Chapter 5
Management of Desmoplastic Small Round Cell Tumor

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5.1 Introduction

DSRCT is a very newly described tumor, characterized in 1989 by Gerald and Rosai, who identified the EWS-WT1 translocation and fusion protein as pathognomonic. If this fusion protein cannot be identified in the tissue, the diagnosis of DSRCT cannot be made. DSRCT was a relatively unknown tumor that was considered by most clinicians to be an aggressive rare sarcoma that was lethal. Identifying the pathology and characteristic translocation was of key importance to developing any treatment strategies [1, 2]. Gerald and Rosai described not only the characteristic translocation but also the histologic appearance. Nests of small round blue cells can be seen separated by desmoplastic stroma (Fig. 5.1). The translocation (11:22), (p13:q12) and the fusion protein of Ewing's sarcoma (EWS) and Wilms' tumor (WT-1), makes the diagnosis [1–3]. Confirming this translocation to make the diagnosis of DSRCT, by percutaneous or open biopsy, is necessary. The five survivals are estimated only at 15–30% [1–3]. If the EWS translocation is not identified, the diagnosis becomes challenging. One author describes the desmin reactivity and cytokeratin staining can be seen in either blastemal predominant Wilms' tumor or DSRCT. Detection of an EWSR1-WT1 rearrangement and selective WT1 carboxy-terminus immunoreactivity (characteristic of DSRCT) or dual immunoreactivity for the WT1 amino-terminus and carboxy-terminus (characteristic of WT) remain the most discriminating diagnostic tools [4].

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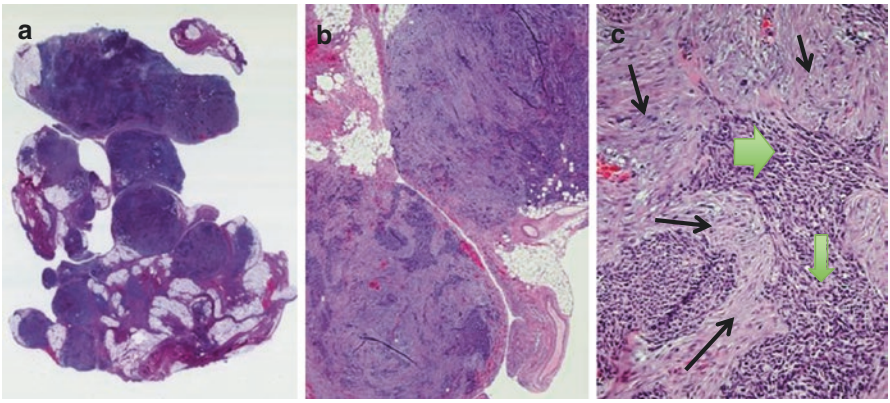

Fig. 5.1 Low- (**a**-5 and **b**-20×) and high-power (**c**-40×) histologic sections of DSRCT from an omental biopsy. In figure (**c**), nests of small round blue cells (*filled arrow*) interdigitate between bands of fibrous stroma (*line arrow*)

5.2 Diagnosis and Staging

The age of presentation is typically 5–30 years, and 85–90% of the patients are male [5].

Large masses, in addition to visceral and parietal seeding of the peritoneum, are a typical presentation in DSRCT. Usually vague abdominal pain brings this to the attention of the patient and prompts imaging examinations. The dissemination of DSRCT throughout the abdominal cavity is characteristic. The reason a large tumor burden exists at diagnosis is few symptoms are present until the peritoneal surfaces are infiltrated with tumor and overwhelm the peritoneum, therefore impairing resorption of peritoneal fluid and causing ascites. Abdominal distension and discomfort are the usual presenting symptoms. Patients can also have pain and constipation. Because of the sarcomatosis seen, these patients are considered Stage 4 at diagnosis. It is rare for a patient to present with a single mass or one or two masses. This only occurs when the mass is found incidentally at the time of another operation or diagnostic radiologic exam for another entity.

Because of the frequent diffuse nature of the presentation of this disease, a new staging system is being considered, and now being used on a trial basis, by Hayes-Jordan and colleagues at MD Anderson Cancer Center. In this proposed staging system, Stage 1 patients would have limited disease, localized to one or two sites in the abdomen or one site elsewhere. Stage 2 patients would have any amount of extensive

peritoneal disease; Stage 3, with liver metastasis and peritoneal disease; and Stage 4 with peritoneal and liver disease and disease also outside of the abdominal cavity, including lymph nodes. This has not been validated and is under investigation.

