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CASE REPORT

Intra-Abdominal Desmoplastic Small Round Cell Tumor

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Background: Intra-abdominal desmoplastic small round cell tumor is a rare malignancy with a predilection for young males. Unique histological and immunocytochemical features distinguish the tumor from other members of the family of small round cell tumors of infancy and childhood. The aggressive nature of tumor spread, relative insensitivity to chemotherapy, and generally incomplete resectability result in a very poor prognosis. The authors report a case of a 39-year-old man with diffuse abdominal and pelvic involvement of intra-abdominal desmoplastic small round cell tumor treated with aggressive chemotherapy and surgery.

Methods: Computed-tomography (CT)-guided biopsy of an omental mass was performed. Histologically, discrete nests of uniform closely packed malignant cells were distributed in a background of focally desmoplastic stroma. Immunocytochemistry demonstrated positivity for epithelial, mesenchymal, and neural markers. On the basis of these unique histological and immunohistochemical characteristics, the diagnosis of desmoplastic small round cell tumor was made. The patient was treated with aggressive neoadjuvant chemotherapy consisting of a high-dose alkylator -based combination regimen, followed by surgery.

Results: The patient had a 10 to 15 percent regression in tumor mass in response to chemotherapy. Laparotomy revealed two large omental masses, another large mass adherent to the left colon and pelvic sidewall, and diaphragmatic, peritoneal and mesenteric studding with small nodules. Complete surgical resection was not possible.

Conclusions: Intra-abdominal desmoplastic small round cell tumor remains an aggressive malignancy with an extremely poor prognosis. Although some response to chemotherapy may be possible, complete resection is rare, and surgical efforts are general palliative.

INTRODUCTION

First described in 1987 by Sesterhenn et al. [1], intra-abdominal desmoplastic small round cell tumor (IADSRCT)[b] is a distinct variant of the small round cell tumors of infancy and childhood. It is an uncommon, highly aggressive tumor with

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[b] *Abbreviations:* IADSRCT, intra-abdominal desmoplastic small round cell tumor; CT, computed-tomography; EMA, epithelial membrane antigen; NSE, neuron-specific enolase; EWS, Ewing's sarcoma gene; WTI, Wilms' tumor suppressor gene.
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a predilection for young males [2-15]. Predominantly intra-abdominal in location, IADSRCT lacks a visceral site of origin and spreads diffusely along serosal surfaces. Histologically, this tumor is characterized by well-demarcated nests of tumor cells surrounded by an abundant desmoplastic stroma. Co-expression of epithelial, mesenchymal and neural markers is a unique feature of IADSRCT [2-6, 9, 16], as is its association with a characteristic chromosomal translocation t(11;12)(p13;q11.2 or q12) [17-20]. Prognosis is uniformly poor because the malignancy is relatively insensitive to chemotherapy and radiation, and surgical excision is rarely complete. Due to the rarity of this malignancy, optimal treatment regimens have yet to be defined. We report the case of a 39-year-old man with diffuse abdominal and pelvic involvement of intra-abdominal desmoplastic small round cell tumor treated with aggressive neoadjuvant chemotherapy and surgery.

CASE HISTORY

A 39-year old white man, previously well, presented to his primary care physician with a six-week history of left lower quadrant abdominal discomfort, early satiety, increasing abdominal girth, rectal pressure during bowel movements, decreased caliber of bowel movements, intermittent night sweats and lower back discomfort, as well as a 12-pound weight loss.

On physical examination, the abdomen was moderately distended with ascites, and two large, firm, nontender, mobile masses were palpable in both lower abdominal quadrants. Laboratory studies were unremarkable except for lactate dehydrogenase 287 u/l (normal 50-240 u/l). Computed-tomography (CT) scan revealed an extensive soft tissue mass filling the pelvis and displacing the rectum posteriorly, as well as severe ascites and evidence of peritoneal carcinomatosis with multiple large solid masses involving the omentum and the bowel wall. CT-guided biopsy of an omental mass was consistent with desmoplastic small round cell tumor.

