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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a patient with peritoneal carcinomatosis from a pancreatic cystadenocarcinoma: A case report

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ABSTRACT

INTRODUCTION: Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is a well-established procedure commonly employed in the management of peritoneal carcinomatosis (PC) from tumors of various specific origins. However, it is not traditionally used in the management of PC of pancreatic origin due to various reasons, including the aggressive nature of pancreatic tumors.

CASE PRESENTATION: A 67-year-old female presented with a large amount of intractable malignant ascites. Computed tomography (CT) imaging showed a nodule in the right paracolic gutter. A diagnostic laparoscopy and omental biopsy showed a well-differentiated adenocarcinoma of pancreatic origin. She was initially not considered suitable for CRS and HIPEC due to apparent liver metastases on CT imaging and was arranged to undergo palliative chemotherapy; however, due to her large amount of refractory ascites and a suspected ruptured right krukenberg tumor, surgical intervention was offered. We performed CRS, bilateral salpingo-oophorectomy, and an omentectomy with a CC (completeness of cytoreduction) score of 1. HIPEC with mitomycin C was also administered. Notably, our patient remains clinically well at 48-months post CRS and HIPEC, with no signs or symptoms suggestive of tumor recurrence.

CONCLUSION: Despite the current lack of evidence supporting the use of CRS and HIPEC in the curation of PC of pancreatic origin, this case report highlights the importance of patient selection in determining suitability for CRS. In the presence of positive prognostic factors and favorable tumor histology, CRS and HIPEC is a potential curative procedure that could be offered to highly selected patients presenting with PC from a primary pancreatic malignancy.

1. Introduction

Cytoreductive surgery (CRS) involving peritonectomy with hyperthermic intraperitoneal chemotherapy (HIPEC) is a well-established procedure that is increasingly being used as a curative therapy in the management of peritoneal carcinomatosis (PC) of multiple origins [1]. As with all surgical procedures, a strict selection criteria which encompasses both patient and tumor factors is key in determining the suitability of patients undergoing CRS involving peritonectomy with HIPEC.

The origin and type of gastrointestinal and gynecological malignancies implicated in PC has been known to be an important factor in influencing long-term survival outcomes post-CRS [2]. Classically, CRS involving peritonectomy with HIPEC has been shown to be associated with positive results and favorable long-term survival rates in the following: appendiceal mucinous neoplasms with pseudomyxoma peritonei (PMP), peritoneal mesothelioma, ovarian cancer and PC from either a primary appendiceal or colorectal adenocarcinoma. In some cases, peritonectomy with HIPEC may also be considered in PC associated with gastric malignancies [3].

Conversely, patients with peritoneal metastases of pancreatic origin are usually managed palliatively and are generally not considered suitable for CRS+HIPEC. This is, in part, due to the aggressive nature of pancreatic malignancies in general, and the lack of evidence surrounding the effectiveness of CRS and HIPEC in improving survival outcomes in patients with PC associated with a primary pancreatic tumor [2,4].

However, in recent years, there has been an emerging field of literature on the potential curative effect of CRS and HIPEC in the treatment of PC from selectively picked unusual cancer origins, including primary tumors of the pancreas with favorable histol-
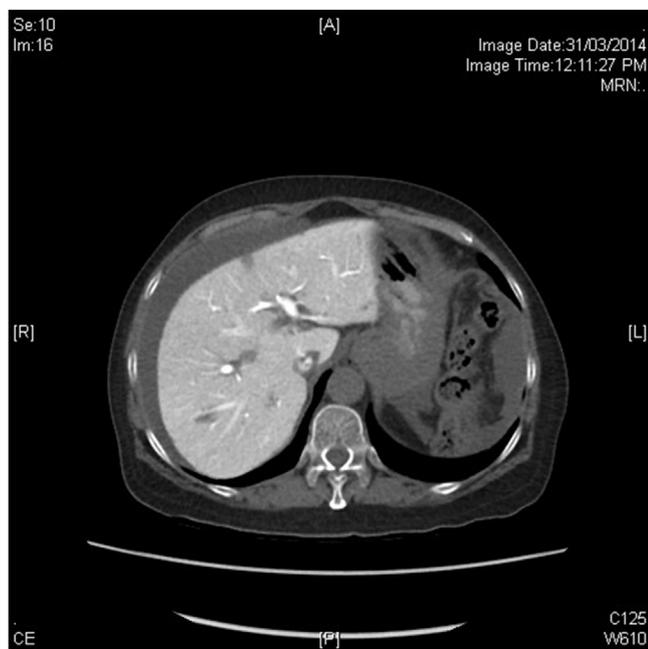
Fig. 1. Computed tomography (CT) of the abdomen in axial view with contrast portography demonstrating parenchymal and surface liver disease with ascites.

