Case Reports

Desmoplastic small round cell tumor (DSRCT) arising in the ovary: report of a case diagnosed at an early stage and review of the literature

G. D'Ippolito[1, 2], M.T. Huizing[3], W.A.A. Tjalma[2]

[1]Department of Obstetrics and Gynecology, University of Modena and Reggio Emilia, Modena (Italy)
[2]Department of Gynecological Oncology and [3]Department of Medical Oncology, University Multidisciplinary Breast and Pelvic Gynecological Oncology Clinic, Antwerp University Hospital, Edegem (Belgium)

Summary

Background: Desmoplastic small round cell tumor (DSRCT) is a rare sarcoma tumor affecting mainly young adult males. It rarely has an ovarian involvement. *Case:* A 29-year-old woman presented to her gynecologist for amenorrhoea. The laboratory results demonstrated a menopausal status and the ultrasound revealed a large mass of the right ovary. The right ovary was completely removed by laparoscopy. Pathology, cytology and immunochemistry revealed a DSRCT. In January 2009 a left salpingo-oophorectomy and a right salpingectomy were performed via laparoscopy. After 35 months from diagnosis there was no clinical evidence of disease recurrence. *Conclusion:* DSRCT is a rare ovarian tumor in adolescence with a general poor outcome. Every ovarian mass regardless of age should be approached with caution.

Key words: Desmoplastic small round cell tumor; Ovarian neoplasm; Early stage tumor; Treatment; Good response.

Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive malignant soft tissue sarcoma that mainly occurs in young males, associated with an extremely poor prognosis even after demolitive surgery and aggressive chemotherapy. The male to female ratio is 4:1. We present a case of a young woman that initially presented an ovarian mass and was thought to have ovarian cancer before pathology, cytology and immunochemistry confirmed the diagnosis of DSRCT.

Case Report

A 29-year-old woman, who had used contraceptive pills for 14 years because of irregular cycles, menstruated spontaneously after she stopped taking them. After a short period of resumption of oral contraceptives, she interrupted the assumption of the pill because of an expressed desire for a pregnancy and presented amenorrhea. At her gynecologist visit the ultrasounds revealed a large mass on the right ovary and the laboratory results showed menopausal status. The patient underwent a laparoscopic right ovariectomy. Also several biopsies were taken intraoperatively from the posterior wall of the uterus, bowel wall, peritoneum and omentum that were not found to be involved with the tumor. Anatomical pathology confirmed a right ovarian mass 8.5 cm in size and weighing 132 g. Microscopic examination demonstrated a tumor rich in necrotic cells composed by small cells with poorly defined borders which were arranged in large fields and nests with the tendency to form trabecule and surrounded by a few blood vessel stroma. The tumor cells had small and medium-sized round nuclei with dotted chromatin. Nucleoli were small or unclear. The cytoplasm was poorly eosinophilic. In one of the pieces examined there was connective tissue, probably of the ovary, with a dense chronic inflammatory infiltrate. Histologically, PAS-D staining revealed absence of mucus and glycogen. Immunohistochemical findings showed that the tumor cells were negative for PLAP, beta-hCG and AFP, which excluded a germ cell tumor like an embryonal carcinoma or a dysgerminoma. The lymphocytes were CD45+. A part of the tumor cells were strongly positive for epithelial membrane antigen (EMA) and immunoreactive for pancytokeratin. The neuro-endocrine differentiation was revealed by immunostaining for synaptophysin and chromogranin. CD99 was highly expressed in most of the tumor cells, but there was no immunoreactivity for vimentin, inhibin, GFAP or CD117. The possible options then were a small cell carcinoma of the ovary (with a preference for the hypercalcemic type), a primitive neuroectodermal tumor (PNET) and a DSRCT. The CD99 immunoreactivity excluded, but not completely, a diagnosis of PNET which became even more definitive after the immunostaining against CD56 and desmin showed reactivity; S100 and TTF1 were negative. The final diagnosis confirmed a multiphenotypic small cell tumor with differentiated epithelial, neuroendocrine and muscular cells, morphologically and immunohistochemically comparable with DSRCT (Table 1). However, the tumor did not have a full typical desmoplastic aspect. Indeed, while on one side, the WT1 staining (Dako, with antibodies against the N-terminal of the WT1 protein) showed a strong dot-like cytoplasmatic positivity in around 50-60% of the tumor cells (which offered an additional argument for the diagnosis of DSRCT [1]), on the other side, the diagnosis of DSRCT was not cytogenetically supported by the FISH, because a few days later it did not show any EWS gene rearrangement.

