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Malignant rhabdoid tumor of the peritoneum, mimicking an advanced ovarian cancer: a case report with literature review

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ABSTRACT

Objective. Extra-renal malignant rhabdoid tumor is an uncommon neoplasm, more commonly occurring in pediatric aged patients. Despite current treatment options, prognosis and survival rate are poor. At present, there are only 20 published cases of primary malignant rhabdoid tumor of the female genital tract and peritoneum and, due to its rarity, there is no standard therapeutic guideline for appropriate treatment.

Methods. We report the case of a young female affected by this extremely rare tumor, who was surgically treated in our gynecologic oncology division and performed a systematic review of the English literature present in PubMed, SCOPUS and Web of Science. The systematic search was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO, no.: CRD 42019138911).

Results. Given the rarity of this tumor, only case reports' studies were available on this topic. A narrative description of the clinical characteristics, treatment and patients' status at last follow up has been carried out.

Conclusions. We believe that the best treatment option for patients with this type of tumor should be an aggressive debulking surgery in addition to prompt adjuvant treatment, especially in advanced cases.

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SOMMARIO

Obiettivo. Il tumore rabdoide extra-renale maligno è una neoplasia non comune, che si verifica più comunemente nei pazienti di età pediatrica. Nonostante le attuali opzioni di trattamento, la prognosi e il tasso di sopravvivenza sono scarsi. Al momento, ci sono solo 20 casi pubblicati di tumore rabdoide maligno primario del tratto genitale femminile e del peritoneo e, a causa della sua rarità, non esistono linee guida terapeutiche standard per un trattamento adeguato.

Metodo. Segnaliamo il caso di una giovane donna affetta da questo tumore estremamente raro, che è stata chirurgicamente trattata nella nostra divisione di ginecologia oncologica. È stata inoltre eseguita una revisione sistematica della letteratura inglese presente in PubMed, SCOPUS e Web of Science. La ricerca sistematica è stata eseguita in accordo con le voci di segnalazione preferite per revisioni sistematiche e meta-analisi (PRISMA) ed è stata registrata nel registro prospettico internazionale delle revisioni sistematiche (PROSPERO, n. CRD 42019138911).

Risultati. Data la rarità di questo tumore, su questo argomento erano disponibili solo studi di casi clinici. È stata effettuata una descrizione narrativa delle caratteristiche cliniche, del trattamento e dello stato dei pazienti all'ultimo follow-up.

Conclusioni. Riteniamo che la migliore opzione terapeutica per i pazienti con questo tipo di tumore debba essere un aggressivo intervento di citoreduzione oltre al pronto trattamento adiuvante, specialmente nei casi avanzati.

Key words:

Malignant rhabdoid tumors of the female genital tract; malignant rhabdoid tumors of the peritoneum; systematic review.

INTRODUCTION

Rhabdoid tumor is an uncommon neoplasm characterized by a population of large, non-cohesive cells with vesicular nuclei and large nucleoli. They have been initially described as atypical and aggressive variants of Wilms tumors in early childhood (1). In 1978, Beckwith and Palmer first described a unique sarcomatous variant of the Wilm's tumor with very aggressive clinical behavior (2). Afterwards, Haas et al. reviewed these renal tumors and identified a distinct renal tumor in children, which they named "malignant rhabdoid tumor" (MRT) of the kidney because of its morphological resemblance to malignant tumors with rhabdomyoblastic differentiation (3). Several studies reported MRT in the central nervous system (4) and in various soft-tissues (5). Extracranial MRTs are rare and often occur in infants with an age standardized incidence ratio of 0.6 per million children in the United Kingdom (UK), with 61% of cases presenting in the first year of life (6) and are even rarer in the adult. The 1-year overall survival (OS) rate in the UK population-based National Registry of Childhood Tumors from 1993 to 2010, was only 31% (6). This poor survival rate was also reflected in the National Wilms' Tumor Study (NWTs) series, and in the Surveillance Epidemiology and End Results (SEER) program in the United States, with an OS at 4 years of only 23.3% and 33.0%, respectively (7, 8).

Given the rarity of extrarenal - extracranial MRTs, no standard therapeutic pathway exists to date, and there are no randomized or prospective trials examining the role of chemotherapy combinations or the addition of new existing agents in treating these tumors.

