Sister Mary Joseph nodule caused by metastatic desmoplastic small round cell tumor: A clinicopathological report

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Abstract. Sister Mary Joseph nodule is an uncommon metastatic intra-abdominal malignancy involving the umbilicus. The present study describes a rare case of desmoplastic small round cell tumor (DSRCT), histological grade 3, high grade, Gilly classification 4, stage IV, in an 18-year-old Thai man presenting with the Sister Mary Joseph nodule, ascites and pleural effusion. The histopathological examination of the umbilical mass revealed the presence of malignant small round cells associated with prominent stromal desmoplasia. Immunohistochemical stains showed positive reactivity to cytokeratin, desmin, neuron-specific enolase, Wilms' tumor 1, CD56, CD99 and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1)/INI1 in the small round cells. Fine needle aspirations of the ascitic fluid and pleural effusion were performed, and immunocytochemistry revealed a metastatic DSRCT. The patient received a VDC/IE regimen of chemotherapy, comprising vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide; however, the patient developed systemic metastasis and succumbed to the disease 6 months later.

Introduction

Desmoplastic small round cell tumor (DSRCT) is an uncommon malignant mesenchymal tumor demonstrating a complex pattern of simultaneous polyphenotypic differentiation, expressing proteins associated with epithelial, muscular and neural differentiation (1). Its various appellations include intra-abdominal desmoplastic small round cell tumor, intra-abdominal desmoplastic small cell tumor with divergent differentiation, polyphenotypic small round cell tumor and mesothelioblastoma (1). DSRCT was first described by Gerald and Rosai in 1989 (2). DSRCT has a highly aggressive clinical course with high risk of local recurrence and distant metastases, and is automatically assigned as high-grade sarcoma. The patterns of metastasis of DSRCT are similar to those of the other abdominal malignancies such as gastrointestinal carcinoma, with both intraperitoneal and retroperitoneal lymphatic routes being frequently encountered (1). The overall prognosis is poor due to the aggressive nature of the disease. Despite aggressive treatment, the 5-year survival rate is <15% (3).

Sister Mary Joseph nodule is a rare and peculiar physical sign that is encountered in 1-3% of patients with intra-abdominal malignancy (4). It is an umbilical intraperitoneal metastasis from an underlying extensive intra-abdominal malignancy. Commonly encountered primary tumors associated with umbilical metastasis include stomach, ovary, colorectum and pancreas. Umbilical metastasis presenting as Sister Mary Joseph nodule from DSRCT is extremely rare (5-7). The present study reports a rare case of Sister Mary Joseph nodule caused by metastatic DSRCT.

Case report

Clinical summary. An 18-year-old Thai man presented with an umbilical nodule and a gradual enlargement of his abdominal mass for 4 months. The patient had no history of significant illness in the past. The patient did not drink alcohol or smoke, and had no history of tuberculosis and cancer among his family members. Physical examination revealed a well-defined, firm violaceous mass, measuring 2.3 cm in its greatest dimension, located at the umbilicus (Fig. 1). There was neither superficial vein dilatation nor evidence of inflammation. The abdomen exhibited an ill-defined firm mass measuring 15x13x10 cm. The cervical and inguinal lymph nodes could not be palpated. An evaluation of the right lung revealed decreased breath sound. Computed tomography (CT, Multidetector CT: Aquilion CX, Toshiba Medical Systems Corporation, Tokyo, Japan) of the abdomen revealed a diffuse peritoneal mass (Fig. 2) and extensive intraperitoneal seeding, and multiple intra-abdominal, pelvic and bilateral inguinal lymphadenopathies, with multiple

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Key words: desmoplastic small round cell tumor, Sister Mary Joseph nodule, umbilical metastasis, ascitic fluid, pleural effusion, adult
bilateral hepatic metastases. Left ureteric obstruction with hydroureter and partial colonic obstruction were detected. The patient underwent a fine needle aspiration (FNA) of the ascitic fluid and right pleural effusion, and a minilaparotomy with incisional biopsy of the intra-abdominal mass and Sister Mary Joseph nodule. The pathological diagnosis was DSRCT, histological grade 3, high grade, Gilly classification 4, classified as stage IV. The patient achieved a stable disease following four courses of VDC/IE regimen of chemotherapy, which consisted of vincristine (1.4 mg/m²), doxorubicin (75 mg/m²) and cyclophosphamide (1,200 mg/m²) alternating with ifosfamide (9 gm/m²) and etoposide (500 mg/m²). The patient desired no further treatment. Finally, the patient succumbed to the disease 6 months following the diagnosis of DSRCT with systemic metastasis. No autopsy was performed.

