Case Report

Primary rhabdoid tumor of the ovary: When large cells become small cells

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Introduction

Malignant rhabdoid tumors (MRTs) are rare soft tissue tumors that often present in childhood and arise most commonly in the kidney; they can arise in extra-renal sites and in adults, albeit rarely. MRTs were first introduced by Beckwith and Palmer as a "rhabdomyosarcomatoid variant of Wilms tumor" in 1978 to describe a rare, pediatric aggressive neoplasia of the kidney, but after they were seen in extra-renal sites and in adults, and ultrastructural and immunohistochemical investigations failed to show the myogenic origin of this tumor, it was renamed "malignant rhabdoid tumor" (Foulkes et al., 2014).

MRTs are rare in the female genital tract, but when they do arise, diagnoses are difficult and equivocal at times, treatment is undefined, and they carry a grave prognosis. When confronted with a likely MRT, physicians face two main challenges: substantiating the diagnosis and

establishing treatment strategies. This diagnostic challenge was greatly aided by the discovery in 1998 that the vast majority MRTs (including those in the brain, called atypical teratoid/rhabdoid tumors [AT/RTs]) harbor deleterious mutations in the SWI/SNF chromatin remodeling gene SMARCB1 (also called INI1), which are accompanied by loss of protein expression in the tumor (Biegel et al., 2014). It was later discovered that those without SMARCB1 alteration have mutations in and loss of expression of its SWI/SNF partner, SMARCA4 (also called BRG1) (Biegel et al., 2014). Until recently, however, it was not appreciated that MRTs in the ovary (where the differential diagnosis of such tumors is broad) are caused by mutations in the same gene as another rare ovarian tumor called "small cell carcinoma of the ovary, hypercalcemic type" (SCCOHT), which show inactivating mutations in SMARCA4, accompanied by loss of expression of the protein (Jelinic et al., 2014; Ramos et al., 2014a; Witkowski et al., 2014). On the basis of their genetic and histological similarity, it was proposed that MRTs of the ovary (MRTOs) and SCCOHT are in fact the same entity and should all be named MRTO (Foulkes et al., 2014). In this context, it should be noted that the previously reported "large cell variant" of SCCOHT is a type of "pure rhabdoid" SCCOHT.

MRTs have been reported in the gynecological tract: twelve cases have been described in the vulva, ten cases in the uterus, one in the uterine cervix, and two in the ovaries (Banzai et al., 2007; Narendra et al., 2010; Tsuda et al., 2001). Here we present an unusual case of an ovarian tumor diagnosed as, prior to genetic analysis, a primary pure MRTO. We discuss how genetic analysis, despite being carried out after the death of the affected woman, has important implications for classification of MRTs and highlights that germ-line mutations are not rare in apparently isolated cases of SCCOHT/MRTO. This patient's children could be offered genetic counseling and possible genetic testing in the future.

Case report

Clinical presentation and operative interventions

A 34-year-old gravida 4 para 4 woman presented in 2010 with a one month history of left lower abdominal pain. Physical exam revealed a large irregular mobile pelvic mass. Ultrasound showed an 11×8 cm irregular hyper-echogenic complex mass with abundant blood flow

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and marginal resistance index (RI = 0.48–0.71). CT demonstrated moderate right hydro-ureteronephrosis secondary to the pelvic mass. No disease was seen at other sites. Tumor markers CA 19-9, CEA, CA 15-3, AFP, HCG, and LDH were within normal limits. CA-125 was slightly elevated at 62 U/ml. The patient underwent explorative laparotomy and frozen sections of the right affected $16 \times 12 \times 6$ cm ovary revealed an undifferentiated carcinoma. Maximal debulking was performed, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymph node dissection, and omentectomy. The tumor replaced the right ovary and extended to involve the right common iliac lymph nodes and omentum.

