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Case report

Second primary rhabdomyosarcoma of the uterine cervix presenting with synchronous ovarian Sertoli-Leydig cell tumor: An illustrative case of DICER1 syndrome

Matthew Cowan[a], Tara Suntum[b], Andrea D. Olivas[c], Melody Perpich[b], Mark A. Applebaum[b], Ricardo R. Lastra[c], S.Diane Yamada[a,*]

[a] Department of Obstetrics and Gynecology, Section of Gynecologic Oncology, University of Chicago, 5841 S. Maryland Ave, Chicago, IL, USA
[b] Department of Pediatrics, Section of Pediatric Hematology/Oncology, University of Chicago, 5841 S. Maryland Ave, Chicago, IL, USA
[c] Department of Pathology, University of Chicago, 5841 S. Maryland Ave, Chicago, IL, USA

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1. Introduction

While rhabdomyosarcoma is the most common pediatric soft tissue sarcoma, primary involvement of the uterine cervix is quite rare (Dehner et al., 2012). As somatic and germline genetic testing has become more common, cervical embryonal rhabdomyosarcoma (cERMS), ovarian Sertoli-Leydig cell tumor (SLCT) and multinodular goiter (MNG) have become linked to DICER1 syndrome, also known as pleuropulmonary blastoma (PPB) familial tumor predisposition and dysplasia syndrome. Because of the nascent understanding of this tumor predisposition syndrome, patients previously-diagnosed with a *DICER1*-associated tumor may not have been tested for genetic mutations, missing an opportunity for increased surveillance or genetic testing of family members. We present a patient with a second primary cERMS presenting synchronously with an ovarian SLCT. This case is unusual in that the patient had multiple primary lesions associated with DICER1 syndrome over a period of 12 years.

2. Case report

A 24-year-old G0P0 female was diagnosed with cERMS at age 17. She had been undergoing routine surveillance pelvic MRIs every six months to detect loco-regional recurrence when she was found to have a pelvic mass. Her previous history was significant for benign MNG which had been biopsied at age 12. At age 17, she experienced hemorrhage from a 7 × 10 × 6.5 cm cervical mass that was prolapsing through the vaginal introitus (Fig. 1A). She was treated surgically for the cervical mass with a partial trachelectomy (Fig. 1B). Histologic examination confirmed embryonal rhabdomyosarcoma with negative margins (Fig. 2). Cytogenic studies were negative for *PAX3* or *FOXO1* fusions that would be indicative of an alveolar component. Her staging evaluation included a normal bone marrow biopsy and bone scan, and otherwise unremarkable CT of the chest/abdomen/pelvis and MRI of the pelvis. She was classified as having Children's Oncology Group (COG) Group I, Stage 1 genitourinary rhabdomyosarcoma (Borinstein et al., 2018). Surgery was followed by combination chemotherapy with an intensified Ewing sarcoma regimen per the Children's Oncology Group study AEWS0031 (Womer et al., 2012) with interval compression VDC-IE (Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide and Etoposide). After adjuvant therapy, she underwent surveillance every six months with chest x-ray and abdominopelvic MRI for over six years, eventually transferring care to a local oncologist after she graduated college.

Eleven months prior to her second diagnosis, she began to have intermenstrual spotting. A cervical polyp was removed in the office and the pathology was consistent with a benign fibroepithelial polyp. A routine pelvic MRI two months later showed a 2.5 cm cystic left adnexal mass that was characterized as a functional ovarian cyst. She denied any androgenic symptoms.

A repeat pelvic MRI six months later demonstrated that the left

* Corresponding author at: The University of Chicago Medicine, 5841 S. Maryland Ave., MC 2050, Chicago, IL 60637, USA.
E-mail addresses: t.obg.mcowan@bsd.uchicago.edu (M. Cowan), tara.suntum@uchospitals.edu (T. Suntum), andrea.olivas@uchospitals.edu (A.D. Olivas), mperpich@peds.bsd.uchicago.edu (M. Perpich), mapplebaum@peds.bsd.uchicago.edu (M.A. Applebaum), ricardo.lastra@uchospitals.edu (R.R. Lastra), sdyamada@bsd.uchicago.edu (S.D. Yamada).

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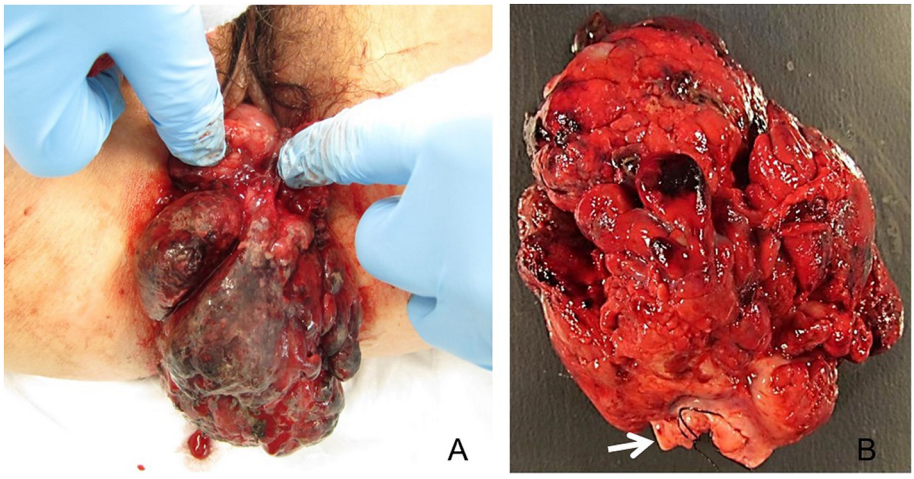

Fig. 1. Large friable, hemorrhagic mass consistent with embryonal rhabdomyosarcoma protruding from the vaginal introitus (A) was excised with a partial trachelectomy (B). The mass was attached to the distal ectocervix (arrow).

