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Management of desmoplastic small round cell tumor

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ABSTRACT

Desmoplastic small round cell tumor (DSRCT) is a soft tissue sarcoma of mesenchymal cell origin that typically presents with multiple intra-abdominal tumors and exhibits a multi-phenotypic pattern of immunohistochemical staining. The specific organ or tissue type of origin has yet to be identified. DSRCT rarely arises as a singular tumor in the abdomen; in most cases, there are dozens to hundreds of abdominal peritoneal tumors that are detected on diagnosis. One very large dominant mass is usually present in the omentum, with an additional one or two large conglomerates of tumors in the pelvis and right peritoneum, respectively. Despite an often overwhelmingly large number of abdominal tumors, symptoms of bowel obstruction are rare. Ascites may be present. In late stages, pleural effusions, pleural implants, mediastinal adenopathy, supraclavicular adenopathy, or bone metastasis may be present. With this challenging disease, multidisciplinary therapy, including aggressive surgery, is warranted. This review will address DSRCT biology and treatment options and discuss outcomes.

Introduction

Desmoplastic small round cell tumor (DSRCT) is a very recently 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, and lethal sarcoma. Categorizing the unique pathology and identifying any characteristic chromosomal translocations were of key importance to developing any treatment strategies.[1,2] Gerald and Rosai described the histologic appearance that is characterized by nests of small round blue cells separated by desmoplastic stroma (Figure 1), and noted the immunohistochemical finding of multi-phenotypic differentiation. Thus, DSCRT stains with desmin, cytokeratin, and S100, which are mesenchymal, epithelial, and neural markers, respectively. Subsequent cytogenetic research by Ladanyi and Gerald identified a unique (11:22), (p13:q12) translocation and demonstrated that this translocation, which results in an active fusion protein involving the Ewing sarcoma (EWS) and Wilms tumor (WT1) genes, is pathognomonic for DSCRT.[1–3] The confirmation of this translocation by percutaneous or open biopsy is now an essential part of the workup and is required to definitively establish the diagnosis of DSRCT. Prognosis for this disease is quite poor, with 5-year overall survival estimated at only 15–30%.[1–3] If the EWS translocation is not identified, then accurate diagnosis is quite challenging. 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]

Diagnosis and staging

DSRCT can present at an age ranging from 5 to 50 years, with a mean age at presentation of 22 years. Overall, about 85–90% of patients are male, but the proportion of females tends to be slightly higher among patients younger than 20 years at diagnosis.[5] Large masses, in addition to visceral and parietal seeding of the peritoneum, are a typical presentation in DSRCT in more than 50%. The reason a large tumor burden exists at diagnosis is that few symptoms are present until the peritoneal surfaces are infiltrated with tumor, overwhelming the peritoneum, and impairing resorption of peritoneal fluid, 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 only one or two masses. However, this can occur when the DSCRT is found

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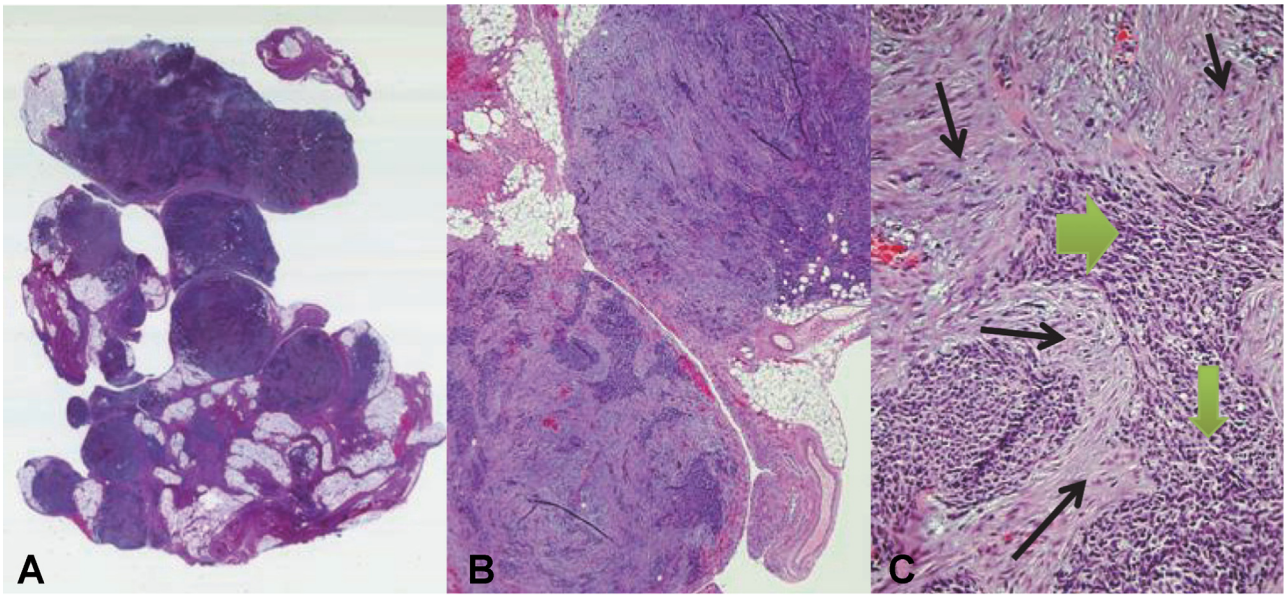

