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Case report

CIC-DUX4 rearranged uterine cervix round-cell sarcoma exhibiting near-complete pathologic response following radiation and neoadjuvant chemotherapy: A case report

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1. Background

Sarcomas harboring CIC-DUX4 fusions have recently been described as highly aggressive variants of small blue round cell tumors, affecting predominantly children and young adults. This uncommon, molecularly-defined entity can arise from various anatomical locations and often involves deep soft-tissue structures and skin. Although clinically analogous and commonly confounded with Ewing sarcoma (ES), several studies have recently shown that this unique condition maintains morphologic and pathological features distinct from ES. In this report, we present and discuss a case of CIC-rearranged sarcoma of the uterine cervix exhibiting a near-complete pathologic response following neoadjuvant chemotherapy. Due to rarity of this entity, this report is a relevant contribution to the scientific community and clinicians facing this challenging and often ominous disease.

2. Introduction

Undifferentiated round cell sarcomas (URCS) and Ewing Sarcoma (ES) are a heterogeneous group of bone/soft tissue neoplasms characterized by small blue round cell morphology and overlapping immunohistochemical findings, nevertheless with diversified molecular abnormalities. One particular group of EWSR-1-negative URCS is characterized by cells harboring a Capicua transcriptional repressor (CIC) rearrangement, predominantly resulting from a gene fusion between CIC (19q13) and one of two Double-Homeobox (DUX4) *retro*-genes (4q35 or 10q26) (Vanderplanck et al., 2018; Kawamura-Saito et al., 2006). CIC-DUX4 rearranged sarcomas (CDS) belong to a highly aggressive subgroup of small round cell sarcomas, affecting a wide age range (6–81 years), but predominantly occurring in children and young adults (mean age, 30 years), with a slight male predominance (Vanderplanck et al., 2018). CDS most often arise in the limbs, and appear to pursue an aggressive clinical course, with frequent early metastasis (Italiano et al., 2012).

These tumors were formerly classified as Ewing-like Sarcomas (ES), but although CDS and ES share morphologic similarities, evidence suggests distinct molecular features. CDS lack translocations of the Ewing Sarcoma breaking point region 1 (EWSR1) and of the E26 transformation-specific (ETS) gene rearrangements, which are pathognomonic of ES, while CDS have variable CD99 expression compared to its stronger-staining ES counterpart (Specht et al., 2014).

ES of the female genital tract is a rare subset of sarcomas that usually involves the ovaries and may present in the vulva, vagina, cervix, and uterus. Conversely, CDS affects the skin and soft tissues of the trunk, pelvis, and extremities (Carter and Patel, 2019). Antonescu and colleagues had shown that CIC-fusion positive URCS have a significantly unfavorable outcomes compared to ES, with inferior 5-year overall survival (43% for the CIC-rearranged cohort versus 77% for the ES cohort) (Antonescu et al., 2017).

In this article, we report the first case to our knowledge of a CDS of the uterine cervix, that adds to a single report of CDS evolving gynecological system (Sedighim et al., 2020).

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3. Case report

We herein describe a case of a 50-year-old female patient with a past medical history of thalassemia minor and without relevant familial history of cancer. Her latest gynecologic examination was performed in November 2019 and said without abnormalities. She first reported vaginal bleeding in April 2020, which prompted additional investigation.

Magnetic resonance imaging (MRI) of the pelvis exhibited an expansive formation with a high heterogeneous signal in T1 and T2-weighted sequences, homogeneous gadolinium-enhancement, and diffusion restriction affecting the superiors two-thirds of the uterine cervix, with extension to the anterior vaginal wall, determining a slight bulging of it, measuring 3.2 × 1.9 × 4.0 cm. No suspicious regional lymph nodes were noted (Fig. 1A and B).

Subsequent work-up included a 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), which exhibited an FDG-enhancing cervical lesion measuring 4.0 cm with maximum standardized uptake (SUVmax) of 12.0 and apparent left parametrial involvement (Fig. 1C and D), but no signs of distant disease.

A uterine cervix biopsy was performed; histological sections showed solid proliferation of small to medium-sized neoplastic cells (Fig. 2A), with extensive areas of necrosis and hemorrhage, without desmoplasia of stroma. Tumor cells were highly pleomorphic, with vesicular nuclei presenting one or multiple prominent nucleoli. Mitotic activity was brisk, with numerous atypical figures. Most of the neoplastic cells were epithelioid with plasmacytoid/rhabdoid features, characterized by eccentric nuclei with light eosinophilic or amphophilic cytoplasm (Fig. 2B). There were foci with less cohesive cells and pseudoacinar arrangements.

