International Journal of Surgery Case Reports 7 (2015) 85–88

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Peritonectomy and hyperthermic intraperitoneal chemotherapy as treatment for desmoplastic small round cell tumour

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ARTICLE INFO

Article history:
Received 24 May 2014
Received in revised form
12 September 2014
Accepted 15 September 2014
Available online 11 December 2014

Keywords:
Desmoplastic small round cell tumour (DSRCT)
Hyperthermic intraperitoneal chemotherapy (HIPEC)
Peritonectomy

ABSTRACT

INTRODUCTION: The St George Hospital specialises in peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of intra-abdominal malignancies. Despite performing around 800 peritonectomy and HIPEC procedures, we have rarely encountered desmoplastic small round cell tumours (DSRCT). We present our experiences with DSRCT, and propose peritonectomy and HIPEC as a treatment option for DSRCT.

PRESENTATION OF CASE: This is a case series of 3 cases. The first case was a 26-year-old male who presented with appendicitis which we diagnosed as DSRCT and treated with peritonectomy and HIPEC. The second case was a 14-year-old male referred to our centre for peritonectomy and HIPEC after initial presentation with a pelvic mass and treatment with chemotherapy. The third case was a 21-year-old male referred to our centre for peritonectomy and HIPEC for recurrent DSRCT after previously being treated with neoadjuvant chemotherapy and surgery without HIPEC.

DISCUSSION: DSRCT is a rare, almost exclusively intra-abdominal malignancy, which predominantly affects young males. Survival prognosis remains poor in DSRCT despite conventional treatment with surgery, chemotherapy and radiotherapy; however, HIPEC has offered promising survival results. Our recurrences with peritonectomy and HIPEC at 6 months and 15 months are comparable with the literature of 8.85 months.

CONCLUSION: In our experience, patients with DSRCT who present with nodal involvement or recurrent disease tend to recur early despite treatment with peritonectomy and HIPEC. Longer term follow up of our patients and future studies involving HIPEC in DSRCT would be useful in assessing long-term clinical outcomes and survival.

1. Introduction

The St George Hospital specialises in peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of intra-abdominal malignancies. Despite performing around 800 peritonectomy and HIPEC procedures, we have rarely encountered desmoplastic small round cell tumours (DSRCT). We present our experience with DSRCT and HIPEC in a series of three cases, and propose peritonectomy and HIPEC as a treatment option for DSRCT.

1.1. Case 1

A 26-year-old gentleman presented with localised right iliac fossa pain after having a colicky lower abdominal pain, which lasted 24 h associated with anorexia, and nausea but no vomiting. His bowel motions were regular, and he did not notice any blood, diarrhoea or tenesmus. He did not notice any weight loss and had been well prior to this episode. Apart from a previous cholecystectomy, his past medical and family history were unremarkable. On examination he was afebrile, tachycardic, had a soft non distended abdomen with no palpable hernias or masses. He was tender over the right iliac fossa, hypogastrium and umbilical regions with guarding, rebound tenderness, and positive Rovsing's sign.

Given the high clinical likelihood of appendicitis, the patient was taken for laparoscopic appendicectomy without imaging. Intraoperatively the appendix was found to be normal, however, a large mass was found on the right hepatic flexure with intra-abdominal pus noted. Given this finding, the procedure was converted to an open appendicectomy and right hemicolectomy with the mass sent off for histological assessment.

A 60 mm mass was resected from the colon with margins of 30 mm distally and 140 mm proximally. No masses were seen

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http://dx.doi.org/10.1016/j.ijscr.2014.09.022