Histopathology and initial immunohistochemistry

Typical features of MRTO were observed. The tumor was composed of sheets of large round to polygonal atypical cells with large nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm (Fig. 1A). The tumor cells exhibited marked pleomorphism and contained scattered cells resembling rhabdomyoblasts. Hyaline globules were scattered throughout the tumor and numerous mitotic figures were seen, as well as tumor cell necrosis. The tumor cells were diffusely strongly positive for vimentin, focally positive for total-cytokeratin, CK8/18, EMA, CD99, and calretinin. They were positive for P53 (>80%), Ki-67 (~80%), NSE, CA125, and CD10. The hyaline globules were positive for alpha-1-antichemotrypsin and PAS. The tumor cells were negative for c-kit, PLAP, inhibin, CD30, AFP, beta-HCG, S-100 protein, MART-1, CK7, CK20, CEA, CD3, CD20, LCA, myeloperoxidase, lysozyme, GFAP, smooth muscle actin, desmin, and myoglobin. Other pathological entities such as rhabdomyosarcoma, epithelioid sarcoma, malignant melanoma, anaplastic dysgerminoma, and hepatoid carcinoma were ruled out and a diagnosis of primary extra-renal MRTO was made based on histology and immunohistochemistry (IHC); no reference was made to SCCOHT.

Treatment and outcome

The patient underwent uneventful post-operative recovery. A CT scan performed four weeks after maximal cytoreduction showed liver metastases and retroperitoneal, peritoneal, and pelvic masses up to 3 cm each. The patient received 3 cycles of combined IEP chemotherapy: ifosfamide 1.5 g/m^2 days 1–5, epirubicin 50 mg/m^2 on day 1 and cisplatin 70 mg/m^2 on day 1, without debilitating side effects, treatment delays, or dose reduction. CT scan following chemotherapy demonstrated complete resolution of all radiologic findings. However, after three additional cycles, CT and PET–CT scans revealed disease recurrence in the liver, retroperitoneum and pelvis. The patient received four injections of second line weekly doxorubicin 20 mg/m^2, but finally succumbed to her disease, eight months after the initial diagnosis.

Revisting the case — immunohistochemical and mutation analysis

The identification of *SMARCA4* mutations in nearly all SCCOHTs, accompanied by loss of expression of SMARCA4 protein as detected by IHC (Jelinic et al., 2014; Ramos et al., 2014a; Witkowski et al., 2014), has rendered diagnosis of this rare tumor substantially more straightforward. This discovery, together with the suggestion that SCCOHTs might in fact be part of the rhabdoid tumor family led us to revisit this case in 2014. IHC analysis of the tumor revealed immunoreactivity with SMARCB1 (Fig. 1B), but loss of SMARCA4 expression (Fig. 1C). Subsequent Sanger sequencing of the *SMARCA4* gene revealed germline (c.1641_1641delC; p.D547Efs*66) and somatic (c.1714A>T; p.K572*)
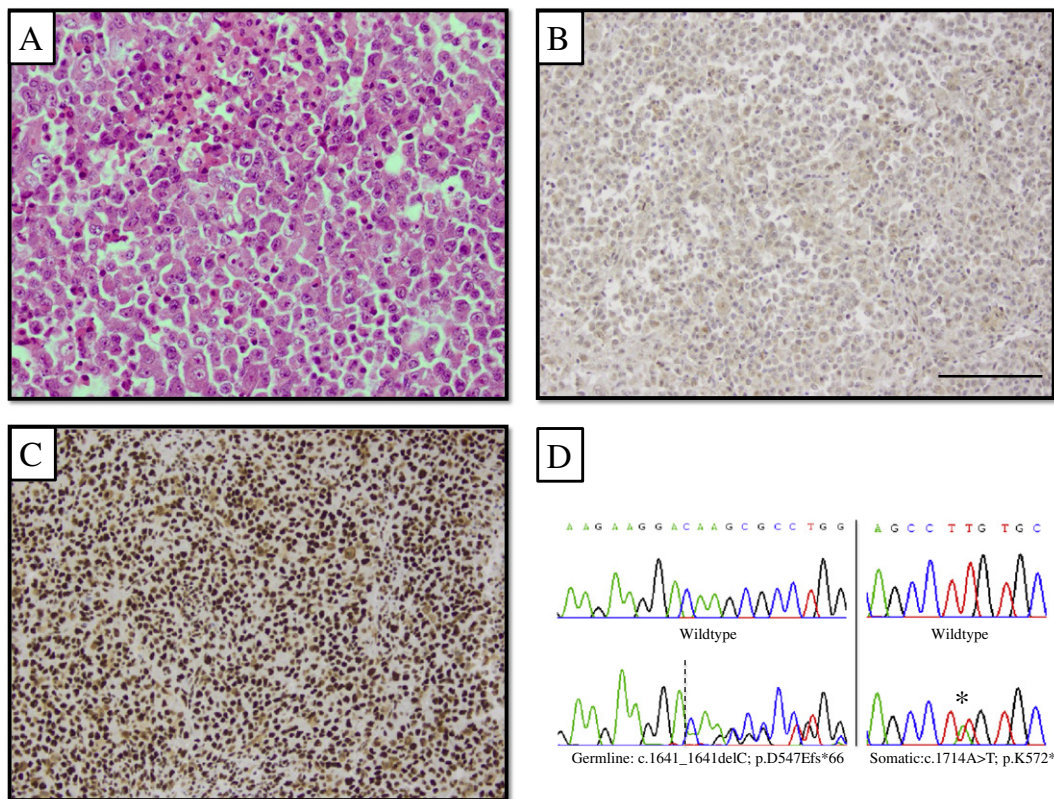