Immunohistochemistry (IHC) staining was performed, including markers for WT1, CD99, FLI1, p53, p16, vimentin, cytokeratins AE1/AE3, desmin, myogenin, INI1 (SMARCB1), PAX8, TLE1, CD138, MelanA, HMB45, p63, chromogranin, synaptophysin, CD34, and CD31.

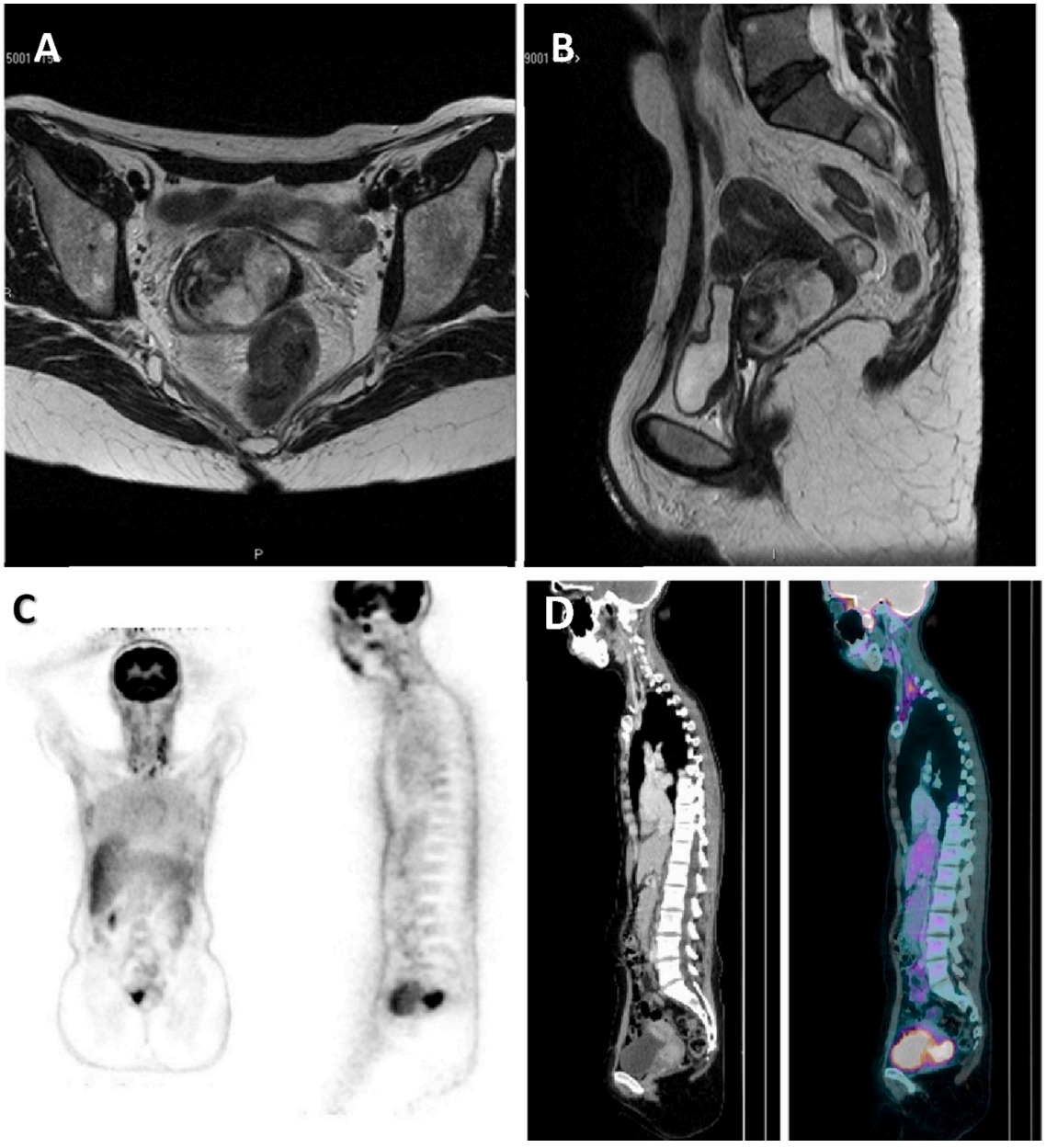

Fig. 1. (A and B) Representative images of abnormal findings on the baseline MRI of the pelvis. (C and D) PET/CT scan images showing a hypermetabolic cervical lesion upon initial diagnosis.