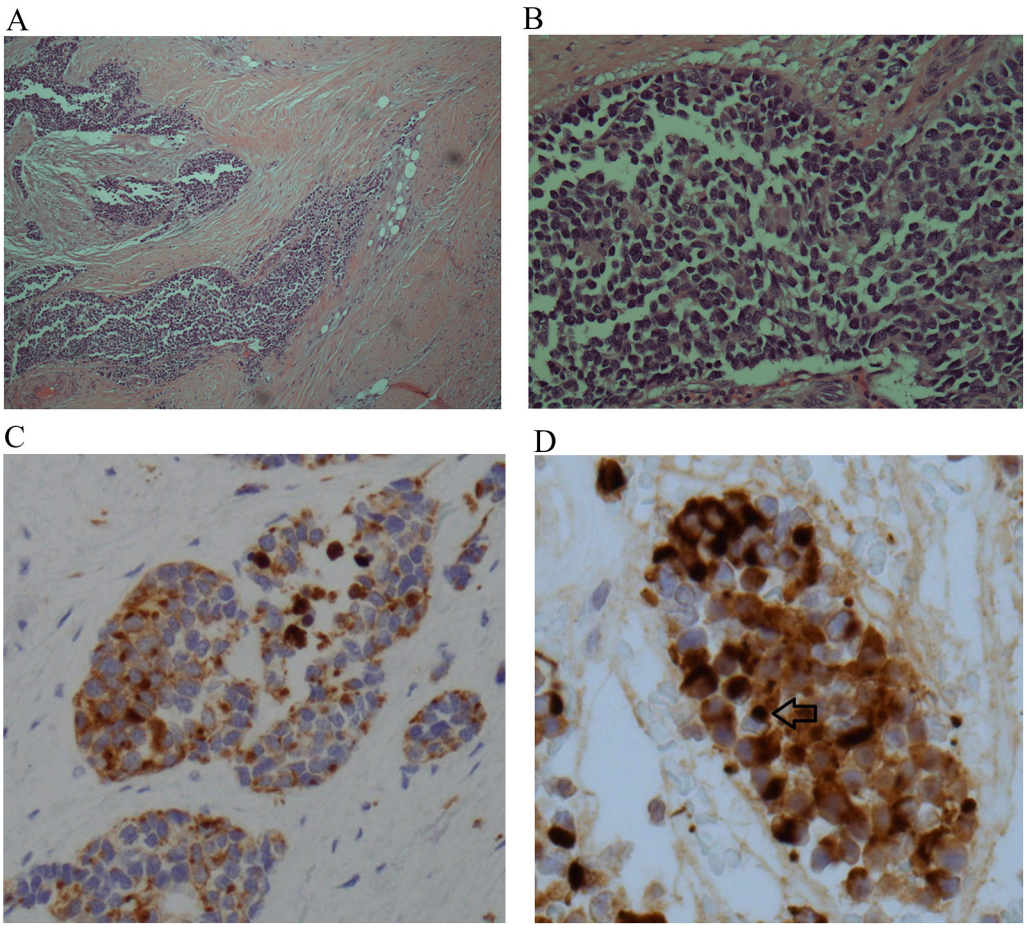

Fig. 1. (A) Nests of tumour cells surrounded by desmoplastic stroma (magnification: 100×). (B) Cells with hyperchromic nuclei and scant cytoplasm (magnification: 400×). (C) Immunohistochemical stain positive for cytokeratin (CAM 5.2). (D) Immunohistochemical stain positive for desmin, with immunoreactivity present in a typical perinuclear dot-like Golgi pattern (large arrow).

on the serosal surfaces. The tumour involved the full thickness of the colon wall invading through the serosal fat, just reaching the serosal surface. No malignancy was identified within fifteen pericolic lymph nodes. Histology and immunohistochemistry confirmed a high grade undifferentiated DSRCT with a Ki67 of 30%. The diagnosis of DSRCT was made on the basis of the tumour morphology showing nests of tumour cells with hyperchromic nuclei and scant cytoplasm surrounded by desmoplastic stroma, and positive immunohistochemistry staining for desmin and cytokeratin (Fig. 1). Furthermore, fluorescence in situ hybridisation (FISH) techniques revealed positive EWSR1 arrangements, which further supported our diagnosis. Interestingly, the tumour did not stain positive with the WT1 antibody which is present in the majority of DSRCT.

Staging workup with chest and abdomen CT, hepatic angiogram CT and PET scans revealed a stage 1 DSRCT. Given the aggressive nature of DSRCT, the patient was treated with a potentially curative peritonectomy two weeks later with the aim of removing microscopic intraperitoneal disease and improving long term survival. The intraoperative assessment revealed a peritoneal cancer index (PCI) of 4, with a small volume of disease in the pelvis. A revision of the ileocolic anastamosis, omentectomy, pelvic peritonectomy, excision of the umbilicus and intraoperative ultrasound for hepatic lesions was subsequently performed. The procedure achieved a complete cytoreduction of the tumour with a completeness of cytoreduction (CC) score of 0. Our procedure involved HIPEC with cisplatin at 41.5 °C for 90 min. Postoperatively, urine output was maintained at 100 ml/h for 24 h given the nephrotoxicity of cisplatin. The repeat histopathology showed peritoneal deposits of DSRCT in the ileocolic anastamosis, and pelvic peritoneum. The surgical margins of resection were clear. No tumour was detected in the lymph nodes examined.