Fig. 1. A) Sheets of large round to polygonal pleomorphic cells with atypical nuclei, conspicuous nucleoli and abundant eosinophilic cytoplasm; numerous apoptotic bodies are evident, predominantly in the upper field (Hematoxylin & Eosin, original magnification ×200). B) Nuclear staining of SMARCA4 is lost in the tumor cells. C) Nuclear staining for SMARCB1 is retained. D) Wildtype (top) and mutated (bottom) chromatograms of the germline (left, c.1641_1641delC; p.D547Efs*66) and somatic (right, c.1714A T; p.K572*) mutations. The chromatogram of the somatic mutation was taken from the sequence of the reverse complement, as the nucleotide change was near the position of the germline deletion, and therefore not as clear in the forward trace.

mutations (Fig. 1D). Thus the diagnosis of SCCOHT/MRTO was established.

Discussion

The diagnosis of MRT is based on light microscopy with supportive immunohistochemistry of SMARCB1 and SMARCA4 proteins. While the usual genetic characteristic of MRTs is loss of the SMARCB1 protein, those arising in the ovary more often show loss of SMARCA4 (Jelinic et al., 2014; Ramos et al., 2014a; Witkowski et al., 2014); only two cases have been found to show loss of SMARCB1 (Ramos et al., 2014b). The reason for this remains unclear, but with the great majority of SCCOHT/MRTO showing loss of SMARCA4 expression, it has been proposed as a diagnostic marker for MRTO (Foulkes et al., 2014). When presented with a tumor showing features of SCCOHT/MRTO, we recommend the following management steps: 1) confirmation of the diagnosis by SMARCA4 staining; if SMARCA4 staining is retained, it is unlikely MRTO (although keeping in mind that 2 cases of MRTO have been reported with retained SMARCA4 staining and likely deleterious mutations in SMARCA4 (Witkowski et al., 2014)). 2) Offer germ-line genetic testing to rule out a transmissible SMARCA4 mutation. 2a) If a germline mutation is found, relevant family members, both male and female, should be counseled and tested for this mutation; male carriers may be at risk for MRTs in other tissues, including the brain. 2b) If no germline mutation is found, further somatic genetic testing should be performed to confirm diagnosis, since loss of SMARCA4 protein expression can occur without a mutation, and, discussed above, vice versa (Witkowski et al., 2014).