5.3 Imaging Characteristics

On initial imaging, typically, CT (computed tomography) scans are done. MRI and ultrasound can also be helpful. On CT scan or MRI, usually multiple peritoneal implants can be seen, making the diagnosis of DSRCT highly suspicious. The most common site of initial organ metastasis is usually the liver. The lungs, pleura, and mediastinum are the next most common locations for metastasis. Lymph node enlargement in the groin and neck can also be seen. Therefore, PET (positron-emission tomography) scan imaging may be a helpful adjunct to evaluate distant metastasis at the time of staging [6].

The extent of disease seen on initial imaging includes many lesions in every portion of the peritoneal cavity. The most common areas are the omentum, right diaphragm, and pelvis (Fig. 5.2). The splenic hilum and various small bowel and colon mesenteric implants are also common. Retroperitoneal disease is very uncommon. In most cases, the disease seen on CT or MRI imaging underestimates the extent of the diseases. One to 2 mm metastasis and "sheets" of tumor in confluence are common intraoperative findings (Fig. 5.3). Metastatic disease outside of the abdominal cavity can be found in the mediastinum, pleura, supradiaphragmatic lymph nodes, lung, and bone.

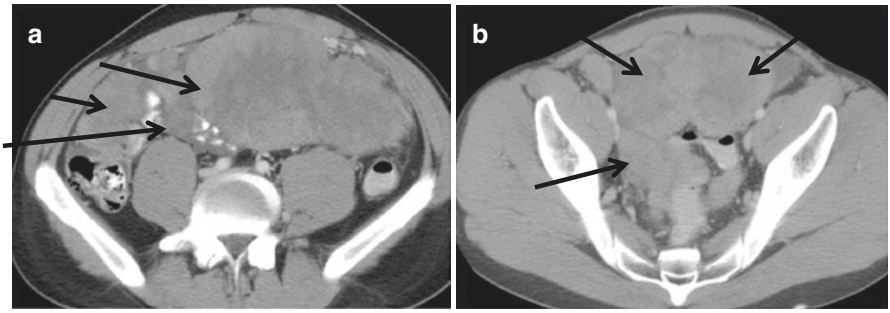

Fig. 5.2 Figure (**a**) shows a large omental mass in a newly diagnosed patient with DSRCT. Figure (**b**) shows a pelvic, paravesical mass, large and lobulated. Pelvic tumors are very typical of DSRCT sarcomatosis

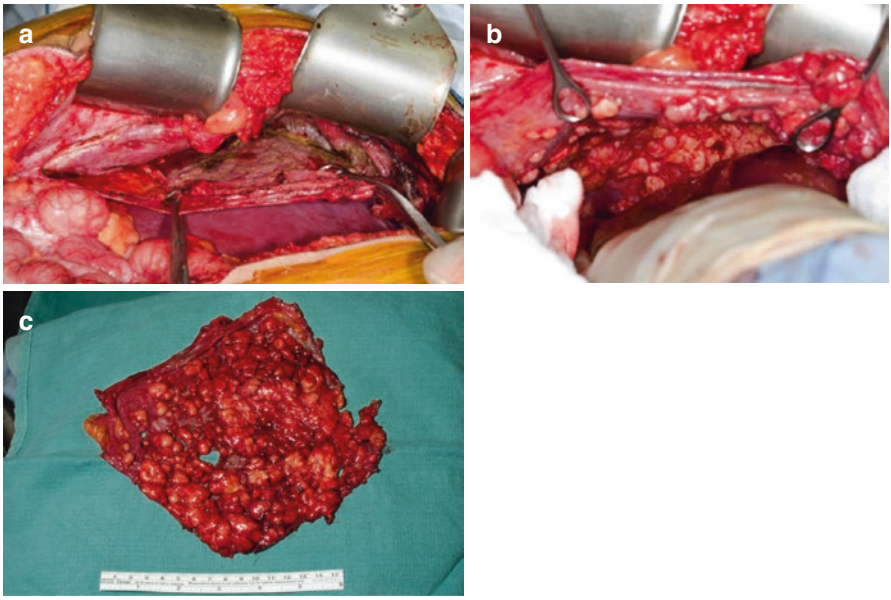

Fig. 5.3 A "sheet" of sarcomatosis from DSRCT in the right diaphragm peritoneum. Figure (**a**, **b**) show the intraoperative dissection of the right diaphragm peritoneum. The final result (**c**) is one "sheet" of tumor without any diaphragm muscle removed