Neoadjuvant chemotherapy was begun with intravenous cyclophosphamide, doxorubicin, and vincristine, alternating with ifosfamide and etoposide. The patient responded clinically to the first three cycles of chemotherapy, requiring paracentesis less frequently. Subsequent CT scan revealed a 10 to 15 percent regression in tumor mass. The patient underwent two additional courses of chemotherapy after which he required stem cell rescue. CT scan showed no further change in tumor mass.

At laparotomy, 2.5 liters of ascites was found within the peritoneal cavity. Two large mobile masses were found attached to the greater omentum, with tumor very closely adherent to the splenic flexure. A third large mass was attached to the left pelvic sidewall and to the sigmoid colon and extended between the bladder and the rectum. The diaphragm was studded with small nodules, and tumor nodules were noted throughout the mesentery and parietal peritoneum. The tumor was mobilized from the splenic flexure and from the sigmoid colon, bladder and rectum and was transected at its attachment to the left pelvic side wall, allowing en bloc resection of the three masses and the omentum. The parietal peritoneum was removed with electrocautery, and the nodules within the small bowel mesentery were maximally resected. Post-operative course has been uneventful, and subse-

quent therapeutic efforts will include radiation and further chemotherapy.

PATHOLOGY

Macroscopic findings

The 2,000-gm specimen consisted of omentum studded with numerous tumor nodules of variable size, some distinct and spherical and others confluent. The specimen measured 20 cm x 20 cm x 11 cm as a whole, with tumor nodules ranging from 0.5 cm to 16 cm in size. The tumor was firm and smooth, and the cut surface of the nodules revealed firm, white densely fibrotic areas alternating with soft, gelatinous myxoid areas.

Histological findings

The specimen obtained by CT-guided biopsy was characterized by discrete nests of uniform closely packed malignant cells distributed in a background of focally desmoplastic stroma. The nests of cells varied in appearance from irregular islands to narrow cords and infiltrating strands. The tumor cells were small, with hyperchromatic round to oval nuclei, scant eosinophilic cytoplasm and indistinct cytoplasmic borders. Nucleoli were generally inconspicuous. Mitotic figures were rare, and anaplastic nuclei were not present. Tubular or glandular foci, rosettes, or other recognizable signs of differentiation were absent. The stroma was dense and collagenous with occasional scattered spindle-shaped fibroblast-like cells. The tumor predominantly consisted of malignant cells, with the stromal component occupying a smaller portion of the specimen. In addition to the characteristics of the biopsy specimen, the resected specimen revealed cystic changes and some myxoid areas within the stroma.

Immunohistochemistry

On immunohistochemical staining, the neoplastic cells were strongly positive for the epithelial marker keratin (AEl/AE3 and CAM 5.2), diffusely throughout the cytoplasm. Although positivity for epithelial membrane antigen (EMA)d was also strong, its distribution was more patchy than that of keratin. Reactions with anti-vimentin antibody revealed diffuse cytoplasmic positivity in the majority of tumor cells, while staining with desmin was sporadically positive and showed a paranuclear cytoplasmic "dot-like" or "globoid" pattern of expression. The tumor cells demonstrated focal positivity for alpha-smooth muscle actin. Staining for neuron-specific enolase (NSE)' and S-100 protein, markers of neural differentiation, exhibited a focal pattern of positivity.

DISCUSSION

IADSRCT is a recently described entity belonging to the category of small round cell tumors of infancy and childhood, including Ewing's sarcoma, primitive neuroectodermal tumor, embryonal or alveolar rhabdomyosarcoma, neuroblastoma, malignant lymphoma, Askin's tumor, and rhabdoid tumor. This group of neoplasms is characterized by small uniform cells with sparse cytoplasm, diffuse growth pattern, and high cellularity.