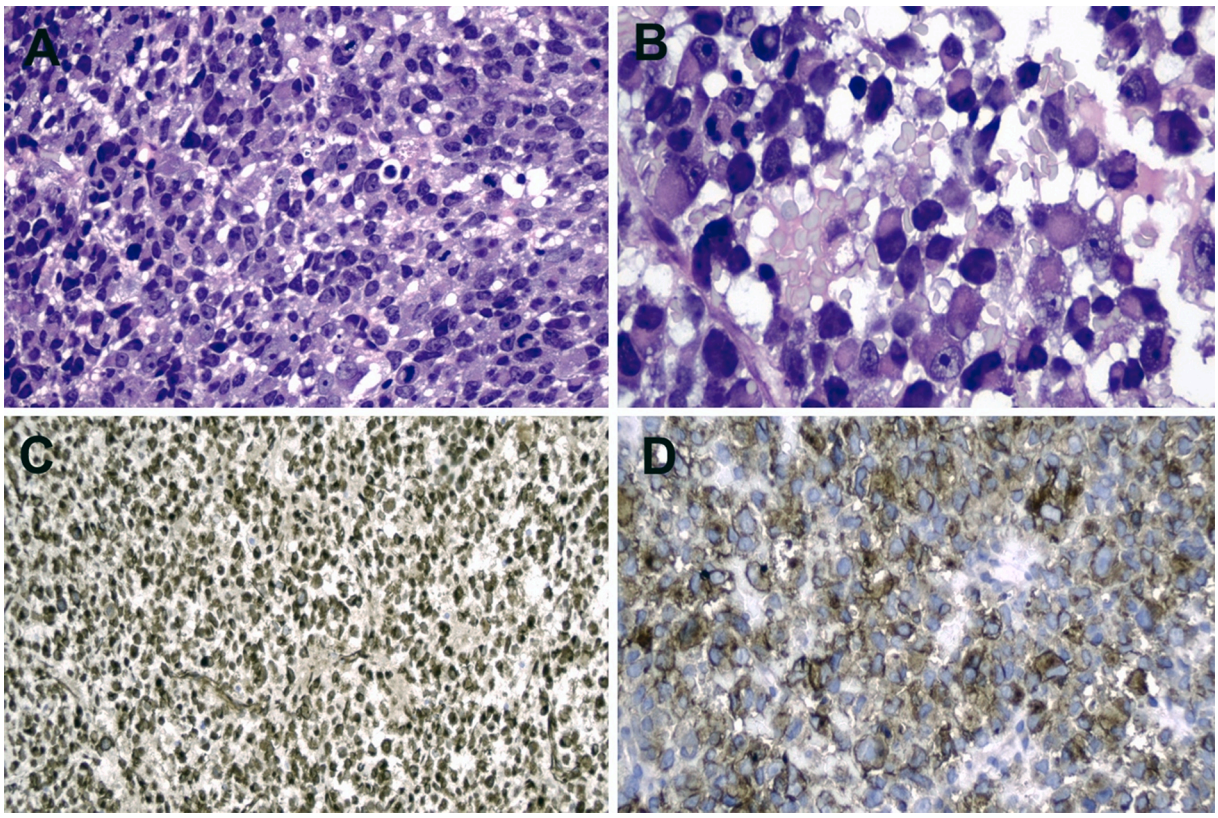

Fig. 2. Histologic findings and immunohistochemistry in cervix CDS. (A) Solid proliferation of pleomorphic small to medium-sized tumor cells. (B) Plasmacytoid/rhabdoid features present in most of the neoplastic cells, some of them with vesicular nuclei and prominent nucleoli. (C) Immunohistochemistry positive for WT1 and (D) CD99.

Immunohistochemical stains were diffusely positive for vimentin, WT1 (Fig. 2C), CD99 (Fig. 2D), and p16; INI1 was preserved. Cytokeratins AE1/AE3, CD138, and FLI1 were positive in scattered tumor cells. No stain was noted for all other markers. The slides were examined by three pathology centers, none of them reaching a definitive diagnosis in addition to malignant undifferentiated neoplasia. It was not possible to establish any association between the morphological pattern of the neoplasia and the location in the cervix.