5.4 Chemotherapy

Since its description in 1989 by Gerald and Rosai at Memorial Sloan Kettering Cancer Center, multimodality chemotherapy has been used for DSRCT. Ewing's type chemotherapy, aggressive surgery, tumor debulking, total abdominal radiation therapy, and high-dose chemotherapy followed by autologous stem cell rescue have all been used in the treatment of DSRCT, with little improvement in survival. Durable remissions remain rare [7]. Control of DSRCT with chemotherapy is most effective in children, with Ewing's type chemotherapy. Ewing's type chemotherapy is the standard because efficacy with this regimen has been demonstrated by Kushner et al. [7]. This chemotherapy is based on alkylating agents cyclophosphamide or ifosfamide along with vincristine and doxorubicin alternating with ifosfamide and etoposide. This regimen was shown to have a favorable outcome in a multidisciplinary approach in 12 DSRCT patients [7]. This chemotherapy regimen was used in combination with aggressive surgical complete excision and postoperative whole abdominal radiation, providing improved survival. With a median follow-up of 22 months, the median disease-free survival was 19 months. The regimen can be quite toxic, and frequent admissions for fever and myelosuppression can be expected. An alternative more tolerable outpatient regimen has been utilized [8]. This includes neoadjuvant vincristine, ifosfamide, dexrazoxane/doxorubicin, and

etoposide. This is followed be aggressive surgical excision and removal of all gross disease, including 1–2 mm peritoneal implants. This was followed by adjuvant radiotherapy (30 Gy whole abdomen) and irinotecan and Temodar for a total of 12 cycles. This regimen yielded a disease-free interval of approximately 2 years. The irinotecan and Temodar therapy provided an excellent quality of life with regular school attendance and participation in plan activities. This regimen may be used after surgery and radiotherapy [8].

5.5 Surgical Therapy

As mentioned, abdominal sarcomatosis is a common finding with tumor implants ranging from 1 mm to 40 cm or more. The extent of disease seen on initial imaging includes many lesions in every portion of the peritoneal cavity. Typically, omental disease is found in most patients in addition to peritoneal studding on the diaphragm, spleen, Morison's pouch, abdominal wall peritoneum, small bowel mesentery, and almost certainly in the pelvis. Peritonectomies are required in these locations for effective complete gross resection and cytoreduction. In most cases, the disease seen on CT or MRI imaging underestimates the extent of the diseases. One to 2 mm metastasis and "sheets" of tumor in confluence are common intraoperative findings.

Because this is usually a very chemo-responsive tumor, the feasibility of surgical resection should not be assessed until a plateau of response from chemotherapy has been reached. This is usually achieved after 4–6 months of neoadjuvant chemotherapy. The partial response to neoadjuvant chemotherapy in DSRCT is an important component to complete surgical resection. In a report of the impact of complete surgical resection of DSRCT, LaQuaglia and colleagues found a 3-year overall survival of 58% with complete resection and 0% when resection was not done, and the patients were treated with chemotherapy and radiotherapy alone [5].

In this setting, even after surgical resection of gross, visible disease, and cytoreduction, microscopic residual can be expected. Hence, a regional approach to local control such as hyperthermic intraperitoneal chemotherapy (HIPEC) could be an effective strategy for DSRCT. HIPEC is a potential adjunct to complete surgical resection of DSRCT. Figure 5.4. shows a schemata of a typical HIPEC setup, including the infusion of heated chemotherapy (41.5 °C) which occurs over a 90-min period in the operating room after complete cytoreduction (Fig. 5.4).

Complete surgical resection, including cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) for carcinomatosis, is standard therapy for appendical carcinoma and pseudomyxoma peritonei, among others [9–16]. Complete cytoreduction and HIPEC have been found to improve survival in many studies of carcinomatosis [14, 18–20]. Intraperitoneal therapy is currently the recommended approach in carcinomatosis of ovarian and mesothelioma origin [2, 17–23]. In the context of a prospective randomized trial, gastric cancer patients with

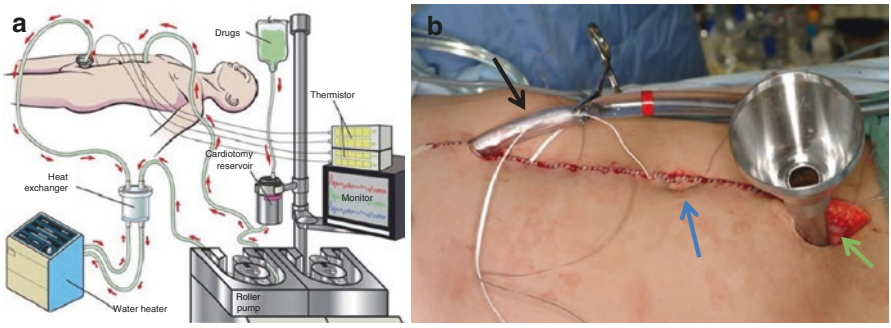

Fig. 5.4 (**a**) A representation of the HIPEC technique with a simple pump that pumps the heated chemotherapy into the abdominal cavity and recirculates, in a closed technique, over 90 min in the operating room, using cisplatin for chemotherapy in the case of DSRCT. (**b**) The closed abdomen of a patient after cytoreduction, ready to begin HIPEC. Temperature probes can be seen exiting from the midline skin closure that will be attached to a computer to provide a constant monitoring of the intra-abdominal temperature. *Black arrow* denotes inflow catheter, *green arrow* is outflow port, and *blue arrow* is the umbilicus of a supine patient

