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A case report and review of the literature

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Cytoreductive surgery plus bicavitary chemohyperthermia as treatment of pseudomixoma peritonei with pleural extension. A case report and review of the literature

AIM: *Intrathoracic extension in patients with pseudomixoma peritonei is a rare event, but spread of the tumour beyond the abdomen in to pleuropulmonary cavity has been reported.*
MATERIALS AND METHODS: *We report a case of a 50-years-old woman with synchronous pleural manifestation of pseudomixoma peritonei by a mucinous ovarian cancer. During the abdominal cytoreductive surgery an extensive disease under the right hemidiaphragm was noted, requiring partial diaphragmatic resection. Once the pleural space was entered, mucinous neoplastic implants on the pleural surface was observed. The diaphragmatic defect was left open during the hyperthermic chemoperfusion to treat both the pleural and peritoneal surfaces. After a postoperative course uneventful she died after 6 months for a myocardial infarction, in presence of a left side pleural effusion with a positive cytology for high-grade malignant cells with a smear background contained wispy mucin.*
DISCUSSION: *Despite the aggressive spread of the pseudomixoma peritonei within the peritoneal cavity, lymphatic and hematogenous metastasis are rare. However, extension of disease into pleuropolmonary cavity has been well described as pleural effusion or pleuropulmonary metastases. This is the first report in literature, to our knowledge, in which the thoracic extension is due to a mucinous ovarian cancer, and is the second case in which a simultaneous bicavitary hyperthermic chemoperfusion was done as a management option for thoracic extension of pseudomixoma peritonei.*
CONCLUSION: *Due to the rarity of the thoracic involvement by pseudomixoma peritonei, its correct treatment is still unclear. Simultaneous cytoreductive surgery associated to intraoperative intraperitoneal and intrathoracic chemohyperthermia can be a potential therapeutic option for these patients.*

KEY WORDS: HIPEC, HITHOC, Pseudomixoma peritonei, Thoracic extension

Introduction

Pseudomixoma peritonei (PMP) is an uncommon clinical entity characterized by diffuse intra-abdominal gelatinous collections (jelly belly) with copious mucinous implants on peritoneal and omentum surfaces [1-2]. The PMP predominantly originates in the appendix in men and, increasingly evidence suggests a similar site of origin in females [3-4], even if a proportion of cases can arise from other organs as ovary, colon and rectum, stomach, gallbladder, bile ducts and so on [5-6]. PMP has generally been considered benign; however its behaviour suggests that it should, be considered a borderline malignancy [7]. Actually, by a pathological point of view, the

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clinical entity of PMP can be classified in low-grade tumours as disseminated peritoneal adenomucinosis (DPAM), high-grade tumours as peritoneal mucinous carcinomatosis (PMCA) and an intermediate group (IG) [8]. Despite the aggressive spread of the disease within the peritoneal cavity, lymphatic and hematogenous metastases are rare [1]. However, extension of PMP into pleuropulmonary cavity has been described in few reports [9-21]. Most of these cases can arise from direct diffusion of the neoplastic cells due to a surgical trauma, from congenital or acquired pleuroperitoneal communications, or from direct pass through an intact diaphragm, via lymphovascular spaces or, more likely, via direct invasion. Finally, in a significant minority of cases, the mechanism remains idiopathic [15]. Nowadays the current treatment consists of CRS plus HIPEC [22] for peritoneal disease, while the approach to pleuropulmonary diffusion, due to the limited number of cases, can no be standardized [1,9-21]. We report a case of a patient with pleural spread of PMCA-PMP, by a mucinous ovarian cancer, that was managed by CRS plus simultaneous Hyperthermic Intraoperative Peritoneal Chemotherapy (HIPEC) that actually represent the gold standard for this type of tumours [23,24] and Hyperthermic Intraoperative Thoracic Chemotherapy (HITHOC).