After the operation performed in July 2008, the first of four

Revised manuscript accepted for publication February 22, 2011

Table 1. — *Immunohistochemistry of the tumor in our case.*

Stain	Result
PLAP	Negative
β-HCG	Negative
AFP	Negative
CD45	Positive
EMA	Focal positive
Pancytokeratin	Focal positive
Synaptophysin	Positive
Chromogranin	Positive
CD99	Diffuse positive
Vimentin	Negative
GFAP	Negative
Inhibin	Negative
CD117	Negative
Desmin	Positive
CD56	Positive
S100	Negative
TTF1	Negative
WT-1	Positive 50-60%
EWS	Negative

cycles of adjuvant chemotherapy with VIDE (vincristine, ifosfamide, doxorubicine, etoposide) was given. The first abdominal/pelvic CT did not reveal any disease activity. The patient underwent chemotherapy, but the somministration of the last cycle was delayed for two weeks through neutropenie. The patient recovered in the hospital and the doses was reduced of the 25%. A month later another abdominal/pelvic CT was performed and also this time it did not show any disease activity.

In January 2009, as prophylaxis, a left salpingo-oophorectomy and a right salpingectomy were performed by laparoscopy. The patient was still alive 35 months from diagnosis of DSRCT with no clinical evidence of disease recurrence at the last follow-up.

Discussion

The first DSRCT case was reported in 1987 as an undifferentiated malignant epithelial tumor involving serosal surfaces of the scrotum and abdomen in a young male [2]. This tumor, in fact, mostly affects adolescents and young males in nearly 80% of cases and the male to female ratio is 4:1. There is no known organ or area of origin but it mostly occurs in the abdomen, although thoracic and paratesticular primary sites have been reported in the literature [3, 4]. Since then, not many other cases have been described and ovarian involvement by DSRCT has been even more rarely described [5-12]. Indeed, before our case, only 13 DSRCT cases with ovarian involvement have been reported in the literature. In the world literature, bilateral involvement of the ovaries is described in 50% (7 of 14) of cases (Table 2). In our case, there was only involvement of the right ovary. Unilateral primary involvement of the left ovary has been described only by Fang *et al*. [10]. Because the disease can be misdiagnosed or remain undetected, tumors frequently grow large within the abdomen and metastasize to other parts of the body – also through the lymph nodes or blood stream. Sites of metastasis include the diaphragm, spleen, liver, large and small intestine, abdominal cavity, lungs, bones, uterus, bladder, genitals, central nervous system and the brain. DSRCT with primary ovarian involvement is seen in young women with age ranging from 11 to 29 years old. Herein we have reported a case of DSRCT involving primarily the right ovary in a 29-year-old woman.