The present study was approved by the Committee on Human Rights Related to Researches involving Human Subjects (Faculty of Medicine, Ramathibodi Hospital, Mahidol University; ID05-51-32).

Pathological findings. FNA of the ascitic fluid and right pleural effusion revealed cohesive groups of tumor cells, revealing the presence of small-sized cells with round, slightly pleomorphic nuclei with inconspicuous nucleoli, and a moderate amount of cytoplasm without definitive differentiation. The histopathology of the intra-abdominal mass and Sister Mary Joseph nodule revealed malignant small round cells, round blue cells embedded in a dense desmoplastic stroma (Fig. 3A and B). The cells exhibited vesicular nuclei, with scant cytoplasm and numerous mitoses. Neither a glandular structure nor rosette formation was detected. The intervening stroma was negligible in several areas, or abundant and densely collagenous in others. No vascular proliferation was identified. There were numerous tumor emboli in the lymphatic channels. The immunocytohistochemical stains for cytokeratin (AE1/AE3) (clone AE1/3; 1/100 dilution), epithelial membrane antigen (EMA) (clone E29; 1/100 dilution), desmin (clone D33; 1/200 dilution) (all from Dako, Carpinteria, CA, USA), neuron-specific enolase (NSE) (clone SE2; 1/100), Wilms' tumor 1 (WT1) (clone WT49; 1/40) (both from Leica, Mannheim, Germany), vimentin (clone Vim3B4; 1/200 dilution; Dako), CD56 (clone 1B6; 1/200; Leica), CD99 (clone 12E7; 1/75; Dako) and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1/INI1) (clone MRQ-27; optimally diluted; Ventana Medical Systems, Inc., Tucson, AZ, USA) were positive in the malignant small round cells (Fig. 3C and D). The MIB-1 (polyclonal; 1/100; Dako) index was 80%. The tumor cells were immunonegative for chromogranin A (clone DAK-A3; 1/100), synaptophysin (polyclonal; 1/100), leukocyte common antigen (LCA) (clone 2B11; 1/100), CD3 (clone F7.2.38; 1/50) and CD20 (clone L26; 1/200) (all from Dako).

Discussion

DSRCT is an uncommon malignant mesenchymal neoplasm composed of small round tumor cells associated with prominent stromal desmoplasia and polyphenotypic differentiation. The average age at presentation occurs principally during the second to third decade, with a range of 6 to 54 years (1,8).

This tumor shows a male predilection of ~10:1 (8). DSRCT is frequently found in the abdominal cavity, although cases with involvement of the thoracic cavity, paratesticular area, kidney, head and neck region have been reported (1,8-10). The most frequently presenting symptoms of abdominal DSRCT are vague abdominal pain, gradual enlargement of
Table I. Summary of four cases of Sister Mary Joseph nodule caused by metastatic desmoplastic small round cell tumor.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Symptoms</th>
<th>Duration</th>
<th>Tumor size</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Systemic metastasis</th>
<th>Survival</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albano et al</td>
<td>F</td>
<td>12</td>
<td>Decreased appetite, vomiting, weight loss, Sister Mary Joseph nodule</td>
<td>1 month</td>
<td>Multiple peritoneal masses</td>
<td>NP</td>
<td>VDC/IE</td>
<td>Ovary, liver</td>
<td>Eight months following diagnosis, the patient is clinically well with stable disease</td>
<td>(5)</td>
</tr>
<tr>
<td>Abdulqawi et al</td>
<td>M</td>
<td>28</td>
<td>Colicky central abdominal pain, Sister Mary Joseph nodule</td>
<td>2 weeks</td>
<td>5.5 cm, with several peritoneal deposits</td>
<td>NP</td>
<td>Systemic chemotherapy</td>
<td>NA</td>
<td>NA</td>
<td>(6)</td>
</tr>
<tr>
<td>Doros et al</td>
<td>M</td>
<td>14</td>
<td>Sister Mary Joseph nodule</td>
<td>2-3 weeks</td>
<td>Multiple peritoneal masses</td>
<td>30 Gy whole abdomen radiation with boosts for a total of 45 Gy to right flank and umbilicus and 36 Gy to the inguinal region</td>
<td>VDC/IE</td>
<td>NA</td>
<td>Succumbed to mortality during the course of treatment</td>
<td>(7)</td>
</tr>
<tr>
<td>Larbcharoensub et al</td>
<td>M</td>
<td>18</td>
<td>Sister Mary Joseph nodule, abdominal mass</td>
<td>4 months</td>
<td>15 cm, with multiple peritoneal seeding</td>
<td>NP</td>
<td>VDC/IE</td>
<td>Liver</td>
<td>Succumbed to mortality after 6 months following diagnosis during the course of treatment</td>
<td>The present study</td>
</tr>
</tbody>
</table>

