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DICER1 associated cervical embryonal rhabdomyosarcoma in a 59-year-old woman

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Embryonal rhabdomyosarcoma (ERMS) of the cervix is a rare mesenchymal tumor accounting for 0.4–1.0 % of all cervical cancer cases. It mainly occurs in pediatric patients and as reported in the literature up to 90 % of cases of ERMS occur in women under the age of 25 years and approximately 60–70 % of cases occur in children younger than 10 years of age (Ibrahim et al., 2017). As adult onset ERMS is extremely rare, it is diagnostically challenging.

We report a case of cervical ERMS in a 59-year-old woman who presented in June 2023 with post-menopausal bleeding for seven months. Physical exam showed a cervical polypoid mass measuring 4.5 cm × 5 cm × 1.9 cm. The vagina and parametrium were free of disease. The rest of the pelvic exam was normal. A biopsy was performed and showed a high-grade tumor, with differential diagnosis including high-grade endometrial stromal sarcoma vs. carcinosarcoma. Pelvic MRI detected a 6.4 cm cervical mass protruding into the vagina with no invasion into paracervical fat and no lymph node involvement. No additional staging was done. The patient underwent a median laparotomy, total abdominal hysterectomy and bilateral oophorectomy, pelvic lymph node dissection and biopsy of the omentum. The surgery was performed by a gynecologist oncologist. There was no residual disease after surgery. The original diagnosis rendered on the hysterectomy specimen was high grade sarcoma with chondrosarcomatous differentiation. This case was subsequently sent to the McGill University Health Centre for review. The tumor showed hypocellular areas with moderately atypical spindle cells in a myxoid stroma and hypercellular areas consisting of solid sheets of primitive-appearing cells. There was a condensed subepithelial layer of tumor cells ("cambium layer"). Focal chondroid differentiation and anaplasia were present, as well as a few entrapped benign endocervical glands (Fig. 1). No conventional component of adenosarcoma (such as a phyllodes morphology depicted by a leaf like growth pattern of benign epithelium with periglandular stromal cuffing) was present. A malignant epithelial component was also absent. On immunohistochemistry (IHC) studies, the tumor cells showed immunoreactivity for desmin and myogenin. Based on these findings, the diagnosis was changed to ERMS of the cervix.

Histologically, ERMS typically exhibits hypocellular and hypercellular areas of primitive mesenchymal cells that show variable degree of skeletal muscle differentiation in a myxoid stroma. The tumor cells commonly form a so called "cambium layer" represented by cells showing condensation beneath the existing benign epithelial lining (Messaoudi et al., 2024; Female Genital Tumours, 2020). On IHC studies, the tumor cells typically stain positive for myogenin and MyoD1, markers indicating skeletal muscle differentiation. Both "cambium layer" and positive reactions to myogenin/MyoD1 have been considered essential diagnostic features for ERMS (Female Genital Tumours, 2020). In recent years, the association between cervical ERMS and *DICER1* pathogenic variants has been established and molecular testing for *DICER1* has been incorporated into the diagnostic workup. In this case, given the patient's age, the possibility of adenosarcoma with rhabdomyosarcomatous differentiation was entertained, but it was ruled out based on the absence of conventional component of adenosarcoma (Table 1). A carcinosarcoma of the endometrium, a tumor that can present as a polypoid mass protruding from the cervix, was also in the differential diagnosis, but this possibility was ruled out due to the

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absence of malignant epithelial component.

DICER1 molecular testing was done for this case to further support the diagnosis of ERMS. Hybrid capture-based next generation sequencing of tumor DNA revealed a hotspot missense variant (c.5125G > A, p.D1709N) as well as a predicted protein truncating variant (c.4339delC, p.E1447fs) in *DICER1* (Fig. 2). The patient was referred to the Medical Genetics service. Genetic consultation did not reveal a history of other DICER1 tumor predisposition syndrome related tumors in the patient or in her family, and germline *DICER1* testing (gene sequencing of coding exons and deletion/duplication analysis, with specific attention paid to the previously identified tumor variants) was negative. Postoperatively the patient received 4 cycles of IVA (ifosfamide, vincristine and dactinomycin) followed by 5 cycles of vincristine and dactinomycin, for a total of 9 cycles of chemotherapy. Surveillance strategy included pelvic exam every 3 months and with PET scan every 3 months for the first 2 years. Unfortunately, the tumor recurred as peritoneal disease with ascites at 15 months post-surgery.