Case report

A 50-years-old woman was referred to our observation for the presence of peritoneal implants associated to abdominal collections. Previously the patient had been submitted, in another institution, for a pelvic mass (size 22 cm) associated to a neoformation of the sigmoid colon and to a mucinous ascites, to right annexectomy, appendectomy, low anterior resection and multiple peritoneal biopsies. The definitive histological examination documented a moderately differentiated (G2) mucinous cystoadenocarcinoma of the right ovary, a chronic appendicitis, a G2 papillary adenocarcinoma of the sigmoid colon with areas of mucinous differentiation (C3 stage) and a low-grade pseudomixoma peritonei with disseminated peritoneal adenomucinosis (DPAM-PMP). Hence an adjuvant chemotherapy (Folfox plus Taxolo) was performed. At 10 months-follow-up the computed tomography (CT) scan documented the presence of a left ovarian neoformation (size 11 cm) with a large amount of intra-abdominal fluid. For this reason she underwent to hysterectomy and left salpingo-oophorectomy with a histological findings of a metastatic poorly differentiated (G3) mucinous cystoadenocarcinoma of the left ovary. Afterwards the patient was submitted to adjuvant cycles of chemotherapy (Paclitaxel/Carboplatin). After 11 months a CT-scan documented the presence of hypodense peritoneal implants that, a percutaneous biopsy, revealed to be metastatic lesions by ovarian cancer. For this reason the patient was submitted to six cycles with Topotecan i.v. with a partial response. Subsequently the patient was referred to our observation. The surgical exploration documented multiple peritoneal implants with a Peritoneal Cancer Index (PCI) of 16, that required a total parietal peritonectomy, splenectomy, superior colpectomy, and a colic resection. The extensive disease under the right diaphragm required its partial resection. The exploration of the following exploration of the right thoracic cavity showed the presence of multiple metastatic pleural implants. During the left subdiaphragmatic peritonectomy we have opened accidentally the pleural space, but, for the absence of neoplastic implants, we have stitched immediately. Removed the right pleural implants with size superior to 3 mm, we have positioned five drainages, 2 intrathoracic (1 inflow and 1 outflow) and 3 intraperitoneal (1 inflow and 2 outflows) and performed the simultaneous pleural and peritoneal chemohyperthermia (HIPEC plus HITHOC) with cisplatin (CDDP) at 25 mg/m^2/l plus mitomycin C (MMC) at 3.3 mg/m^2/l for 60 min at a temperature between 41-43°. Before to perform the chemohyperthermia, was necessary placed a right-side double-lumen tube to permit mechanical ventilation with lung isolation and partial inflation of the nondependent lung with CPAP, monitored the core body temperature through seven separate temperature probes (nasopharynx, right pleural cavity, upper and lower abdomen, inflow and outflow, rectum) and was placed a cooling blanket on the bed and the ice packs to the head and neck for to avoid systemic hyperthermia. During chemohyperthermia the oxygen saturation was maintained at or above 99%, even during one-lung ventilation. There was no change in peak airway pressure, and no cardiopulmonary side effects were observed during the perfusion. Urinary output was maintained before HIPEC plus HITHOC at 50 mL/h, while during and after HIPEC plus HITHOC between 100 and 300 mL/h. The routine monitoring of all vital signs showed during chemohyperthermia procedure a reduction of the systolic blood pressure between 60 and 100 mmHg associated to the reduction of diastolic blood pressure between 30 and 50 mmHg and with a heart rate between 90 and 110 bpm. At the end of the procedure, the patient was transferred to the intensive care unit without reveal any evidence of new-onset of cardiopulmonary abnormalities. The definitive histological diagnosis of the peritoneal and pleural lesions documented a high-grade peritoneal mucinous carcinomatosis (PMCA-PMP) by ovarian cancer. The postoperative course was uneventful and the patient was discharged after 22 days. Afterwards she was submitted to an adjuvant treatment (Taxolo/Carboplatin) for 4 cycles. The patient died 6 months after the end of chemotherapy for a myocardial infarction, in presence of a left side pleural effusion with a positive cytology for high-grade malignant cells with a smear background contained wispy mucin, but without other relapses.