F, female; M, male; NA, not available; NP, not performed; Gy, gray; VCD/IE, vincristine, doxorubicin, cyclophosphamide/ifosfamide and etoposide.
the abdominal mass, abdominal distension, abdominal pain, 
weight loss and other symptoms associated with obstruction of 
the intestinal or urinary tract (5-10). The most common site 
of metastasis is the regional abdominal lymph node. Distant 
metastases usually involve the lung, liver and bone (1,8). The 
routine initial laboratory investigations and serum tumor markers 
are non-contributory. The most useful diagnostic 
tool is the CT scan, which reveals a characteristic pattern 
of multiple intra-abdominal masses without any apparent 
association with the primary organ. FNA of the affected 
organs may allow early recognition of malignant soft tissue tumors. Core needle or opened biopsy is required for an 
accurate immunohistopathological diagnosis. Identification 
and confirmation of the primary tumor is important in order to 
facilitate treatment.

The macroscopic findings of DSRCT are solid, firm and 
multilobulated masses, with a gray-white cut surface. The 
tumor size ranges vary from 1 to 40 cm, with an average size of 
10 cm (1,8,10). The microscopic findings demonstrate solid 
sheets, large nests, small clumps, or cords of cohesive, small, 
round, ovoid or spindled cells lying in a hypocellular, desmo-
plastic, collagenous stroma. The tumor cells are characterized 
by small, round, oval or elongated hyperchromatic nuclei, 
clumped chromatin, inconspicuous nucleoli and ill-defined, 
lightly eosinophilic cytoplasm with an indistinct cytoplasmic 
border.

The differential diagnoses of primary malignant small 
round cell tumor of the abdomen include lymphoma, primiti-
ve neuroectodermal tumor (PNET)/Ewing sarcoma, small 
cell carcinoma, rhabdomyosarcoma, neuroblastoma, Wilms' 
tumor and extrarenal rhabdoid tumor (8-13). Lymphoma 
histologically reveals atypical lymphocytes infiltrating and 
replacing normal structure. Negative results of immunohis-
tochemical stains for LCA, CD3 and CD20 may be helpful 
in excluding lymphoma. The PNET/Ewing sarcoma may be 
histologically indistinguishable from DSRCT. In the present 
case study, the immunohistochemical stains were positive for 
desmin, vimentin, keratin and WT1, which are typically nega-
tive for PNET/Ewing sarcoma (10-13). Small cell carcinoma 
demonstrates many cytological and histological similarities to 
DSRCT. Clinically, small cell carcinoma is associated with a 
much older patient population, and usually originates in the 
lung. On histological examination, a desmoplastic stroma is 
not identified to be a feature of small cell carcinoma. However, 
small cell carcinoma demonstrates immunore-
activity with epithelial markers, including cytokeratin and 
EMA, but is negative for myogenic markers, such as desmin. 
Rhabdomyosarcoma may reveal small blue cells arranged in 
nests or sheets. Immunohistochemically, rhabdomyosarcoma 
is positive for muscle markers, but usually negative for cytoker-
atin and neural markers, including NSE (6-9). Neuroblastoma 
and Wilms' tumor also share several histological features with 
DSRCT, although they occur predominantly in young children 
and are typically associated with adrenal and renal masses, 
respectively. Extrarenal rhabdoid tumor is characterized by loss 
of SMARCB1/INI1, as revealed by immunohistochemistry.