The patient's recovery was complicated by a pulmonary embolus on postoperative day 10, for which heparin infusion was initiated and subsequently switched to therapeutic enoxaparin. The patient was discharged from hospital on postoperative day 19 and commenced on systemic chemotherapy using cyclophosphamide, doxorubicin and vincristine. The patient had one episode of febrile neutropenia after his first cycle of chemotherapy and was admitted to hospital for intravenous antibiotics. He has since tolerated his cycles well and was on his fourth of nine cycles at the time of submission and would continue with ongoing oncologist follow up. The patient had repeat colonoscopies and PET scans with no evidence of recurrence at 6 months post peritonectomy. He remained asymptomatic with ECOG performance status grade 0, and was continuing with gym training.

1.2. Case 2

A 14-year-old male was referred to our unit with stage 2 DSRCT after being treated with 11 weeks of vincristine, doxorubicin, ifosfamide, and etoposide. He originally presented with a large pelvic mass which was compressing against his right ureter, bladder and prostate. He was referred to our centre after his initial chemotherapy and had an intraoperative PCI of 12. We performed a laparotomy for right diaphragm strip, cholecystectomy, right

Table 1
shows published studies on survival outcomes of DSRCT, including the study out line and survival results.

Author	Study outline	Survival
Hayes-Jordan et al. [1]	8 patients treated with surgery + HIPEC vs. 16 patients treated with chemotherapy ± radiation therapy or surgery alone	71% 3 year survival with HIPEC 26% 3 year survival without HIPEC Mean relapse free survival 8.85 months (HIPEC) versus 5.46 months (No HIPEC)
Lal et al. [15]	66 patients with histologically diagnosed DSRCT	58% 3 year survival in patients with complete surgical resection, chemotherapy and radiotherapy 0% 3 year survival in patients without surgery
Desai et al. [16]	31 patients treated with chemotherapy, surgery and radiation therapy	20% 5 year survival 50% 3 year survival 24% 3 year progression free survival
Liping et al. [17]	18 patients treated with chemotherapy and surgery	27.29% 5 year survival 27.29% 3 year survival 52.36%, 1 year survival
Saab et al. [18]	11 patients treated chemotherapy and surgery	21.1% 5 year survival
Ordóñez [19]	39 patients with histologically diagnosed DSRCT with surgical debulking. 35 available to follow up, 25 deaths at time of publication	Mean survival 25.2 months

hemicolectomy, anterior resection of the rectum, urinary bladder strip, and lymph node dissections, to remove all visible tumours. We then performed HIPEC with Cisplatin at 41.5 °C for 90 min. The histopathology confirmed DSRCT with a Ki-67 of 20–30%, with clear resection margins but metastatic disease in the right common iliac vein lymph nodes. Post operative recovery was complicated by haemorrhage from the right psoas, for which we performed a laparotomy for haemostasis and evacuation of the blood clot. Despite ongoing chemotherapy with irinotecan/temozomide and external beam radiation therapy, the patient developed recurrence in the liver and right iliac lymph node chain at 15 months after our procedure, as evident on PET scans, and he would continue with ongoing oncologist follow up. The patient was asymptomatic, ECOG grade 0 and competing in Go Kart racing at 20 months after initial diagnosis.

1.3. Case 3

A 21-year-old male was referred to our unit for recurrence of stage 1 DSRCT. He initially presented 17 months prior with 3 months of increasing left inguinal lymphadenopathy associated with pain, but otherwise asymptomatic. His biopsy was positive for DSRCT and he was subsequently treated with vincristine, doxyrubicin, cyclophosphamide, alphosphomide and etoposide, followed by surgical resection of the mass. This recurred in the pelvis 6 months later and he was referred to our centre. Had an intraoperative PCI of 5 and we performed a laparotomy for removal of all visible tumour from the rectum, iliac vessels, obturator nerve, pelvic peritoneum, and performed aortic node dissection. We then performed HIPEC with cisplatin at 41.5 °C for 90 min. The histopathology confirmed DSRCT with a Ki-67 of 5–20%, with clear resection margins and metastatic disease in 6/6 lymph nodes. His post operative stay was complicated by bowel obstruction which was treated conservatively. Despite ongoing chemotherapy with irinotecan/temozomide, the patient developed recurrence in the left external iliac and para-aortic lymph nodes 6 months after our procedure, as evident on PET scans, and he would continue with ongoing oncologist follow up. The patient remained energetic, asymptomatic, ECOG grade 0 and was working on a ranch at 25 months after initial diagnosis.