This case is noteworthy because of its onset in late adulthood and its heterogeneous morphology. It has been reported that while ERMS is generally considered as a rare tumor of pediatric patients, it can also affect adults. A recent study of 94 cases of cervical ERMS reported the age range of ERMS patient to be 7–59 (mean, 28; median, 23) years (Devins et al., 2022).This study also reported morphologic variability in ERMS, with cartilage and anaplasia being noted as part of the spectrum. Some authors have reported that chondroid differentiation is more commonly seen in DICER1-associated tumors (González et al., 2022). It

Table 1
Contrasting features between ERMS and adenosarcoma.

	Embryonal rhabdomyosarcoma	Adenosarcoma
Age distribution	Most arise in children	Mean age 48 years old
Clinical presentation	Vaginal bleeding, protruding polypoidal mass	Vaginal bleeding, cervical mass/polyp
Microscopic findings	Cambium layer beneath the surface epithelium; Not a biphasic tumor – Entrapped glands could be present but not part of tumor	Biphasic tumor with a benign glandular component and a malignant stromal component, periglandular stromal cuffing
Immunohistochemical studies	Positive for myogenin and Myo-D1	Positive for myogenin and Myo-D1 only if rhabdo myosarcomatous differentiation
Molecular studies	*DICER1* pathogenic variants in almost all cases	If rhabdomyosarcomatous overgrowth, about 20 % associated with *DICER1* pathogenic variants
Associated syndromes	About 50 % associated with *DICER1* tumor predisposition syndrome	No associated syndromes
Prognosis	Poor prognosis. The overall 5-year survival rate is about 70 %	Indolent course unless sarcomatous overgrowth