Fig. 2. CT of the abdomen in axial view with oral and IV contrast demonstrating the large krukenburg tumor and ascites.

ogy [5,6]. We present the results of a patient who underwent CRS and HIPEC after being diagnosed with peritoneal metastases that originated from a pancreatic cystadenocarcinoma. This work has been reported in line with the SCARE criteria [7].

2. Case presentation

A 67-year-old female presenting with ascites and right-sided abdominal pain was diagnosed with pseudomyxoma peritonei at another hospital and referred to the peritonectomy unit at St George Hospital, Australia in 2014 for consideration of CRS and HIPEC. She had previously undergone a distal pancreatectomy and splenectomy after being diagnosed with a mucinous cystadenocarcinoma (MCAC) of the pancreas in 2008 and had been in remission until her presentation in 2014.

Her initial presenting symptoms were associated with a right paracolic nodule found on computed tomography (CT) imaging. A diagnostic laparoscopy showed a small to moderate amount of free intra-peritoneal fluid and a soft omental nodule in the right paracolic gutter, which was biopsied surgically and found to be a well-differentiated adenocarcinoma, favoring a pancreatic origin.

During workup for CRS+HIPEC in 2014, she was found to have liver metastases on CT imaging (Fig. 1) and was thus not considered a suitable candidate. Subsequently, she was referred to the palliative care team and underwent nine cycles of chemotherapy with gemcitabine. She was unexpectedly referred back to our hospital in 2015 for the management of refractory, high volume malignant ascites which required drainage of approximately 3–4 l of fluid daily. At that point in time, an abdominal CT scan showed a Krukenberg ovarian metastasis (Fig. 2). There was no longer evidence of liver metastases (Fig. 3) which could have either responded to chemotherapy or may have represented peritoneal surface disease with liver scalloping. Surgical intervention was deemed necessary and an exploratory laparotomy was offered to the patient in an attempt to palliate her symptoms related to the impressive amount of neoplastic ascites. Intraoperative findings included blood stained mucinous ascites from a ruptured right Krukenberg tumor of the ovary, widespread peritoneal mucinous deposits and a small amount of disease on the liver surface. An intraoperative
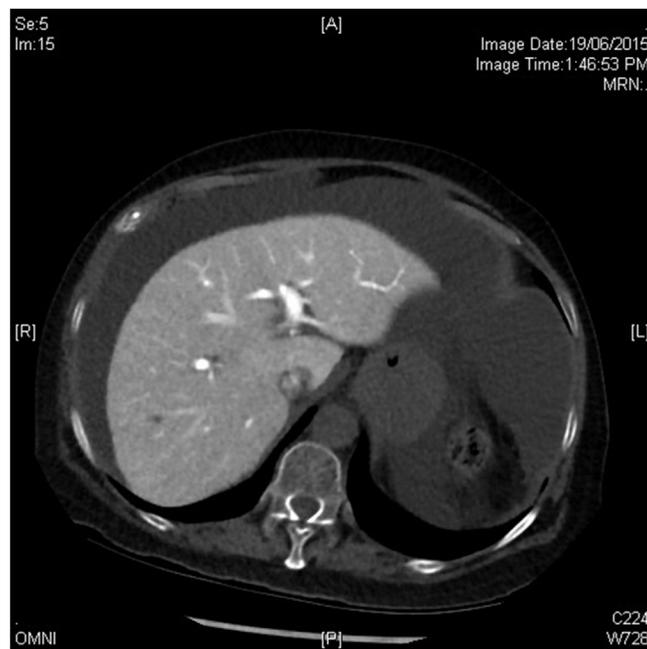

Fig. 3. CT of the abdomen in axial view with contrast portography demonstrating ascites and significant, if not complete response of the liver disease.

ultrasound of the liver was performed that did not show any apparent intrahepatic liver metastases. The peritoneal cancer index (PCI) score was 10.