We report the case of a 32-year-old female patient with peritoneal rhabdoid tumor whose symptomatology mimicked that of an advanced ovarian cancer. We reviewed the pertinent medical literature to accompany this case.

CASE REPORT

A 32-year-old woman, 0 gravida 0 para, was admitted to the emergency room of Policlinico Universitario A. Gemelli Foundation complaining of abdominal pain and dyspnea. Clinical examination showed a large abdominal mass.

Abdominal and pelvic computed tomographic scans revealed a large pelvic mass of 11 cm in the

right adnexal region, presumed to be of ovarian origin, omental cake and diffused carcinomatosis. No liver, splenic or renal metastasis were detected (**figure 1**). A chest CT scan showed an abundant bilateral pleural effusion but no pulmonary metastasis were evident. All pre-operative radiological exams and patient symptoms indicated advanced ovarian cancer. Considering the abundant pleural effusion and the patient's dyspnea, a pleural drain was placed before performing debulking surgery. We performed an initial diagnostic laparoscopy to assess the possibility of complete debulking surgery. More than 2000 ml of ascites fluid was drained. The laparoscopic examination of the pelvis confirmed an 11 cm peritoneal mass, infiltrating the right adnexa and rectum. Furthermore, widespread signs of carcinomatosis were distributed all over the pelvic, parietal and diaphragmatic peritoneum. Lab results of the frozen section revealed a malignant rhabdoid neoplasm. Unfortunately, despite the young age of the patient, the aggressiveness of the tumor coupled with the advanced stage of disease did not allow for a conservative fertility preserving approach and led our clinical judgment to opt for a demolitive surgery (9,10). Therefore, we decided for complete surgical tumor resection. After laparotomic conversion, an en-bloc resection of the uterus, adnexa, pelvic peritoneum, sigmoid colon and rectum was performed. To eradicate the tumor, the following procedures were performed: radical removal of the lesser and greater omentum, bilateral diaphragmatic peritonectomy, ileo-cecal resection plus anastomosis and radical lumbo-aortic lymphadenectomy. An ileostomy was performed to prevent anastomotic dehiscence. At the end of the operation, no gross residual disease was evident. There were only a few postoperative complications including anemia, fever and pleural effusion in the 9 days following surgery, and the patient was discharged in stable general condition. Histopathological examination revealed a high-grade neoplasm, consisting of large-sized epithelioid elements with nuclei and evident nucleoli and abundant eosinophilic cytoplasm of rhabdoid appearance. Immunohistochemistry showed positivity for vimentin, Estrogen Receptor (ER), focal positivity for EMA (Epithelial Membrane Antigen), Progesterone Receptor (PR) and negativity for Wilms' tumor 1 (WT1), S100 protein, myogenin, myoblast determination protein 1 (MYO D1), calretinine, Gross cystic disease fluid protein 15 (GCDFP 15), Human Melanoma Black 45 (HMB45), ERG, leu-

Figure 1. Computed tomography images showing a large pelvic mas of the right adnexal region, omental cake and ascites. A. Coronal scan B. Sagittal scan C. Transverse scan.

kocyte common antigen (LCA), desmin, caldesmon and Cytokeratin AE1 / AE3 (CKAE1/AE3). Further investigations showed the loss of nuclear expression of integrase interactor 1 (INI-1). This type of histological profile is usually indicative of the progression of other malignant tumors but, in this case, a specific differentiation line was not provable and INI-1 was unequivocally lost (**figure 2**).

On histopathological examination, both ovaries measured approximately about 5 cm and were covered by multiple carcinomatosis nodules as well as an “ab extrinseco” infiltration by the pelvic mass. Based on these findings, we diagnosed an extra-renal rhabdoid tumor, originating from the peritoneum.

In absence of clear guidelines for adjuvant therapy, and due to its sarcomatous disease similarities, we decide to treat the peritoneal MRT as a uterine sarcoma, administering a cycle of anthracyclines (Doxorubicin) + Olaratumab. The CT scan performed before chemotherapy (9 weeks post-surgery), showed extensive peritoneal and lymph

node recurrences and a hepatic metastasis of about 3 cm. The examination also depicted abundant ascites and neoplastic peristomal tissue.