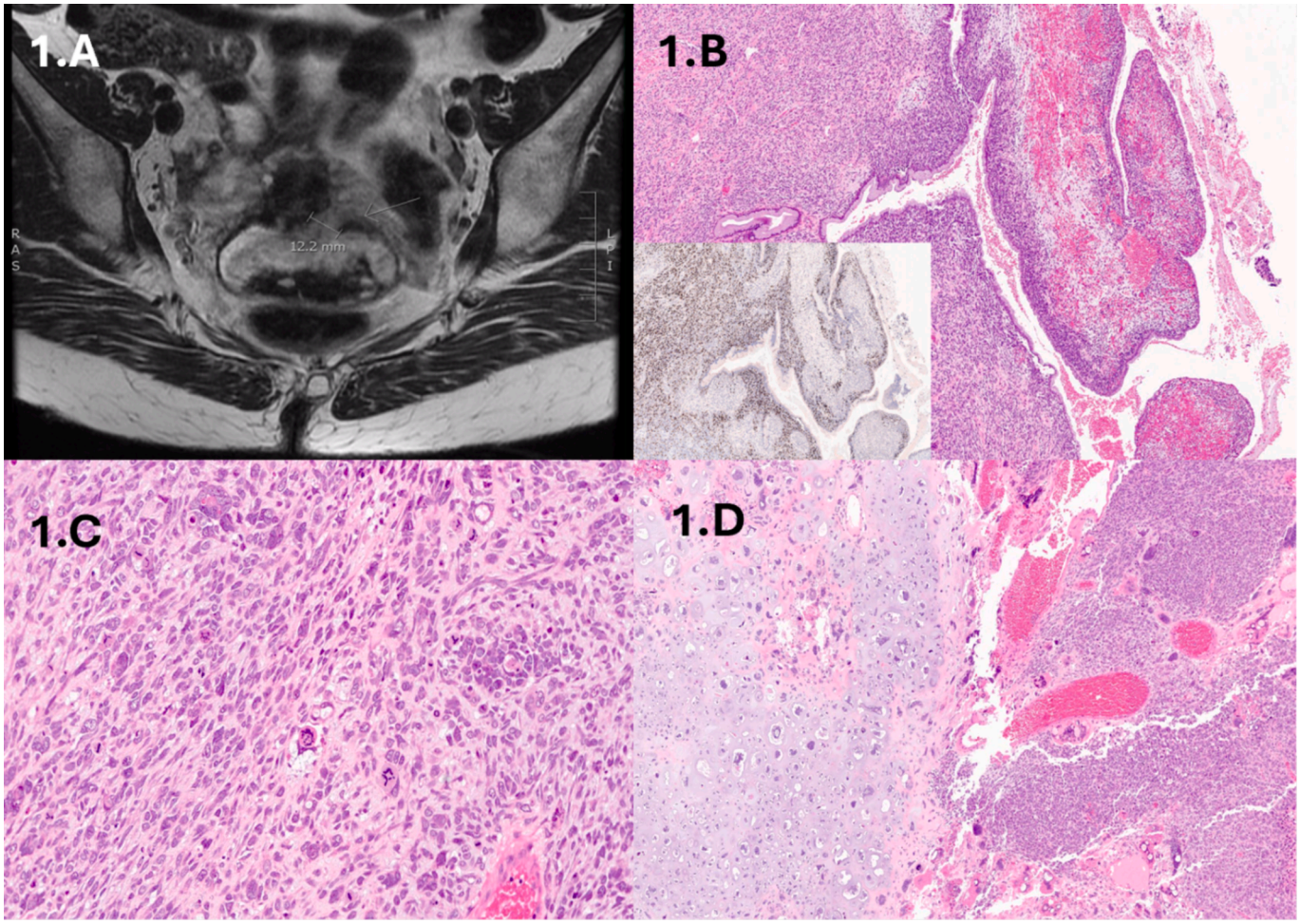

Fig. 1. 1.A: Preoperative MRI shows a pedunculated necrotic cervical lesion originating from a pedicle on the posterior cervix with no infiltration into adjacent organs. 1.B: The tumor cells aggregate underneath the surface epithelium ("cambium layer"). Inset: Positive nuclear staining for myogenin on immunohistochemistry study. 1.C: Areas of anaplasia are present.1.D: Cartilage is focally seen.

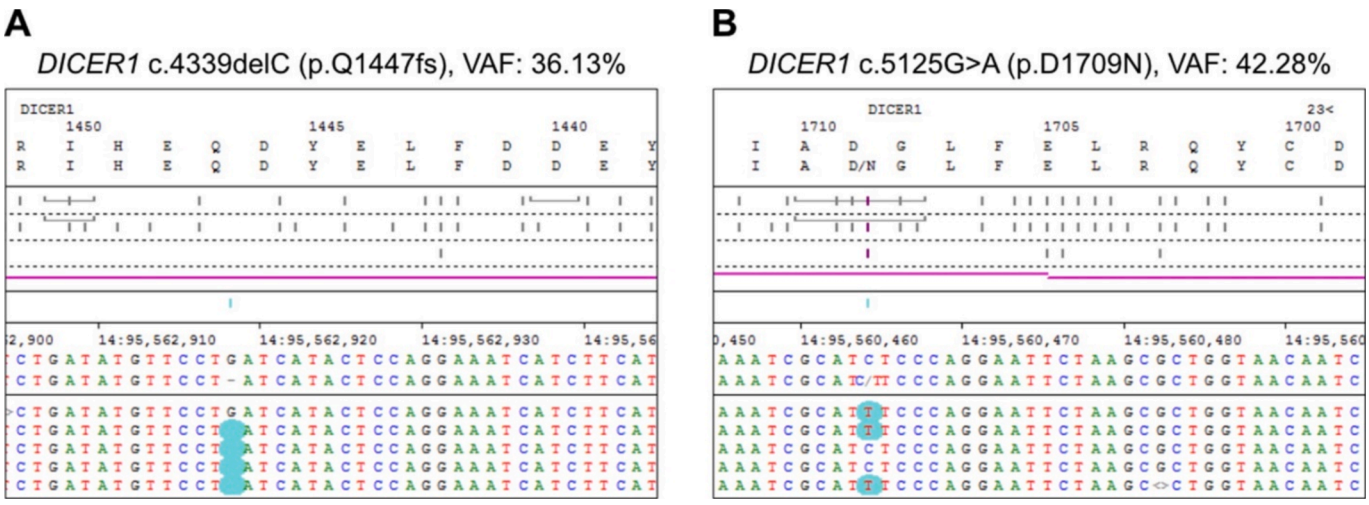

Fig. 2. Panel-based sequencing of tumor DNA revealed (a) a predicted protein truncating variant (c.4339delC, p.Q1447fs) as well as (b) a hotspot missense mutation (c.5125G > A, p.D1709N) in *DICER1*.

is therefore important to be mindful of the possibility of adult onset ERMS, and being aware of the morphologic heterogeneity will help avoid confusion with other tumors and allow for a correct diagnosis to be made.