Fig. 1. Histologic sections of DSRCT from an omental biopsy, shown at low (A) 5 ×, (B) 20 ×, and (C) high (40 ×) magnification. (C) Nests of small round blue cells (filled arrow) interdigitate between bands of fibrous stroma (line arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

incidentally at the time of another operation, like hernia repair, or diagnostic radiologic exam for another entity.

Because of the frequently diffuse nature of the disease on presentation, a new staging system is being considered and is now being used on a trial basis by Hayes-Jordan and colleagues at MD Anderson Cancer Center in Houston, Texas. In this proposed staging system, stage 1 patients are those with limited disease, localized to one or two sites in the abdomen or one site elsewhere. Stage 2 patients are those with any amount of extensive peritoneal disease; stage 3, with liver metastasis and peritoneal disease; and stage 4, with peritoneal and liver disease, as well as disease outside the abdominal cavity, including in the lymph nodes. This staging system is under investigation and has not yet been validated.

Imaging characteristics

Computerized axial tomography (CT) is the most useful initial imaging study and should be performed with both gastrointestinal and intravenous contrast. Magnetic resonance imaging (MRI) is helpful in cases where pelvic and hepatic lesions are present. On CT or MRI, multiple peritoneal implants typically can be seen, which significantly increases the suspicion of DSRCT. 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, positron emission tomography (PET) imaging may be a helpful adjunct to evaluate distant metastasis at the time of staging.[6]

On initial imaging, the observed extent of disease may include lesions throughout the peritoneal cavity, commonly in the omentum, right diaphragm, and pelvis (Figure 2). Disease spread to the splenic hilum and various small bowel and colon mesenteric implants is also common. Retroperitoneal disease, however, is very uncommon. In most cases, the disease seen on CT or MRI imaging actually underestimates disease extent, as metastases may develop as 1- to 2-mm “sheets” of confluent tumor, which is a common intra-operative finding (Figure 3). Metastatic disease outside of the abdominal cavity may be found in the mediastinum, pleura, supradiphragmatic lymph nodes, lung, and bone.

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 treated with Ewing's type chemotherapy, which has become the standard after efficacy with this regimen was demonstrated by Kushner et al.[7] This chemotherapy is based on the 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 post-operative 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 that includes neoadjuvant vincristine, ifosfamide, dextrazoxane/doxorubicin, and etoposide.[8] This is followed by aggressive surgical excision and removal of all gross disease. Adjuvant therapy consists of radiotherapy (30 Gy whole abdomen) and irinotecan and temozolomide for a total of 12 cycles. This regimen yielded a disease-free interval of approximately 2 years and a good quality of life with regular school attendance and participation in plan activities. This regimen was tolerable after surgery and radiotherapy.[8] Based on preclinical data indicating elevated expression of pro-angiogenic factors in DSRCT,[9] irinotecan, and temozolomide in combination with bevacizumab-induced blockade of angiogenesis administered prior to Ewing's type chemotherapy are also being studied in a pilot study in newly