Discussion

There has been considerable confusion in the literature about the site of origin and pathological classification of PMP [25]. High-grade colonic mucinous neoplasms, adenocarcinoma of the appendix and mucinous adenocarcinoma originating from any other intra-abdominal organ can simulate the clinical, radiological and pathological features of PMP [25]. Recent pathological, genetic and immunohistochemical evidence supports the theory that the majority of classical PMP originate from ruptured low-grade appendiceal tumours [25]. Undoubtedly a proportion of cases can arise from other organs and it is likely that the ovarian origin may be the commonest one between colon, rectum, stomach, gallbladder, bile ducts, and the other intra-abdominal organs [5,6]. PMP has generally been considered benign; however its behaviour suggests that it should, be considered a borderline malignancy with disease progression over time, to massive abdominal distension and nutritional compromise in most cases [7]. Actually the PMP is classified in low-grade tumours as disseminated peritoneal adenomucinosis (DPAM) and high-grade tumours as peritoneal mucinous carcinomatosis (PMCA), with an intermediate group (IG) demonstrating a mixture of DPAM and PMCA [8]. The 5-year survival ranges from 62.5% to 100% for low-grade and, 0%-65% for high-grade disease with a related morbidity and mortality ranges from 12 to 67.6% and 0% to 9% respectively [7]. Despite the aggressive spread of the disease within the peritoneal cavity, lymphatic and hematogenous metastasis are rare [1]. However, extension of PMP into pleuropolmonary cavity has been well described in only few reports [9-21], as pleural effusion or pleuropulmonary metastases representing the 5.4% of cases [15]. Several mechanisms have been proposed to explain the means by which neoplastic cells spread from the peritoneal cavity to the pleural space [15-16]. Several workers believe that iatrogenic damage to the diaphragm occurs with a considerable frequency when a subdiaphragmatic peritonectomy is performed [15-16]. In some reported cases, the surgeon recognized, at operation, that the pleural space had been already infiltrated [17]. In a small proportion of cases, patients may have congenital or acquired pleuroperitoneal communications that allow to the neoplastic cells to reach the pleural spaces [17]. Otherwise, it has been suggested that tumor may directly pass through an intact diaphragm, via lymphovascular spaces or, more likely, via direct invasion [15]. Finally, in a significant minority of cases, the mechanism remains idiopathic [15]. In literature are described only 30 cases of pleural effusion and 12 cases of pleuropulmonary metastases by PMP (Table I and Table II) [9-21]. In the patients with pleural effusion the ages ranged from 34 to 79 years at the time of initial diagnosis. The interval between the initial diagnosis and the discovery of thoracic disease related to this syndrome has ranged from less than 1 year to nearly 15 years [17]. However, in most patients, the interval is between 2 and 6 years. Of these 30 patients, 17 were men and 13 were women. Right-sided effusions were reported in 15 cases, whereas in 12 cases, the disease was on the left side; in 3 cases, pleural effusions were bilateral. Pleural fluid in cytologic specimen had been examined previously in only 5 cases [12-13,17]. In two cases the smears showed only extracellular mucinous material without neoplastic cells [12-13], while in the other 3 cases the smears showed extracellular mucinous material associated to neoplastic signet-ring cells [17]. Pleural biopsies were obtained in 14 cases [15-16]. In one case the biopsy sample contained only mucin without associated malignant cells [16], while in the other 13 cases pleural biopsy specimens confirmed the neoplasm without describe the histologic features of the thoracic disease or of the primary neoplasm [15]. In the patients with pleuropulmonary metastases the ages ranged from 39 to 65 years at the time of initial diagnosis of PMP. When reported the interval between the initial diagnosis of PMP and the discovery of thoracic disease has ranged from 1 month to 7 years [17-21]. Of these 12 patients, 9 were men and 3 were women. Right-sided metastases were reported in 5 cases, whereas in 2 cases it was on the left side; in 5 cases, the metastases were bilateral. In 9 cases the metastases involved the lung and in 3 cases the pleural surface. In 10 cases the metastases were multiple, while in 2 cases were solitary neoplastic implants. Unlike the patients with pleural effusion the histopathological features in patients with pleuropulmonary metastases by PMP have been better documented. In fact in all patients the primary neoplasm

TABLE I - *Cases of Pleural Effusion due to Pseudomyxoma Peritonei*

Reference	No. of cases	Sex/Age(y)	Side of Effusion
Mets et al.[10]	1	M/47	Right
Radosavljevic et al.[12]	1	M/41	Left
Peek et al.[14]	1	M/38	Bilateral
Pestieau et al.[15]	23	F,13; M,10/34-79[a]	Right,12; Left,9; Bilateral,2
Lee et al.[16]	1	M/60	Left
Geisinger et al.[17]	3	M/36,45,38	Right,2; Left,1

[a]Ages were not described separately for men and women.