The association between cervical ERMS and *DICER1* pathogenic variants has been well established. This association can be exploited clinically for diagnostic purpose, as differentiating between ERMS and its mimics is of clinical significance due to management differences, prognostication, and syndromic manifestations (Lautz et al., 2023). For example, the most important differential diagnosis of cervical ERMS is adenosarcoma with rhabdomyosarcomatous differentiation, a tumor that mainly affects postmenopausal women and shows considerable morphological overlap with ERMS. Testing for *DICER1* pathogenic variants can help in distinguishing between these two entities as almost all cases of cervical ERMS harbor *DICER1* pathogenic variants, while only approximately 20 % of cervical adenosarcoma carry it. Therefore, a negative result following *DICER1* molecular testing makes ERMS less likely (Apellaniz-Ruiz et al., 2021). The prognosis of ERMS is generally poor (Baiocchi et al., 2011; Nasioudis et al., 2017) while adenosarcoma typically has indolent course (but adenosarcoma with sarcomatous overgrowth has a worse prognosis). ERMS is typically treated by surgical excision followed by adjuvant chemotherapy, while adenosarcomas in low stage disease often require complete surgical resection only, without adjuvant therapy (Messaoudi et al., 2024; Rizzo et al., 2019). Note that adenosarcoma with sarcomatous overgrowth might be treated as a sarcoma.

About 50 % of *DICER1* pathogenic variants associated with ERMS are germline variants associated with DICER1 tumor predisposition syndrome (de Kock et al., 2020). This syndrome is transmitted with an autosomal dominant inheritance pattern but exhibits reduced penetrance (many individuals carrying a germline pathogenic variant will not present clinical manifestation of the disease), for these reasons the absence of a positive family history is not uncommon. This condition should be suspected in children under the age of six years affected with pleuropulmonary blastoma, as well as in young individuals (under the age of 40) presenting with other tumors including thyroid gland neoplasia (multinodular goiter, adenomas, and/or thyroid cancer), ovarian tumors (Sertoli-Leydig cell tumor, gynandroblastoma, and sarcoma), cystic nephroma, ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, pituitary blastoma, pineoblastoma, or central nervous system sarcoma, among other entities (Schultz et al., 2014). The diagnosis of DICER1 tumor predisposition syndrome is established by the identification of a heterozygous germline pathogenic variant in *DICER1*, therefore molecular testing is mandatory in individuals presenting with suggestive features, such as in the case of ERMS.

While pediatric cervical ERMS is among the prototypical malignancies that arise in DICER1 tumor predisposition syndrome, occasional adult onset ERMS with *DICER1* germline pathogenic variants have also been reported. De Kock et al reported two cases of adult onset DICER1 associated ERMS, one of them (in a 53-year-old) had carried a germline pathogenic variant (Apellaniz-Ruiz et al., 2021; de Kock et al., 2019; de Kock et al., 2016). Therefore, even in adult onset ERMS, it is still relevant to rule out DICER1 tumor predisposition syndrome given its significant clinical implications including the need to monitor the patient for other DICER1-associated neoplasia, and to offer predictive testing to family members.

Our case highlights the importance of keeping ERMS in the differential diagnoses of a cervical sarcoma in an adult patient. Being aware that ERMS can have an onset in adulthood, knowing its different morphological components, and performing molecular studies to identify *DICER1* variants can help reaching the correct diagnosis, which will lead to a significant clinical impact regarding treatment choice, prognostication, and referral for genetic counseling.

Consent statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRediT authorship contribution statement

Mona Alfaraidi: Writing – review & editing, Writing – original draft. **Felix KF Kommoss:** Writing – review & editing, Writing – original draft. **Leonie-Anne Dallaire-Nantel:** Writing – review & editing. **Nelly Sabbaghian:** Writing – review & editing. **Josianne Leblanc:** Writing – review & editing. **Xing Zeng:** Writing – review & editing. **Tania Cruz Marino:** Writing – review & editing. **William D Foulkes:** Writing – review & editing. **Lili Fu:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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