Chemotherapy was started 11 weeks after surgery in relation to the aggressive surgery performed and time required for histopathological results. According to RECIST criteria, the CT scan after 3 chemotherapy cycles revealed a progression of all the previous metastasis detected despite negative tumor markers results and good general patient conditions.

Therefore, we stopped the ongoing treatment with anthracycline and changed to trabectedin.

Unfortunately, the patient died due to disease progression 9 months after diagnosis.

MATERIALS AND METHODS

We performed a systematic review of the English literature present in PubMed, SCOPUS and Web of Science, regarding cases of female genital tract and peritoneal MRT.

Figure 2. Histology is characterized by proliferation of “rhabdoid cells” with large nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm arranged in a discohesive solid growth pattern (a); immunohistochemical expression of INI-1 observed in endothelial and inflammatory cells, is loss in neoplastic cells (B). H&E (A), immunoperoxidase (B).

The systematic search was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11, 12), and was registered in the International Prospective Register of Systematic Reviews (available at <http://www.crd.york.ac.uk/PROSPERO>; CRD 42019138911).

The terms “malignant rhabdoid tumor of the ovary”, “malignant rhabdoid tumor of the uterus (corpus and cervix)”, “malignant rhabdoid tumor of the vulva”, “malignant rhabdoid tumor of the omentum” and “peritoneal malignant rhabdoid tumor” were used to search in the above-mentioned database. A hand search of the references of both potentially relevant articles and articles qualifying for inclusion was also performed. The exclusion criteria included duplicate publications, non-English language literature, papers based on animal models and laboratory studies.

No publication period restrictions were adopted. The search has been concluded in May 2019.

The titles and abstracts of studies retrieved using the search strategy, and those from additional sources, has been screened independently by two review authors (VV and LCT) to identify studies that potentially meet the inclusion criteria. The full texts of these potentially eligible studies have been then retrieved and independently assessed for eligibility by the two authors. Any disagreements between the two parties over the eligibility of particular studies have been solved through discussion with a third senior reviewer (BC).

The extracted information included tumor location and size, age of patients, presence of metastasis at

diagnosis, treatment approach, disease free survival and overall survival. Data supplied for included case reports have been checked by two researchers (VV and LCT) for: missing data; treatment and follow-up. Any discrepancies or unusual patterns have been checked with the study investigator (BC). Missing data have been requested from study authors when possible.

A narrative description of the findings from the included studies structured around treatment, disease free survival and overall survival of patients affected by malignant extra renal rhabdoid tumor originating from the female genital tract and from the peritoneum, has been carried out.

No statistical analysis or meta-analysis has been performed. The Cochrane risk of bias tool was not applicable to our review because the only studies available were case reports.

After a crossmatch research, 254 articles were screened. The number of full text articles assessed for eligibility was 121. Exclusion criteria were studies not in English language, the unavailability of full text article and non-pertinence with the present topic, as different genetic mutation, different histopathological characteristics or different site of localization of the tumor. Finally, 20 articles have been detected plus our case report (**table I**).

RESULTS

We reviewed 10 MRT cases of the vulva, 4 of the uterus, 1 of the uterine cervix, 4 of the ovary and 1 of the omentum as well as our present case.

Table I. Study flow diagram of search results (up to May 2019).

Table II shows the clinical characteristics, treatment and the status of the patient at last follow up (dead of disease, alive with disease or no evidence of disease at last follow up) of the analyzed cases. Overall, surgery was the first treatment choice, usually followed by chemotherapy. Various combination of chemotherapeutic agents, such as ifosfamide - epirubicin - cisplatin (IEP), vincristine - doxorubicin - cyclophosphamide/ifosfamide - etoposide (VDC/IE) and carboplatin - etoposide - ifosfamide or cisplatin alone, were administered in advanced MRT cases as first line chemotherapy with little benefit. Doxorubicin or cisplatin have been used as second line therapy. Surgery plus adjuvant treatment (chemo- or radiotherapy) has been the treatment of choice in 11 out of 21 patients. Five patients were treated with radical surgery alone, two received chemo- plus

radiotherapy (one EBRT and one BRT) while just one patient received external beam radiotherapy as sole treatment. In 7 cases EBRT and/or BRT was administered alone or in combination with surgery and/or chemotherapy and just in one case with a palliative aim. In 1 case radiotherapy was provided at recurrence. No information regarding the treatment approach were available in the remaining 2 cases. The median survival, considering the different time of follow up, in patients receiving surgery as first treatment was 9 months (range 0.5 months to 61 months). Eleven out of 21 patients died of the disease, just 6 out of 21 had no evident disease at the time of publication of the case report and 2 had a stable disease. No information is available about the remaining 2 patients.