Table 2. — *DSRCTs with ovarian involvement.*

Authors	Age	Side	Tumor location	Treatment	Outcome
Young *et al.*[5] - Case 1	15	both	Intraabdominal and pelvic	Surgical debulking + multiagent chemotherapy	DOD at 4 mo
Young *et al.*[5] - Case 2	15	both	Intraabdominal and pelvic	Hysterectomy	No follow-up
Young *et al.*[5] - Case 3	14	right	Pelvic and nodules in omentum	Surgical debulking	No follow-up
Zaloudek *et al.*[6]	22	both	Pelvic	Surgical debulking + multiagent chemotherapy	DOD at 18 mo
Slomovitz *et al.*[7]	11	right	Intraabdominal and pelvic	Surgical debulking + multiagent chemotherapy	DOD at 11 mo
Parker et al.9	23	right	Pelvis	Surgical debulking + Pacl/Cis x 4 cy	PD. No further treatment
Elhajj *et al.*[8]	27	both and pelvis	Intraabdominal	Surgical debulking + Etop/Cis d1-3 x 3 cy	SD.PD after 3 mo, unresponsive to further chemotherapy. DOD at 42 mo
Fang *et al.*[10] - Case 1	13	Left	Intraabdominal and Pelvis	Surgical debulking + multiagent chemotherapy + radiotherapy	DOD at 20 mo
Fang *et al.*[10] - Case 2	23	both	Intraabdominal and pelvis	Surgical debulking + Thiotepa and Cyclophosphamide followed by stem cell transplant	Alive NED at 7 mo after therapy
Engohan-Aloghe *et al.*[11]	21	right	Pelvis	Surgical debulking + multiagent chemotherapy	PR. Follow-up ongoing
Sang H. Lee *et al.*[15]	16	both	Intraabdominal and pelvis	Surgical debulking + VACIE	PR, then PD. AWD at 28 mo
Ota *et al.*[12] - Case 1	26	both	Intraabdominal	Surgical debulking + P6 protocol chemotherapy + radiotherapy	DOD at 23 mo
Ota *et al.*[12] - Case 2	19	both	Intraabdominal	Surgical debulking + BEP	DOD at 11 mo
Our case	29	right	Pelvis	Surgical debulking + VIDE x 4 cy	NED at 22 mo

NED: no evidence of disease; DOD: dead of disease; AWD: alive with disease; PD: progressive. disease; PR: partial response; SD: stable disease.

Tumor markers

Based only on cytological and histological examination, it is very difficult to diagnose DSRCT: a large num-

Table 3. — *Tumor markers*.

	Keratin	Ema	Vimentin	Desmin	NSE	CD56	CD99	WT1	PLAP	BHCG	AFP	CD45
DSCRT	+	+	±	+	+	+	±	±	–	–	–	+
Ewing sarcoma	–		+	–		–	+					+
Small cell carcinoma	+	+		–	+	+						
Lymphoma	–	–		–	–	+						±
Embr. & alv. Rhabd.	–			+	–							
Neuroblastoma						+						
Wilm's tumor						+		–				
Germ cell tumor									+	+	+	
Our case	+	+	–	+		+	+	±	–	–	–	+

ber of distinct histologic findings are present in this malignancy and the cells usually show evidence of polyphenotypic differentiation. Many other tumors present similar histological characteristics: small cell carcinoma of the ovary, embryonal carcinoma, dysgerminoma, primary primitive neuroectodermal tumor of the ovary, undifferentiated ovarian carcinoma of surface epithelial type, and small cell tumors that involve the ovary secondarily like lymphoma, melanoma, rhabdomyosarcoma, and primitive neuroectodermal tumors/Ewing's sarcoma. In this regard, the immunohistochemical stains which also include muscle differentiation (myogenin and myoD1), chromogranin HMB-45 and CD45 (leukocyte common antigen) can be really helpful in excluding some types of tumors [12]. Immunostaining comprises epithelial, mesenchymal, myogenic and neural markers. Tumor cells are immunoreactive for cytokeratin and epithelial membrane antigen, desmin, neuron-specific enolase, CD56, WT1, CD99, vimentin and actin [13]. This can address now to define a correct diagnosis, but not always does the tumor show immunoreactivity against all those markers, e.g., vimentin is a marker present in 80% of DSRCTs [7].