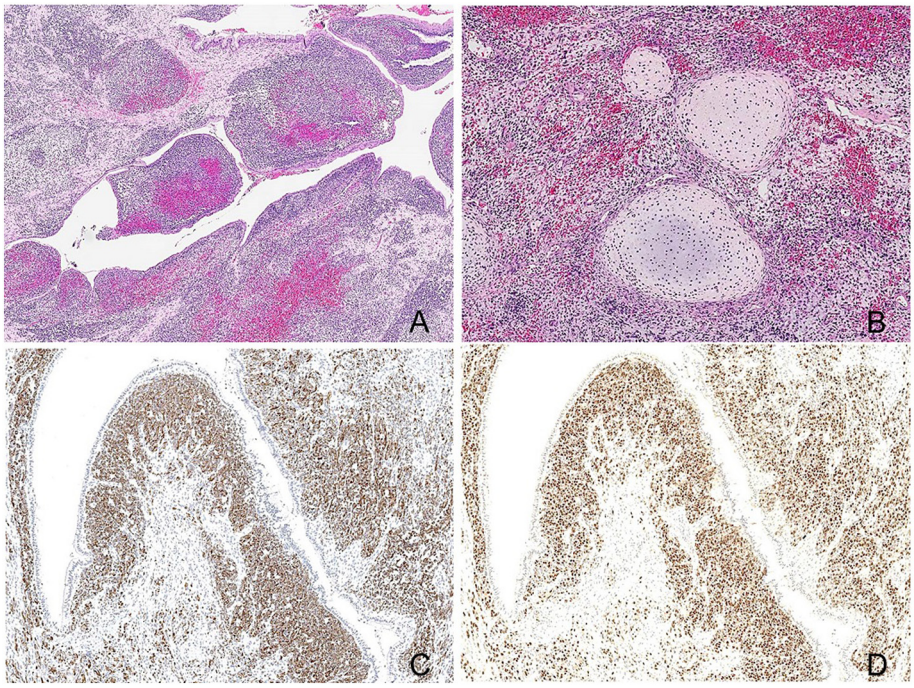

Fig. 2. Histologic evaluation of the cervical mass revealed a phyllodes-like growth pattern with characteristic subepithelial neoplastic stromal condensation (cambium layer) (A) and small islands of heterologous benign fetal cartilage (B). Immunohistochemical staining for muscle marker desmin (C) and skeletal muscle marker myogenin (D) confirmed the diagnosis of rhabdomyosarcoma.

adnexal mass had increased to 7.3 cm with a 4.5 cm irregular solid component. Pelvic examination showed a new 2 × 5 cm cervical polyp which was resected in the office. Histology revealed an embryonal rhabdomyosarcoma at the distal tip of the polyp, confirmed by focal desmin and myogenin staining. Additional staging evaluation did not demonstrate any metastatic lesions.

After extensive counseling, the patient underwent a total laparoscopic hysterectomy with bilateral salpingectomy and a left oophorectomy. Her right ovary appeared normal and was transposed above her pelvic brim to avoid damage from future pelvic radiation therapy, if needed. The hysterectomy specimen revealed no residual rhabdomyosarcoma. The ovarian mass was a SLCT with intermediate differentiation, FIGO stage IA (Fig. 3). Spindle cell elements in the tumor stained negatively for desmin and myogenin, and somatic testing (OncoPanel - Brigham and Women's Hospital molecular diagnostics laboratory) showed two *DICER1* mutations (Table 1). She recovered well from surgery and was referred to endocrinology for re-evaluation of her thyroid nodules.

After her recurrence, somatic mutation testing was performed on her original trachelectomy specimen (OncoPlus Large Tumor Universal Cancer Mutation Analysis Panel - University of Chicago Labs) and compared to *DICER1* mutation testing from the recent polypectomy specimen (ResourcePath, Sterling, VA) (Table 1). The original tumor showed two pathogenic *DICER1* mutations, a pathogenic *BCOR* mutation and variants of unknown significance (VUS) in *BRCA2*, *PALB2* and *MLH1*. The new polyp had one *DICER1* mutation in common, which was presumed to be germline, and a second unique pathogenic mutation, confirming a second primary tumor and not a late recurrence of her primary disease.

Due to the findings on somatic mutation testing, the patient was referred for genetic counseling and testing. Her three-generation pedigree was significant for a brother with benign thyroid biopsy at age 13, her mother had a goiter diagnosed in her twenties, and her maternal aunt had Hashimoto's disease diagnosed in her twenties. A targeted sequence analysis germline genetic test was performed on the patient (Invitae, San Francisco, CA) and identified the pathogenic *DICER1*