Specific clinical, topographical, morphological and immunohistochemical fea-

tures, however, differentiate IADSRCT from other members of its family. Although not as marked as reported in the first series of IADSRCT by Gerald et al. in 1991 [3], the male predominance of this tumor has been described in several subsequent reviews (male-to-female ratio, greater than 3:1) [8, 21-23]. Adolescents and young adults are typically affected, with a mean age between 18 and 20 years (range 3 to 48) [23], and greater than 70 percent of patients present before the age of thirty in reviews of larger series [3, 21, 22]. The most common presenting symptoms of IADSRCT are abdominal pain and distention, related to enlarging tumor burden and sometimes to ascites, as in our case. The tumor tends to arise intra-abdominally on serosal surfaces without an obvious visceral primary site. A dominant omental or pelvic mass is common with multiple surrounding smaller satellite nodules adherent to the peritoneum. Grossly, the tumor is firm, smooth and bosselated, with a gray-white cut surface and focal necrotic and hemorrhagic regions [2-4].

Histologically, IADSRCT is characterized by well-defined nests or strands of uniform small round tumor cells surrounded by an abundant desmoplastic stroma. Generally, morphologic signs of differentiation are absent. However, tubular lumina have been noted in pathologic specimens of IADSRCT [2], and glandular and neural components have, likewise, been reported [4, 16, 21, 22]. Although the malignant cells and the stromal component usually occupy equal proportions of the tumor, the stroma in IADSRCT can be highly variable, with some tumors being predominantly cellular and others predominantly stromal [2, 21, 23]. Within the dense collagen-rich stroma, spindle cells resembling fibroblasts or myofibroblasts can be identified. The stroma may consist of myxoid areas, cystic degeneration and calcification [21]. In our case, the CT-guided biopsy specimen did not reveal these components, suggesting that the myxoid areas and cystic changes found in the resected specimen may have been associated with the neoadjuvant chemotherapy received. Alternatively, tumor heterogeneity may account for the histological differences.

Although the clinical and histological features of IADSRCT may be sufficiently distinctive to suggest its diagnosis, IADSRCT is most easily distinguished from other members of its family by the unique immunoreactivity for epithelial, mesenchymal and neural markers. Immunopositivity for keratin and EMA, markers of epithelial differentiation, is usually diffuse throughout the cytoplasm and widespread. Some reports have demonstrated, however, that EMA reactivity is variable, with patchy or scattered distribution and localization adjacent to the cytoplasmic membranes [6, 24]. The mesenchymal markers, vimentin and desmin, are consistently expressed in IADSRCT. Vimentin usually exhibits widespread, diffuse cytoplasmic staining, while desmin positivity has a classic paranuclear "dot-like" or "globoid" pattern, though a diffuse, cytoplasmic quality has been noted [16, 22]. Despite immunoreactivity for keratin, EMA and desmin, microscopic features of epithelial or myoid differentiation are generally absent. In our case, neoplastic cells were focally positive for alpha-smooth muscle actin, an uncommonly expressed antigen in IADSRCT [22]. Although neurosecretory dense-core granules, ultrastructural evidence of neuroendocrine differentiation, have been reported only rarely [3, 4, 16], IADSRCT is usually immunopositive for NSE and occasionally expresses S-100 protein as well [16, 21, 25]. Co-expression of epithelial, mesenchymal, and neural antigens in the same cell suggest that IADSRCT may arise during development from a primitive pluripotential stem cell.

However, the histogenesis of IADSRCT remains unknown.