Sister Mary Joseph nodules are rare physical signs that are 
encountered in 1-3% of patients with intra-abdominal and/or 
pelvic malignancy (4). Commonly encountered primary tumors 
associated with umbilical metastasis include stomach, ovary, 
endometrium, large intestine and pancreas. The occurrence of 
a Sister Mary Joseph nodule metastasizing from the DSRCT 
is very rare. Table I compares the present rare case of DSRCT 
with three reported cases of Sister Mary Joseph nodule caused 
by metastatic DSRCT that have been previously described in 
the literature (5-7). The presence of Sister Mary Joseph nodule 
often means a poor prognosis, with a median survival time 
of 6 months for metastatic DSRCT. Metastases to the umbi-
licus occur predominantly through the lymphatic and venous 
channels, although contiguous extension from the peritoneal 
surface and embryonic remnant has been reported (4). In the 
present case study, the presence of tumor nests on the peri-
toneal surface and in numerous lymphatic channels indicated 
that more than one mechanism could have been involved.

Reports of DSRCT have identified reciprocal transloca-
tion (11;22)(p13;q12), resulting in a fusion gene between exon 
7 of the Ewing sarcoma RNA-binding protein 1 (EWSR1) gene 
on chromosome 22 and exon 8 of the WT1 suppressor gene on 
chromosome 11 (1). The resultant chimeric protein is consid-
ered to be a transcriptional activator that fails to suppress 
tumor cell growth. The EWSR1-WT1 chimeric transcript also 
induces expression of endogenous platelet-derived growth 
factor-A (PDGFA) (14,15). PDGFA is a potent fibroblastic 
growth factor that could contribute to one of the most distinctive 
histological features of DSRCT: The dense fibrous or desmo-
plastic stroma, consisting of collagen fibers and an important 
component of elongated mesenchymal cells with features of 
fibroblasts or myofibroblasts (14). In addition, studies of the 
EWSR1-WT1 aberrant transcription factor have revealed 
deregulation of several target genes, including interleukin 2 
receptor β (IL-2Rβ), BAII-associated protein 3 (BAIAP3), 
myelodysplasia/myeloid leukemia factor 1 (MLF1), T-cell 
acute lymphoblastic leukemia-associated antigen 1 (TALLA-1) 
and leucine-rich repeat containing 15 (LRRC15) (15).

The pathogenesis of DSRCT has yet to be fully elucidated. 
The possibility that DSRCT is of mesothelial origin has been 
suggested due to the diffuse peritoneal pattern of spread, 
the presence of epithelial differentiation in the tumor cell, 
and the fact that fetal mesothelium co-expresses keratin and 
desmin (16). The small cell mesothelioma also frequently 
expresses NSE. It has been suggested that DSRCT may be 
blastosomas arising from the lateral mesoderms or intraem-
bryonic coelom (17). Moreover, the serosal lining of body 
cavities of splanchnic lateral mesoderm, the most common 
site of DSRCT, has high transient fetal expression of the WT1 
gene (15). However, EWSR1-WT1 is typically expressed in 
tissues derived from the intermediate mesoderm (1). Further 
molecular study in DSRCT patients is warranted, and has 
important implications for the study of the pathogenesis of 
disease.

Radical surgery and adjuvant or neoadjuvant chemotherapy 
remain the cornerstone of the treatment of DSRCT. However, 
a complete resection is rarely possible, since DSRCT tends to 
be large, multifocal and invasive. Several chemotherapy regimens, 
including alkylating agents and an aggressive chemotherapy 
regimen followed by myeloablative chemotherapy and 
autologous stem cell rescue, have been tried, although the 
result failed to demonstrate a clear benefit for autologous 
stem cell transplant in improving the clinical outcome (18).

Current treatment protocols include multiagent chemotherapy
and adjuvant surgery and radiotherapy (19). The emphasis is on achieving a complete and durable response. DSRCT has a highly aggressive clinical course, with a high risk of local recurrence and distant metastases. The median survival time is ~17-25 months (18). Improved survival rates are associated with complete resection of the tumor. Poor survival rates, with a median survival time of 6 months, are associated with Sister Mary Joseph nodule caused by metastatic DSRCT (5-7). Until more effective forms of treatment are found, the authors of this case study recommend multimodality treatment, including chemotherapy, surgery and radiotherapy.

In conclusion, DSRCT must be considered in the differential diagnosis of metastatic tumor of the umbilicus forming Sister Mary Joseph nodule. The application of an immunocytohistochemical investigation, in conjunction with the clinical, radiological and histopathological findings, may assist in making the diagnosis, leading to the appropriate treatment.

References