Table II. Literature review of genital tract and peritoneal malignant rhabdoid tumor.

Author	n of cases	Age (year)	Site	Size (cm)	Treatment	Metastasis At diagnosis	CHT	DFS	DOD/ AWD/NED
#	1	32	Peritoneum	11	Surgery + Adjuvant CHT	Ovarian, diffuse peritoneal carcinomatosis	Anthracycline, trabectedine at recurrence	5 Mo	DOD 9 Mo
Dolanbay 2016 (13)	1	51	Vulva	3	EBRT	None	No	NA	NED 12 Mo
Rabinovich 2015 (14)	1	34	Ovary	12	Surgery + Adjuvant CHT	Omentum, Pelvic lymphnodes	IEP (ifosfamide, epirubicin, cisplatin) second line weekly doxorubicin	3 Mo	DOD 8 Mo
So-Hyun Nam 2014 (15)	1	10	Greater Omentum	9	Surgery + Adjuvant CHT	Diffuse peritoneal carcinomatosis	VDC/IE (Vincristine, Doxorubicin, Cyclophosphamide/ Ifosfamide, Etoposide)	4 mo	DOD 9 Mo
Venugopal 2014 (16)	1	17	Clitoris	5	CHT + RT	NA	NA	NA	DOD 6 Mo
H. Narendra 2010 (17)	1	50	Vulva	8	Surgery + RT	None	No	NA	NED 30 Mo
Banzai 2007 (18)	1	19	Ovary	14	Surgery + Adjuvant CHT CHT CHT + palliative RT	Lombo-aortic lymphnodes	IEP on recurrence ifosfamide and cisplatin on 2nd recurrence	2 Mo 9 Mo	AWD 18 Mo
Leath 2003 (19)	1	18	Ovary	NA	CHT	NA	NA	NA	DOD 2 Mo
Tzilinis 2002 (20)	1	63	Vulva	6	Surgery + BRT	None	No	NA	NED 30 Mo
Tsuda 2001 (21)	1	36	Cervix	7	Surgery + Adjuvant CHT	None	carboplatin, etoposide and ifosfamide	NA	NED 38 Mo
Sert 1999 (22)	1	NA	Vulva	NA	Surgery + RT + CHT	NA	NA	NA	DOD 8 Mo
Igarashi 1998 (23)	1	25	Vulva	6	Surgery + Adjuvant CHT	None	NA	8 Mo	AWD 8 Mo
Stastny 1996 (24)	1	36	Ovary	NA	Surgery	Pelvic	No	NA	DOD 0,5 Mo
Hsueh 1996 (25)	1	37	Uterus	10	Surgery + Adjuvant CHT	Lombo-aortic lymphnodes	Cysplatin	3 Mo	DOD 4 Mo
Lupi 1996 (26)	1	NA*	Vuvla	NA	NA	NA	NA	NA	NA
Matias 1990 (27)	1	45	Vulva	5	Surgery + Adjuvant CHT	None	NA	1 Mo	DOD 9 Mo
Perrone 1989 (28)	1	19	Vulva	NA	Surgery	None	No	26 Mo	NED 38 Mo
Cho 1989 (29)	1	46	Uterus	NA	NA	NA	NA	NA	NA

Abbreviations: # = present case, N= number, NA = not available, DFS= disease free survival, NAD= neo adjuvant, CHT= chemotherapy, RT= radiotherapy, AWD= alive with disease, NED= not evidence of disease,
DOD = dead of disease, EBRT= external beam radiotherapy, Mo= months