Evidence demonstrating the association of a specific chromosomal abnormality with some cases of IADSRCT may provide insight into the histogenesis of this tumor at a molecular level. In most cases analyzed cytogenetically, the genetic alteration involves a unique reciprocal translocation, t(11;12)(pl3;ql1.2 or q12), and is not the same 11;12 translocation found in other small round cell tumors, giving further support to the notion that IADSRCT is a distinct, yet related, tumor type [17-20]. The breakpoint loci involve the chromosomal regions of the Ewing's sarcoma gene (*EWS*) and the Wilms' tumor suppressor gene (*WTI*), which have been implicated in other malignant developmental neoplasms [26, 27]. Recent studies have demonstrated evidence of expression of chimeric *EWS-WTI* RNA in IADSRCT resulting from the fusion of the *EWS* and *WTI* genes [27]. As suggested by Parkash et al. [29], the divergent differentiation of IADSRCT may be the result of the *EWS-WTI* fusion, allowing a combination of neural differentiation of Ewing's neoplasms with the multidirectional differentiation of Wilms' tumors. Although chromosomal analysis has been conducted in only a small number of cases, the t(11;12)(pl3;ql1.2 or q12) appears to be a specific alteration and may prove useful in the elucidation of the molecular pathogenesis of IADSRCT and perhaps in the molecular diagnosis of the tumor.

The diagnosis of IADSRCT is usually not made until tissue is obtained at laparotomy, thereby precluding the use of neoadjuvant therapy. In our case, diagnosis was made by CT-guided biopsy, with obvious therapeutic consequences. In 1992, Setrakian et al. [30] described the case of a 20-year-old man with a subhepatic soft tissue mass biopsied by CT-guided fine needle aspiration. Cytologic analysis revealed small round cells with scarce cytoplasm and occasional fibroblast-like cells, and immunostaining was positive for cytokeratin, desmin and NSE, confirming the diagnosis of IADSRCT. The specificity of immunopositivity for epithelial, mesenchymal and neural markers makes CT-guided fine needle aspiration a very useful technique in the diagnosis of IADSRCT.

IADSRCT exhibits an extremely aggressive clinical course and in general, carries a very poor prognosis. Although a standardized treatment protocol is lacking, several studies have attempted to define the biological behavior of the tumor and its response to various therapeutic modalities. In the series by Gerald et al. [3] in 1991, 19 patients underwent surgical "debulking," followed in most cases by multi-drug chemotherapy with or without irradiation. Generally, an incomplete surgical resection and partial response to chemotherapy was followed by rapid, uncontrollable relapse. In 1993, Ordonez et al. [22] likewise reported only rare complete surgical resection but initial tumor reduction with adjuvant multi-agent chemotherapy. Again, however, progressive tumor growth was the rule. With evidence in these studies of some degree of chemosensitivity in these tumors, Farhat et al. [31] described four patients with IADSRCT who were treated with an adjuvant cisplatin-based multi-drug regimen following suboptimal surgical debulking or biopsy. All four patients demonstrated stable disease after four to nine courses of chemotherapy. In a prospective study by Kushner et al. [9] in 1996, five of eight previously untreated patients experienced complete remission following a high-dose neoadjuvant alkylator-based regimen and surgical resection. Another two patients had complete surgical resection at the time of diagnosis and were in complete remission following adjuvant chemotherapy. With or without consolidative radiotherapy and/or myeloablative chemotherapy, five of the seven patients remained in complete remission 10 to 39 months from

the start of the alkylator-based regimen, demonstrating that progression-free survival of prolonged duration is attainable. In Amato et al. [7], four of five patients treated with various multi-agent chemotherapeutic regimens with or without surgical intervention had evidence of a partial response but eventually died from their disease within 3.5 years from diagnosis. Treated with a regimen similar to that described Kushner et al., our patient had an apparent clinical response to therapy, but CT scan demonstrated only a 10-15 percent reduction in tumor mass, and complete surgical resection was not possible. Adjuvant therapy will include irradiation and additional chemotherapy.

IADSRCT remains an aggressive malignancy with an extremely poor prognosis. Although some response to chemotherapy may be possible, in particular to high-dose alkylator-based regimens, complete surgical resection is rare, and despite aggressive therapy, survival rates remain low due to the refractory nature of the tumor. Additional studies are necessary to further elucidate the biology of the disease and to optimize treatment regimens.

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