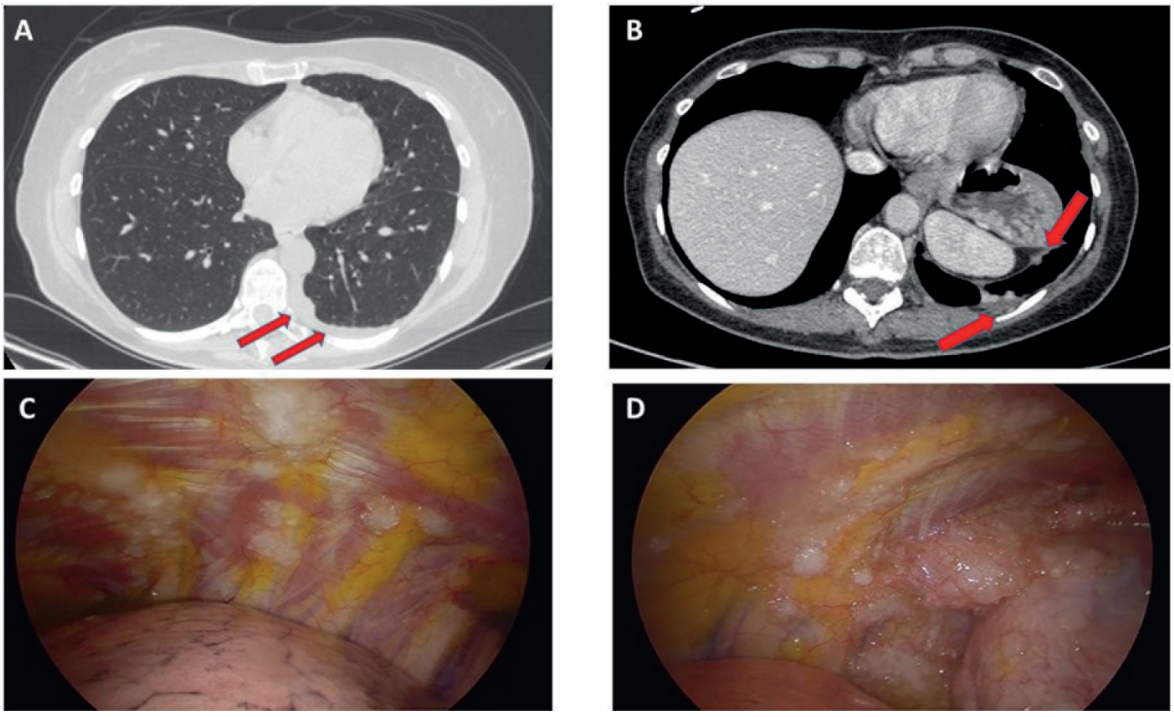

Figure 1. CT-scan showed left pleural carcinosis (red arrows), especially at the level of parietal and diaphragmatic pleura (**A-B**); at surgical exploration, we confirmed with multiple neoplastic implants without pulmonary/lymph nodal metastasis (**C-D**).