carcinomatosis underwent cytoreduction accompanied by normothermic or hyperthermic mitomycin C. The overall 5-year survival of surgery alone, normothermic, or hyperthermic perfusion was 42%, 43%, and 61%, respectively [2]. In ovarian carcinoma, significantly superior survival has been found in the intraperitoneal chemotherapy group compared to intravenous cisplatin and paclitaxel in a national prospective randomized trial [23].

This same principle was applied in the initial study of HIPEC in DSRCT. In the past, when evaluating a patient with DSRCT, surgeons were reluctant to offer surgical resection in the "face" of enormous disease burden in the abdomen and no known hope for disease control or cure. As in carcinomatosis, for sarcomatosis, HIPEC can provide control of microscopic disease in DSRCT after resection of 100% of gross disease. A phase 1 clinical trial of HIPEC in pediatric patients was completed. This trial demonstrated safety of HIPEC in children using cisplatin. The maximum tolerated dose (MTD) was 100 mg/m^2 with the dose-limiting toxicity (DLT) being grade 3 renal failure [24]. The addition of HIPEC has been used in DSRCT for effective local control. In a cohort of 26 DSRCT patients, who underwent surgical resection and HIPEC after neoadjuvant chemotherapy, the completeness of cytoreduction determined outcome. Median survival of only 26 months was reached when incomplete resection was accompanied by HIPEC compared to 63 months, with complete resection [25].

Recently, results from a phase 2 study of HIPEC in 20 pediatric sarcoma patients, including DSRCT, revealed superior survival results for patients with DSRCT compared to other sarcoma histologies. One-year survival for DSRCT patients was 93%, compared to 67% for other histologies ($p = 0.0073$). DSRCT patients had an 80% 30-month overall survival compared to children with other sarcoma histologies whom all succumbed by 15 months post-HIPEC [26]. There were no perioperative mortalities and no reoperations ("take backs"). Transient leukopenia or thrombocytopenia was seen in 15% of patients. Thirty-five percent of patients experienced serious complications including wound infections requiring drainage, urinary tract infections, and enterocutaneous fistula (in patients treated with abdominal radiation prior to HIPEC). (Operating time averages about 12 h.)

The technique of cytoreduction, decision for cytoreduction and HIPEC in DSRCT, is different from that done for adults with carcinomatosis. DSRCT is much more nodular and much less infiltrative than carcinoma, particularly in the area of the small bowel mesentery and pelvis. Dissection of tumors from the jejunal and ileal mesentery peritoneum is most often possible and can be complete without small bowel resection. Also, what can appear to be pelvic tumor-encasing ureters can be dissected free of the ureter, bladder, and rectum in most circumstances (Fig. 5.5). This is usually not the case in carcinomas [27].

In summary, DSRCT is a unique type of sarcoma for which improvements in treatment strategies are being made that have resulted in longer survival. Chemotherapy treatment should be offered despite what may be extensive disease on imaging, since aggressive surgery to completely extirpate the disease is possible, if there is a response to chemotherapy.

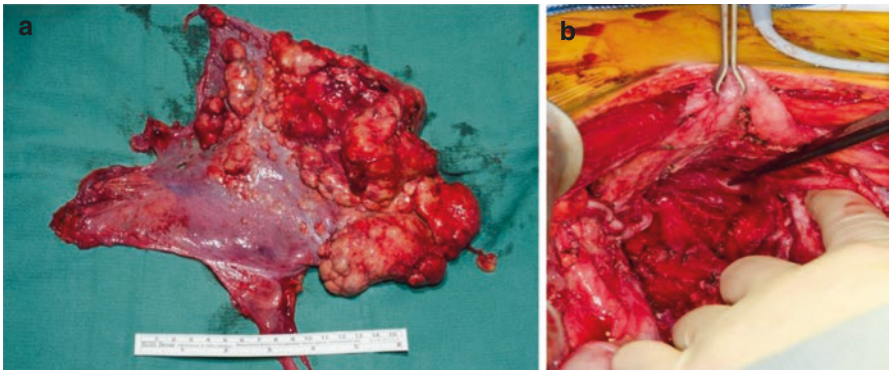

Fig. 5.5 (**a**) Pelvic peritonectomy in an 11-year-old male. (**b**) Appearance of pelvis after peritonectomy, demonstrating bladder, ureters, and vas deferens spared down to the seminal vesicles

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