Molecular evaluation through next-generation sequencing (NGS) using FoundationOne®Heme panel revealed microsatellite stability, tumor mutational burden of 2 Muts/Mb, and CIC-DUX4, EGFL7-NOTCH1, and SEC16A-NOTCH1 fusions. After the CIC-DUX4 fusion information, the pathology slides were reviewed, and the findings were considered consistent with CIC-rearranged sarcoma.

Due to persistent vaginal bleeding after the biopsy, the patient received hypofractionated hemostatic radiation therapy to a total dose of 12 Grays (Gy) divided in 3 fractions of 4 Gy. Upon completion of radiotherapy, decision was made to proceed with neoadjuvant chemotherapy with vincristine, adriamycin, cyclophosphamide (VAC), alternating with ifosfamide and etoposide (IE), according to standard protocols applied to ES (Grier et al., 2003). Re-staging scans following four cycles of systemic therapy revealed a complete response of the cervical lesions on MRI performed at this point. Patient then underwent a bilateral salpingo-oophorectomy and total hysterectomy, without lymph-node dissection **(**Fig. 3**)**. Pathology report revealed a near-complete tumor regression, exhibiting minimal residual disease with a neoplasic cell agregate measuring 0,4mm. Tumoral regression area around residual cervical neoplasia measured 3.0 mm **(**Fig. 3**).**

4. Discussion

To our knowledge, this is the first reported case of a CIC-rearranged round cell sarcoma of the uterine cervix. Sarcomas with CIC-DUX4 fusion account for up to 68% of the URCS negative for EWSR1 rearrangements (Italiano et al., 2012). Several CDS cases have been referenced in larger case series in the pelvis, perineum, and retroperitoneum (Antonescu et al., 2017; Yoshida et al., 2016) and their clinical course and treatment have been poorly characterized. Until recently, CDS was considered a part of the ES family of tumors and treated according to ES protocols. However, over the last several years, mounting evidence suggests that CDS is a distinct entity from ES, not only genetically (Brčić et al., 2020), but also with regards to clinical course, response to treatment, prognosis and pathologic features (Specht et al., 2014; Antonescu et al., 2017; Yoshida et al., 2016).

Although both ES and CDS express CD99 on immunohistochemical analysis, investigators have shown that CDS often displays a focal or patchy staining pattern (Specht et al., 2014). WT1 nuclear expression is also frequently seen in CDS. These findings are consistent with our current report. A definitive diagnosis of CDS depends on the molecular profiling of the tumor. This entity is defined by peculiar cytogenetic abnormalities, including t(4;19) or t(10;19) with CIC-DUX4 fusion, while ES have the pathognomonic EWSR1-ETS translocation (Specht et al., 2014). A gold standard test for the identification of known and unknown genetic alterations is still not established in this setting. Using CIC break-apart FISH analysis, a false-negative rate of 14% for CIC-rearranged sarcomas was reported (Yoshida et al., 2017). It has been estimated that approximately one third of sarcomas carry a detectable driver fusion gene (Barr and Zhang, 2006). RT-PCR has a higher sensitivity for detection of specific fusions in cases with small amounts of tumor tissue, making exclusion of other differential diagnoses possible (Bridge et al., 2006). Although not widely available, NGS platforms covering translocations are becoming standard ancillary techniques. The use of the NGS platform FoundationOne®Heme Panel, demonstrating the CIC-DUX4 fusion, was essential for our patient's accurate diagnosis.