The surgical procedure performed included a complete cytoreduction, electroevaporation of the liver surface disease, bilateral salpingo-oophorectomy, omentectomy, and an intra-operative liver ultrasound. Cytoreduction with a completeness of cytoreduction score [8] of 1 (CC-1) was achieved and HIPEC with mitomycin C was administered for 90 min, at a temperature of 41.5 °C. The patient tolerated the procedure well, there were no post-operative complications and she was discharged 7 days after her operation.
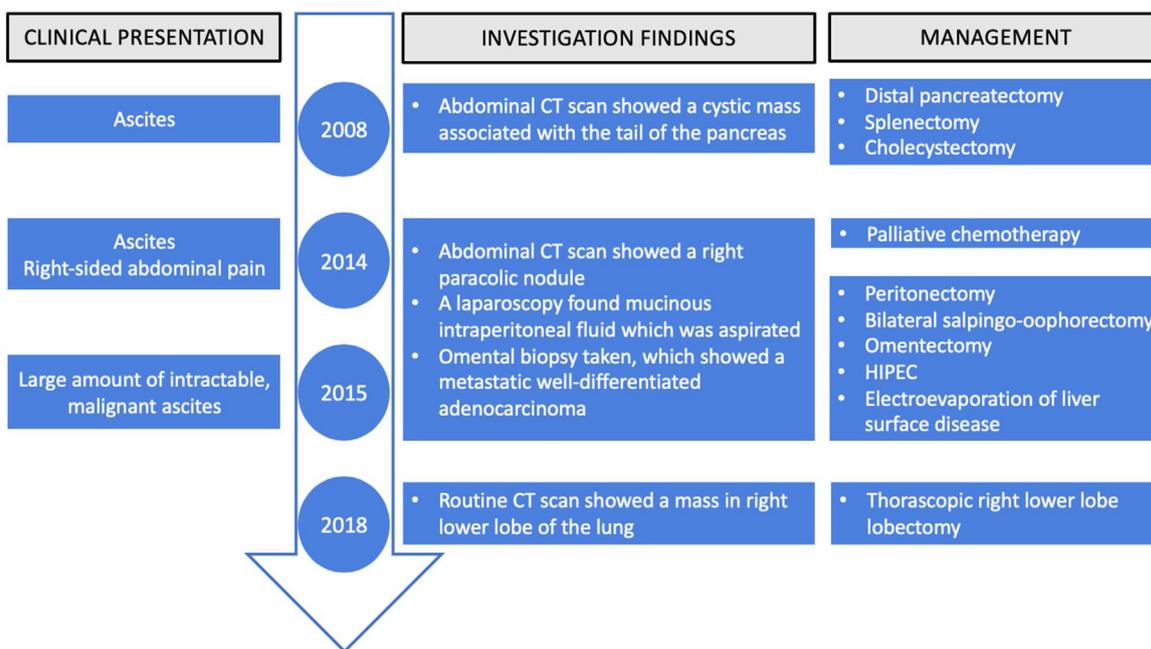
Fig. 4. Timeline of events.

Table 1

Levels of tumor markers post cytoreductive surgery (CRS)+hyperthermic intraperitoneal chemotherapy (HIPEC). CEA = carcinoembryonic antigen; CA19.9 = carbohydrate antigen 19-9; CA125 = cancer antigen 125.

Date	CEA	CA 19-9	CA125
04/01/2016	1.7	10.0	6.0
30/3/2016	1.4	7.0	5.0
17/10/2016	1.4	9.0	5.0
25/10/2017	1.9	10.0	7.0
22/08/2018	1.7	5.0	5.0
03/04/2019	1.7	7.0	8.0

The patient's resected organs were fixed with formalin and sent for histopathological analysis. Macroscopically, there was widespread mucinous material over all the specimens. There were two intact fallopian tubes; the right fallopian tube was attached to a ruptured ovary comprising of a fungating exophytic mass with multiple papillary friable fronds. The left ovary had a normal macroscopic appearance. The omentum specimen was noted to have a congested, glistening surface and multiple hard nodules. There was also a papillary nodule (measuring 25 mm in diameter) found on the specimen of peritoneum. Microscopic analysis of the specimens revealed deposits of metastatic mucinous well differentiated adenocarcinoma with papillary architecture, spread over the peritoneum. Immunoperoxidase staining of the tumor cells were positive for cytokeratin (CK) 7 and carcinoembryonic antigen (CEA), which is consistent with a primary tumor of pancreatic origin.

After discharge from hospital, the patient underwent regular follow-up at our outpatient clinic at 3 to 6-monthly intervals for the first year after her surgery. The first outpatient review found the patient to be recovering well with no complaints and a normal gastrointestinal function. Imaging scans of the chest and abdomen, and the measurement of tumor markers (Table 1) were performed prior to every appointment to monitor for signs of disease recurrence. Subsequent reviews also indicated that she did not have any signs of disease recurrence both clinically and on imaging, and her tumor markers remained within normal range (Table 1).

She was subsequently reviewed once yearly at our outpatient clinics. In 2017, a small, cavitating lesion in the right lower lobe of her lung was detected on routine CT imaging and it was subsequently surgically resected via a thoracoscopic right lower lobectomy in 2018; however, histopathological analysis revealed that it was a 2 cm adenocarcinoma consistent with a primary lung cancer. There were no features suggestive of lung metastases from a primary pancreatic tumor. At 48 months post CRS and HIPEC, the patient is alive and remains disease and symptom free. Fig. 4 is an overview of the timeline of events that occurred.