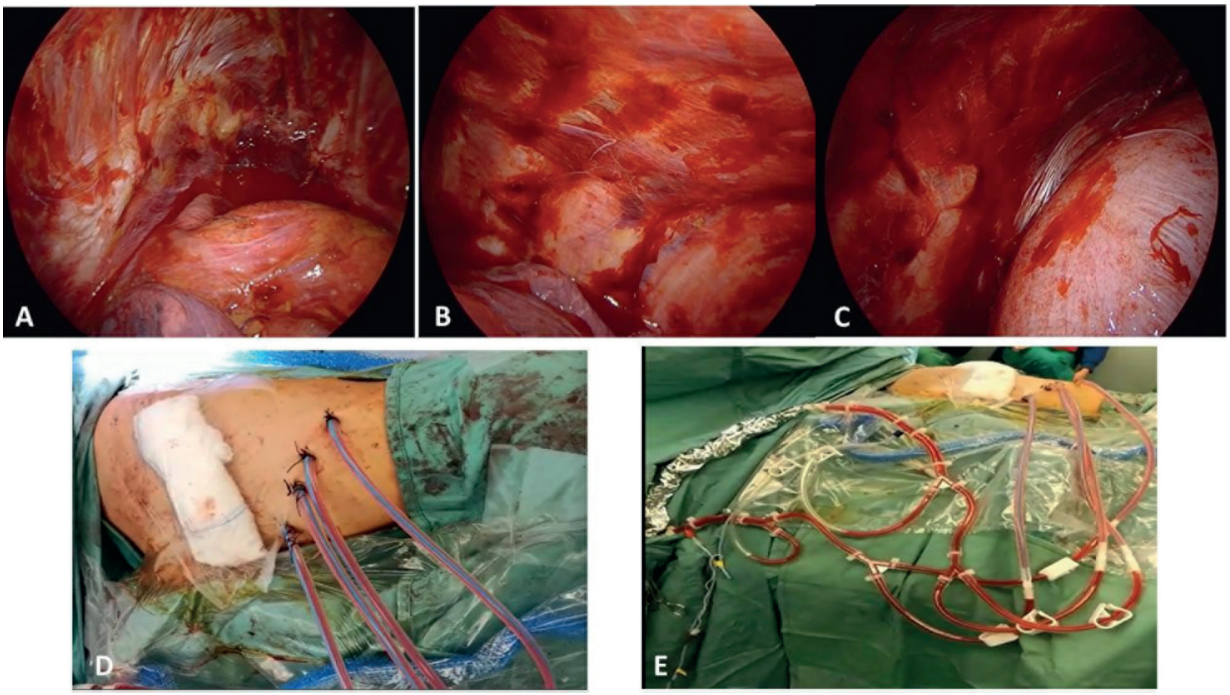

Figure 2. Surgical results: surgical view after complete pleurectomy at the level of the upper thoracic cavity and mediastinum (**A**), medium thoracic cavity (**B**) and lower thoracic cavity and diaphragm (**C**). The HITHOC procedure with a detail of the chest drains placement (**D-E**).

pendix[2]. From a pathological view, we may distinguish low-grade *vs.* high-grade PMP with the latter associated to poor survival (5-year overall survival 23% *vs.* 63% for high-grade disease[5]).

Considering that PMP usually presents with local invasiveness but rarely spreads through the lymphatic or blood system, surgical treatment and even iterative debulking approaches were previously generally accepted as the treatment of choice[4]. In addition, in the last decade the use of HIPEC as part of an aggressive locoregional therapy has been largely reported with satisfactory results in specialized oncological centers[6] but is still the subject of controversy at the majority of institutions, due to the high morbidity and mortality associated. In the present case, we have reported an aggressive locoregional multimodal approach consisted of combined sequential abdominal cytoreductive surgery + HIPEC and intrathoracic cytoreductive surgery + HITHOC. This strategy has been discussed by a multidisciplinary Team of experts and was justified on the basis of the good performance status, age and oncological evolution. No toxicity and no morbidity were observed and patient showed an optimal functional recovery.

Regarding the extension of PMP to the thoracic cavity, only few reports reported this extremely rare conditions[4]. Pestiue et al[2] have demonstrated that 23 of 426 PMP-patients (5.4%) developed a pleural extension. This was the consequence of an iatrogenic damage of the diaphragm during peritonectomy, the presence of congenital or acquired pleuroperitoneal communication, or, more rarely, a direct diaphragmatic invasion as already postulated[2-4].

The intrathoracic extension of PMP carries a poor prognosis[3] and stays as a real therapeutic challenge due to the lack of studies in this extremely rare condition. However, recently Kawaguchi et al[4] reviewed the clinical outcomes of 17 PMP-patients who underwent resection of intrathoracic lesions after abdominal cytoreductive surgery (the largest series reported so far). Among them 5 patients undergone HITHOC-procedure (cisplatin+mitomycin or mitomycin alone at 42-43°C) associated to different lung and/or pleura resection. They also reported good early and long-term outcome in the overall surgical series (mortality-morbidity rates: 6%-29% and 5-yrs survival: 46%).

The present case was accurately selected for this aggressive protocol (no comorbidities and good local control of the disease). HITHOC was well tolerated during surgery and no major com-

plication neither toxicities occurred. Compared to cisplatin, the mitomycin-C plasmatic concentration is very lower (as reported in a pharmacokinetic study[7]), thus reducing the risk of adverse effect related to the drug in the post-op.

From a surgical point of view, we preferred not to resect diaphragm and pericardium because the pleura resection was judged complete at these levels. This conservative management could have a protective impact on post-op stay and should be taken into account when a macroscopic resection appears achievable without an extended resection of these two organs.

Conclusions

Loco-regional combined treatment (cytoreductive surgery+HITHOC) has been successfully performed. This strategy could be considered as a therapeutic option only in very selective cases and specialized centers with a dedicate team of experts.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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