In this case, the IHC was done post-mortem and therefore could not have influenced management; however, given the detection of a germline mutation, her children can now be offered testing for this mutation and any daughters can be screened for this cancer if they are mutation carriers, or possibly be offered preventive oophorectomy (Berchuck et al.). In the case of unilateral localized disease, affected germline mutation carriers may opt for a contralateral prophylactic oophorectomy as it is theoretically possible that a new primary cancer could arise in the remaining ovary (Berchuck et al.). Irrespective of the tumor site, the prognosis of MRT is extremely poor. Although some intensive protocols with autologous bone marrow transplantation have achieved some notable successes (Distelmaier et al., 2006), there is a desperate need for new, more effective therapies. At the moment, the identification of mutations in SMARCA4 as the main cause of these tumors does not have any chemotherapeutic implications, but perhaps because of the quiescent genome of these tumors, epigenetic therapies are a better option. Such approaches are being actively pursued, in the hope of improving the outcome for women afflicted by this rare, but highly aggressive neoplasm.

Conclusion

We describe the clinico-pathological features of a primary pure MRTO. Although these tumors are rare, correct diagnosis is essential, due to their highly aggressive, often fatal, and possible hereditary nature. Interestingly, this tumor might have been initially diagnosed as SCCOHT, but was referred to as MRTO from the outset. At that time, SMARCA4 alterations had not been identified as the cause of SCCOHT, so the molecular association between MRTO and SCCOHT could not have been made. Irrespective of the IHC or molecular links, the prior description of a rhabdoid-cell enriched, large cell variant of SCCOHT makes the point that MRTO and SCCOHT are histologically very similar, if not identical. Incorporation of immunohistochemical and molecular techniques into the work-up of probable SCCOHT/MRTO cases will increase the number of correctly diagnosed cases and, in turn, may provide a better insight into tumor behavior and novel treatment options.

Consent

The authors confirm patient's family permission to publish this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References

Banzai, C., Yahata, T., Sasahara, J., et al., 2007. Advanced malignant rhabdoid tumor of the ovary effectively responding to chemotherapy: a case report and review of the literature. Gynecol. Oncol. 105, 261–265.

Berchuck, A., Witkowski, L., Hasselblatt, M., et al., 2015. Prophylactic oophorectomy for hereditary small cell carcinoma of the ovary, hypercalcemic type. Gynecologic Oncology Reports.

Biegel, J.A., Busse, T.M., Weissman, B.E., 2014. SWI/SNF chromatin remodeling complexes and cancer. Am. J. Med. Genet. C: Semin. Med. Genet. 166, 350–366.

Distelmaier, F., Calaminus, G., Harms, D., et al., 2006. Ovarian small cell carcinoma of the hypercalcemic type in children and adolescents. Cancer 107, 2298–2306.

Foulkes, W.D., Clarke, B.A., Hasselblatt, M., et al., 2014. No small surprise — small cell carcinoma of the ovary, hypercalcaemic type, is a malignant rhabdoid tumour. J. Pathol. 233, 209–214.

Jelinic, P., Mueller, J.J., Olvera, N., et al., 2014. Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. Nat. Genet. 46, 424–426.

Narendra, H., Ray, S., Rao, L., et al., 2010. Malignant extrarenal rhabdoid tumor of the vulva in an adult. J. Cancer Res. Ther. 6, 82–85.

Ramos, P., Karnezis, A.N., Craig, D.W., et al., 2014a. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. Nat. Genet. 46, 427–429.

Ramos, P., Karnezis, A.N., Hendricks, W.P.D., et al., 2014b. Loss of the tumor suppressor SMARCA4 in small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). Rare Dis. e967148.

Tsuda, H., Maed, K., Hashiguchi, Y., et al., 2001. Malignant rhabdoid tumour of the uterine cervix. BJOG 108, 120–123.

Witkowski, L., Carrot-Zhang, J., Albrecht, S., et al., 2014. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. Nat. Genet. 46, 438–443.