3. Discussion

The prevalence of pancreatic cystic tumors in the general population ranges from 2.4 to 14%; of these, mucinous cystadenocarcinomas (MCAC) of the pancreas make up approximately 15% of all pancreatic cystic neoplastic lesions, making them relatively rare tumors [9,10]. Traditionally, pancreatic cancer with peritoneal metastases has been regarded as a terminal illness and is typically managed palliatively [11]. In our case, there were several positive prognostic factors that led us to consider palliative CRS and HIPEC, which unexpectedly ended up being a potentially curative procedure. Firstly, our patient enjoyed a relatively long disease-free interval after her initial pancreatectomy in 2008. The post-operative pathology report also reported her tumor to be well-differentiated, suggesting that it is possibly a low-grade tumor, which is known to be associated with better prognosis. Additionally, the patient had a PCI score of 10 which not only allows for easy optimal cytoreduction, but is also known to be a significant positive predictor of long-term survival outcomes in patients with PC of intraabdominal origins [12,13]. From a review of the literature, another common positive prognostic factor in patients undergoing CRS and HIPEC is also achievement of a complete cytoreduction, with no residual tumor nodules visible at the end of the procedure [12,14,15].

There has been an increasing interest amongst researchers surrounding the use of CRS and HIPEC in patients with PC from unusual cancer origins, albeit with mixed results. Arjona-Sanchez et al. [16] published a case report of a patient with mucinous PC from an intraductal papillary mucinous neoplasm (IPMN) of the pancreas who had undergone complete CRS and HIPEC with mitomycin C, and remained symptom-free at 70 months post CRS and HIPEC.

Honore et al. [17] has also demonstrated the possible efficacy of combining the use of CRS and HIPEC with oxaliplatin and irinotecan in the management of peritoneal metastases from a solid pseudopapillary neoplasm of the pancreas. Conversely, Farma et al. [14] examined the outcomes of 7 patients with PC of pancreatic origin who were treated with CRS and HIPEC with cisplatin and found the median progression-free survival time to be approximately 16 months. However, the high incidence of post-operative complications led the authors to conclude that using CRS and HIPEC with cisplatin in the management of PC in their group of selected patients was associated with a high rate of complications and had little to no effect on altering the natural progression of the disease. The histological characteristics of the tumors were not commented on in this study and might explain the poor outcome.

Given the lack of high-quality evidence supporting the employment of radical cytoreductive surgery combined with HIPEC in patients with PC of pancreatic origin, the choice of whether to perform CRS and HIPEC in this group of patients remains a challenging one. It is likely that we will continue to lack high-quality randomized controlled trials in this field of study due to the rarity of these tumors; however, this case study allows us to appreciate the importance of patient selection in surgical oncology. To quote surgical oncologist Dr Blake Cady, "In the world of surgical oncology, biology is king; selection is queen; technical maneuvres are the prince and princess" [18]. In selecting patients who are suitable to undergo CRS and HIPEC, tumor biology, histology and patient factors including age and presence of co-morbidities are key, and will be the main factors influencing long-term survival outcomes [19].

4. Conclusion

Despite its increasing prevalence, there is currently a lack of evidence-based guidelines regarding the treatment of PC from pancreatic cancers with favorable histologies in the literature. We have presented an extraordinary case of a patient with a mucinous cystadenocarcinoma of the pancreas with peritoneal metastases who would have otherwise been palliated medically, if not for her intractable, malignant ascites, which required surgical intervention. Remarkably, our patient remains symptom free up to the point of the writing of this manuscript (48-months post CRS and HIPEC), and does not display any signs of tumor recurrence. Caution should be exercised in cases whereby expected surgical morbidity is high as there is currently insufficient data and evidence to support the long-term benefit of radical surgical interventions such as CRS and HIPEC in patients with PC from rare primary tumors. On the other hand, an important takeaway from this case is that we should not refrain from offering CRS and HIPEC to patients with unusual yet favorable tumor histology and who are otherwise fit and have a low expected morbidity and a high probability of long-term survival.

Ethical approval

Exemption of ethics approval has been obtained from the South East Sydney Local Health District (SESLHD) Human Research Ethics Committee (HREC).

Consent

Written informed consent was obtained from the patient for publication of this case report.

Author's contribution

DLM provided intellectual and conceptual input for the drafting of this case report. JL provided patient data and reviewed manuscript. MLS interpreted patient data including radiographic imaging scans, investigations and details from the operation report. SDL wrote the first draft of the manuscript and all authors read, reviewed and approved the final manuscript.

Registration of research studies

Not applicable.

Guarantor

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Provenance and peer review

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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