TABLE II - *Cases of Pleuralpulmonary Metastases due to Pseudomyxoma Peritonei*

Reference	No. of cases	Sex/Age(y)	Solitary/Multiple	Laterality
Berge. [9].	1	M/59	Multiple	Bilateral
Kreissig et al. [11]	1	M/39	Multiple	Bilateral
Mortman et al. [13]	3	F/47;M/41,48	Multiple,2;Solitary	Right,2;Left
Lee et al. [16]	1	M/60	Multiple	Left
Geisinger et al. [17]	2	F/45;M/61	Multiple;Solitary	Bilateral;Right
Khan et al. [18]	1	M/65	Multiple	Bilateral
Dang et al. [19]	1	M/43	Multiple	Right
Senthil et al. [20]	1	F/54	Multiple	Right
Fujisaki et al. [21]	1	M/64	Multiple	Bilateral

seems to be a low-grade mucinous tumour of the appendix with a DPAM-like lesion involving the pleuralpulmonary parenchyma [17-21]. The type of treatment reported for the pleural effusion is represented by a thoracentesis or pleural biopsy [10,12,14,16-17], while only Pestieau et al. [15] have reported some cases treated with CRS plus HITHOC. For this patients the reported survival ranges from 2-years to 4-years, with a median survival of 55 months [10,12,14-17]. Instead for the pleuropulmunary metastases the treatment reported is represented by a lobectomy or wedge resection associated in some cases to systemic chemotherapy [9,11,13,16-18], otherwise by CRS plus HITHOC [19], or CRS plus HIPEC and HITHOC [20], or only with CRS associated to systemic chemotherapy [21]. In this case the reported survival ranges from 6 mo to 13-years [9,11,13,16-21]. Compared to the other cases of pleural effusion and pleuropulmonary metastases by PMP, is the first report in literature, to our knowledge, in which the thoracic extension is due to a high-grade PMCA by ovarian cancer, and is the second case in literature in addition to the case reported by Senthil et al. [20], in which a simultaneous bicavitary hyperthermic chemoperfusion was done as a management option for thoracic extension of PMP. In the our case we have detected the right pleural metastases intraoperatively during abdominal cytoreductive surgery probably due to a directly pass through an intact diaphragm, via lymhovascular spaces or, more likely, via direct invasion. Our case was characterized by the onset, during the follow-up, of a left pleural neoplastic effusion, probably due to the intraoperative lesion of the left diaphragm without other relapses.

Conclusion

This clinical case, in our opinion, permit to do two final considerations: the first is that the iatrogenic origin of the pleural metastases by PMP is a possible event, so it is advisable to avoid diaphragmatic injury and, possibly, perform an intraoperative prophylaxis; the second is that in absence to standard therapy, on the basis of results obtained with the HIPEC in the treatment of PMP, the rare cases of pleural diffusion of PMP can be treated with simultaneous bicavitary chemoperfusion.

Riassunto

La diffusione dello pseudomixoma peritonei in cavità toracica è una eventualità molto rara. Presentiamo il caso di una donna di 50 anni affetta da pseudomixoma peritonei con estensione pleurica sincrona, secondario ad un carcinoma mucinoso dell'ovaio. Identificate, durante la chirurgia citoriduttiva addominale, plurime lesioni ripetitive peritoneali sottodiaframmatiche destre, è stata effettuata una resezione parziale del diaframma, che ha consentito di visualizzare numerosi impianti neoplastici pleurici. Eseguita anche la citoriduzione intratoracica, abbiamo optato per una chemioperfusione ipertermica peritoneale e pleurica destra. Dopo un decorso postoperatorio scevro da complicanze maggiori, la paziente è deceduta dopo 6 mesi per un infarto del miocardio, in presenza di un versamento pleurico sinistro di origine neoplastica da ricondurre alla malattia primitiva. Nonostante la potenziale aggressività dello pseudomixoma peritonei all'interno della cavità celomatica, le metastasi extraaddominali sono rare. La sua estensione nella cavità pleuropolmonare è stata descritta sia sotto forma di versamento che di metastasi macroscopiche. Questo è il primo lavoro in letteratura, a nostra conoscenza, in cui l'estensione toracica sia dovuta a uno pseudomixoma peritonei secondario ad un carcinoma mucinoso dell'ovaio ed è il secondo caso in cui è stata eseguita una chemioipertermia bicavitaria simultanea. Attualmente rimane ancora incerto il tipo di trattamento più adeguato, tuttavia la chirurgia citoriduttiva associata alla chemioipertermia intraoperatoria intraperitoneale e intratoracica simultanea può rappresentare una potenziale opzione terapeutica per questi pazienti.

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