Ewing sarcoma/PNET shows many cytologic and histologic similarities to DSRCT; immuhistochemically it is typically positive for CD99 and vimentin, but negative for cytokeratins and myogenic markers. Small cell neuroendocrine carcinoma that usually arises in the lungs can also demonstrate a lot of similarities with DSRCT and is positive for epithelial and neuroendocrine markers, but it is negative for myogenic markers (desmin); high-grade lymphoma shows negativity to epithelial, neuroendocrine and myogenic markers. Embryonal rhabdomyosarcoma is positive for muscle markers like desmin and myoglobin, but usually negative for cytokeratin, S100 protein and neural markers (Table 3). Neuroblastoma and Wilms' tumor, which share many findings with DSRCT, at last, occur in very young children and show typical chromosomal translocation [13]. Concerning this last aspect, chromosomal analysis can also be performed to reach an accurate diagnosis. DSRCT is usually associated with a reciprocal chromosomal translocation t(11;22) (p13;q12), resulting in the fusion of the EWS and WT1 genes but, as in our case, it does not always occur. This translocation is different from the t(11;22)(q24;q12) translocation observed in Ewing sarcoma/PNET [1]. The EWS/WT1 translocation product targets ENT4, also known as PMAT. Equilibrative nucleoside transporter 4 (ENT4) is a protein that in humans is encoded by the *SLC29A4* gene and which catalyzes the reuptake of monoamines into presynaptic neurons, thus determining the intensity and duration of monoamine neural signaling [14]. CA-125 levels have not been well investigated in patients with DSRCT. Increased levels of CA-125 have been reported in a few cases of DSRCT [7, 9, 10, 12, 15, 16]. Ordóñez and Sahin [16] studied the trend of CA-125 serum level in a 34-year-old patient with DSRCT and found a decreased level after she had received chemotherapy after which her tumor was removed, but it became elevated again when the disease recurred. Hence, CA-125 is more a tumor marker for epithelial ovarian cancer, but it could be used as a marker of persistent and recurrent disease. Moreover an elevation of its levels should not mislead the clinician into diagnosing a primary ovarian cancer, but rather should lead the clinician to consider DSRCT, at least, in the differential diagnosis.

Clinical diagnosis

As with the majority of women with ovarian cancer, even the patients with DSRCT show symptoms much later and they are vague and non specific. The patients present symptoms like abdominal bloating, abdominal pain, symptoms related to obstruction of the viscus and ascites, and also unspecific symptoms like nausea, vomiting and weight loss. In a case described by Fang *et al*. [10], a patient presented with symptoms of acute appendicitis with high fever, which had never been described before. The most important clinical signs are the presence of an ovarian mass, especially if it is irregular, fixed and bilateral, the presence of multiple nodules in the Douglas pouch, abdominal distension due to ascites or caused by partial occlusion of intestines or pelvic spread of the disease. Usually patients with an ovarian mass also present amenorrhea. In young patients, an ovarian mass is usually a functional cyst due to anovulation that will resolve spontaneously within several days to two weeks. Ovarian masses due to hemorrhagic corpus luteum can be up to 10 cm and the rupture can cause acute abdomen. However also ovulating patients can present, although rarely, with a functional ovarian cyst which can cause abdominal or pelvic pain. An accurate examination of the abdomen can be helpful, especially in case of peritoneal spread of the cancer, because of an occasionally painful lump known as a "Sister Mary Joseph nodule", a peculiar sign which can be detected in the umbilicus secondary to

metastatic cancer in this location [17, 18]. After clinical examination, it is important to perform US and tumor marker investigations. In addition to the standard markers like CA-125, CA19-9 and SCC (squamous cell carcinoma antigen), it is very important to determine also markers like AFP, hCG and LDH, especially in patients under 20 years of age who present with an abdominal or pelvic mass in order to exclude a germ cell tumor. Whether in case of positivity or in case of negativity of those markers, surgery remains the initial approach to DSRCT treatment, also because a definitive diagnosis is only made through it. A useful tool to lead the clinician to suspect a malignancy could be the risk of malignancy index (RMI). The formula of the index is U x M x CA-125 and comprises the ultrasound score (U) (from 1 to 5 points depending on the presence of multilocular cysts, presence of a solid mass, evidence of metastases, presence of ascites and bilateral involvement), the level of a menopausal status (M) (3 is the maximum score and it is given to women in menopause), CA-125 is considered in its absolute value. Depending on the RMI value we can have:

RMI	Tumor risk	
< 25%	< 3%	Low risk
25-250	20%	Medium risk
> 250	75%	High risk

Preoperative investigations can include non invasive examinations like CT, MRI, Intravenous pyelogram (IVP), chest X-ray, double contrast barium enema (DCBE) and invasive examinations like lymphography, peritoneal cytology and laparoscopy. However, in the end, the diagnosis can only be made by tissue examination (tissue is the issue).

Treatment

The tumor – in both men and women – is associated with an extremely poor prognosis, even after aggressive surgery and chemotherapeutical intervention. Schwarz *et al*. [19], after a retrospective survey of 32 patients who underwent aggressive surgical debulking, chemotherapy, and radiotherapy, reported an overall progression-free five-year survival rate of 18%. Median survival is reported to be less than 30 months [20]. In 2002, Elhajj *et al*. described the first case of a patient with DSRCT with ovarian involvement treated with aggressive surgical debulking and multiagent chemotherapy (etoposide, cisplatinum and cyclophosphamide) who survived for 42 months after diagnosis [8]. In 2006, Church *et al*. reported two cases of women with intrabdominal and pelvic tumor localization, both treated with chemotherapy: in the first case the patient died at the 27th month after she had resolution of symptoms for a year and progressive disease unresponsive to further chemotherapy; the other patient showed a complete response after four cycles and recurrence six weeks after treatment. She died within 12 months from the diagnosis [19]. There is only one case described by De Lena *et al*. in 1998 in which the patient survived with no evidence of disease 15 months after surgical debulking and three alternating chemotherapy regimens [21]. Because of the rarity of this disease, a gold standard therapy is not yet established. Many authors have reported some patients respond to high-dose (P6 protocol) chemotherapy, maintenance chemotherapy, debulking surgery, cytoreductive surgery, and radiation therapy. Kushner *et al*. treated 12 patients with P6 protocol chemotherapy, including four courses of cyclophosphamide, doxorubicin, and vincristine alternating with three cycles of ifosfamide and etoposide, but also in this case, the overall progression-free five-year survival was only 18%. Most patients relapsed and died soon after diagnosis [22]. Other treatment options include: hematopoietic stem cell transplantation, intensity-modulated radiation therapy, radiofrequency ablation, stereotactic body radiation therapy, intraperitoneal hyperthermic chemoperfusion, and clinical trials. Prognosis depends on stage of the cancer, but nonetheless it remains really poor. Despite aggressive therapy, three-year overall survival has been estimated at 44% and the five-year survival rate remains around 15% [3, 23, 24].

Conclusion

DSRCT is a very rare tumor and the occurrence in women is even more rare, but a good gynecologic oncologist should be familiar with it. The recent world literature showed an increase in diagnosis of this tumor which means that in reality it occurs more than it seems. It should be considered in the differential diagnosis of ovarian cancer. Our experience indeed proves that a patient affected by this neoplasm, if initially diagnosed as having it and if treated with aggressive cytoreductive surgery in combination with aggressive adjuvant chemotherapy, could have a favorable outcome like our patient who did not show any clinical evidence of disease recurrence at the last follow-up.

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Address reprint requests to:
W.A.A. TJALMA, M.D.
Department of Gynecology
Antwerp University Hospital
Wilrijkstraat 10
2650 Edegem (Belgium)
e-mail: wiebren.tjalma@uza.be