2. Discussion

DSRCT is a rare sarcoma with fewer than 200 cases reported between 1989 and 2010.[1] This highly aggressive sarcoma predominantly occurs in males aged between 5 and 35.[2,3] It involves translocation t(11; 22) (p13; q12), which fuses the N-terminus of the Ewing sarcoma (EWS) gene to the C-terminus of the Wilms tumour (WT1) gene, resulting in a EWSR1/WT1 fusion product and activation of the PI3K/Akt/mTOR pathway.[4,5]

Macroscopically, DSRCT show areas of necrosis and may also have myxoid changes.[2] Microscopically, DSRCT has a nesting pattern of growth with focal rhabdoid features and intense desmoplastic reaction.[6] A distinctive feature of DSRCT is its divergent differentiation that immunohistochemically stain positive for epithelial (keratin, epithelial membrane antigen), mesenchymal (vimentin), neural (neuron-specific enolase, CD56), and myogenic (desmin) markers.[6,7] Interestingly, DSRCT almost always stain positive with WT1 antibodies, which detects the WT1 component of the EWSR1/WT1 fusion product.[8] Even though our first case did not stain positive with WT1 antibodies, the diagnosis of DSRCT was made based on morphology, positive cytokeratin and desmin staining showing divergent differentiation, and positive FISH for the EWSR component of the mutation.

DSRCTs are located almost exclusively in intra-abdominal locations and classically involve a large intra-abdominal mass in the retroperitoneum, pelvis, omentum or mesentery, with diffuse peritoneal deposits that spread along peritoneal and mesothelial surfaces.[2,6] DSRCT directly spreads to various organs including liver, pancreas, spleen, and testes, with no consistent pattern of organ involvements, and can metastases to lung, and lymph nodes of the groin, neck and mediastinum.[9,10] In rare cases, primary DSRCT have been reported outside of the abdominal cavity to affect thorax, and head and neck regions.[10,11]

Diagnostic investigations include abdominal imaging, either with computed tomography (CT), or magnetic resonance imaging (MRI) to assess peritoneal and extra abdominal lesions, followed by a histological diagnosis with tissue samples from laparoscopy.[2] The current proposed staging system based on comparison of outcomes involves stage 1: PCI < 12, without liver metastases; stage 2: PCI ≥ 12 without liver metastases; stage 3: liver metastases; and stage 4: extra abdominal metastases.[1]

There is currently no standardised treatment option for DSRCT. Traditional treatments include induction chemotherapy using agents such as cyclophosphamide, doxorubicin, vincristine, ifosfamide and etoposide,[12] followed by aggressive debulking and external beam radiotherapy.[13] Despite treatment, survival prognosis remains poor (Table 1), with most patients experiencing resistant and recurrent disease before end of life.[14,15] The data on use of HIPEC in DSRCT is scarce, however, Hayes-Jordan et al. showed that HIPEC has improve survival outcomes with patients receiving neoadjuvant chemotherapy followed by cytoreductive surgery and HIPEC having a 3 year survival of 71% compared to 26% ($p = 0.021$) in patients who did not receive surgery or HIPEC.[1] Our

follow up has been shorter and hence we were unable to make a direct comparison in terms of survival. Our recurrences at 6 months and 15 months are comparable to the mean of 8.85 months reported by Hayes-Jordan et al. (2010).[1] Our remaining patient had no disease recurrence after 6 months and we hope for better outcomes given that he had no nodal disease, which is associated with better outcomes.[3] Our patients all had favourable prognostic factors including, young age at diagnosis, and high functional status at time of diagnosis,[3] and all three patients have survived with good function and quality of life.

3. Conclusion

Survival prognosis remains poor in DSRCT despite conventional treatment with surgery, chemotherapy and radiotherapy; however, HIPEC has offered promising survival results. In our experience, patients with DSRCT who present with nodal involvement or recurrent disease tend to recur early despite treatment with peritonectomy and HIPEC. Despite this recurrence, our patients have recovered well following peritonectomy and HIPEC treatments. Longer term follow up of our patients and future studies involving peritonectomy and HIPEC in DSRCT would be useful in assessing long-term clinical outcomes and survival.

Conflict of interest

No conflicts of interest.

Consent

Written informed consent was obtained from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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