DISCUSSION

MRT was first described as a distinctive, highly malignant round cell neoplasm of the kidney in children (1). Cytogenetic and molecular analyses showed abnormalities in the long arm of chromosome 22 (30,31) and alteration of the hSNF5/INI1 (SMARCB1) gene (located at 22q11.2) in renal, extra-renal and intracranial MRTs. This chromosome deletion led to the inactivation of a tumor-suppressor gene SMARCB1 (also known as INI1, BAF47, and hSNF5, a core member of the SWI/SNF chromatin-remodeling complex), involved in renal and extra-renal rhabdoid tumor pathogenesis (32). This characteristic implicates SMARCB1 as a tumor suppressor gene, as defined by Knud-

son in the “two-hit model” (33). The hSNF5/INI1 tumor-suppressor gene has been reported to modulate cell growth and actin cytoskeleton organization, through an ATP-dependent manner to remodel chromatin (34). These genetic aberrations have been regarded as specific for MRT. However, Modena et al. recently demonstrated that this gene is frequently inactivated in proximal-type of epithelioid sarcoma (35). Because of INI-1 gene alterations, immunohistochemical loss of the INI-1 (BAF47/SNF5) protein has been observed in MRT, whereas positive nuclear staining is preserved in other non-rhabdoid tumor cells. Therefore, immunohistochemical study for INI antibody is useful to confirm the histological diagnosis of renal or extra-renal MRT (36,37).

Recently, mutations in a 2nd locus of the SWI/SNF complex, the SMARCA4 gene, also known as BRG1, located at 19p13.2, were found in rhabdoid tumors with retention of SMARCB1 expression (38,39,40,41). The SMARCA4 mutation is typical for the small-cell carcinoma of the ovary, hypercalcaemic type (SCCOHT), a very rare and highly malignant ovarian tumor, considered a type of MRT (42). Familial cases may occur in a condition known as rhabdoid tumor predisposition syndrome.

Up to one third of patients with rhabdoid tumors harbor SMARCB1 germline inactivating mutations (43,44,45). MRTs are aggressive, often widely metastatic at diagnosis, respond poorly to therapy, and are uniformly fatal, except for localized disease, and for these reasons, most of the mutations described above seem to occur *de novo*. Furthermore, the diagnosis is difficult and is based on light microscopic findings with supportive immunohistochemistry. The first most common localization site after the kidney is the CNS. Other relatively frequent onset sites of this tumor are deep axial locations such as the neck, paraspinal region, perineal region, abdominal cavity or retroperitoneum and pelvic cavity. Extremities, especially the thigh, or cutaneous lesions are also well-documented. This tumor can also affect visceral organs such as the liver, thymus, gastrointestinal system and the genitourinary tracts (46).

In our case, the disease manifested itself mimicking the typical presentation of an advanced ovarian cancer, with acute abdominal distention, dyspnea, ascites and diffused carcinomatosis.

Surgery was deemed essential to obtain a histopathological diagnosis and to evaluate the possibility of complete excision of the disease.

Furthermore, based on the experience gained from the treatment of advanced ovarian cancer, we know that the complete disease removal (residual tumor RT=0) has the greatest impact on overall survival and progression free survival (47). This is particularly true for some ovarian cancer histotypes such as the Low-Grade Serous Carcinoma, whose response rates to chemotherapy are significantly lower than those of High-Grade Serous Carcinoma, and where complete removal of the disease

leads to decisively better oncological outcomes (48). This is also the case for ovarian carcinosarcoma where optimal debulking surgery can improve overall survival of these patients. The frozen section showed rhabdoid features, so considering the absence of clear guidelines and the scant benefit of a neo-adjuvant treatment, we decided to perform a highly debulking surgery notwithstanding the disease's widespread.

Due to the rarity of this disease and its difficult histological diagnosis, the patient was able to begin chemotherapy 11 weeks after surgery, unfortunately when the disease had already recurred with liver metastasis. Based on our results, that showed minimal benefits of treating patients with chemotherapy and radiotherapy alone, we believe that the best treatment option should be an aggressive debulking surgery plus a prompt adjuvant treatment, especially in advanced cases. Given the similarities of MRT to uterine sarcomas we choose doxorubicin as first line treatment.

CONCLUSIONS

The rare occurrence of extra-renal MRT complicates adequate survival-improving protocols.

Generally, patients are very young with few comorbidities. Therefore, maximum surgical effort, in a specialized oncological surgery center with dedicated pathologists must be provided in order to deliver the best treatment options and obtain a timely histopathologic diagnosis.

Due to the rarity of extra-renal malignant rhabdoid tumors, prospective studies choosing the right therapeutic plan are difficult to perform. However, future patients presenting this disease should be routed to a single specialized center in order to find a personalized approach, which could ultimately lead to a better prognosis.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interests.