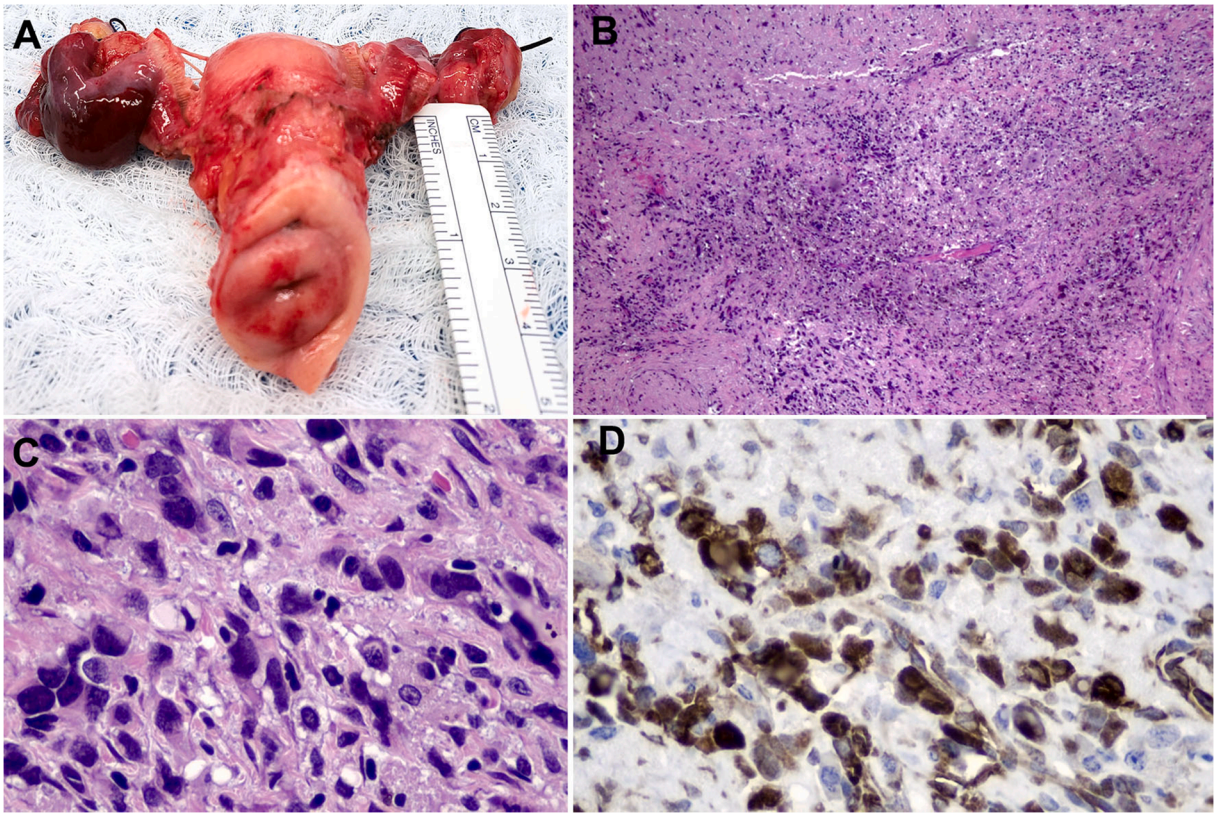

Fig. 3. (A) Gross surgical specimen with no signs of macroscopic disease. (B) Area of tumor regression showing oedema, mononuclear inflammatory cells and some suspicious cells. (C) Detail of area with residual tumor cells (D) highlighted by WT1 stain.

Currently, there is no therapeutic regimen tailored to CDS, despite the rapid and aggressive clinical course and poor outcomes. In addition, rearranged sarcomas are reported to be less sensitive to standard Ewing chemotherapy regimens (Mariño-Enríquez and Fletcher, 2014), which are often extrapolated for the treatment of CDS patients. Given its characteristics, one reasonable approach for localized disease can include surgery to achieve local control as quickly as possible, followed by adjuvant chemotherapy, or, in the setting of large masses or locally advanced disease, systemic therapy upfront, followed by definitive treatment, including surgery or radiation. There are few reports of CDS in unusual anatomical locations, like in the dermis, showing an indolent clinical course of these superficially located tumors, unlike the behavior of most CDS tumors described in the literature (Yoshida et al., 2016; Brčić et al., 2020). Our patient was submitted to neoadjuvant chemotherapy treatment with vincristine, adriamycin, cyclophosphamide alternating with ifosfamide and etoposide, achieving a clinical complete response on imaging assessment before total abdominal hysterectomy, with a minimal residual disease later observed in the surgical specimen.

As clear treatment guidelines for patients with CIC-DUX4 fusion sarcomas are lacking, case reports such as ours should be collected in prospective registries. Thus, important information and data on diagnostics, treatment, and follow-up of these patients could be shared within the international sarcoma community in order to guide future clinical management of this condition. Taking that into consideration, together with the distinctive, aggressive clinical behavior in the majority of reported CDS cases, these tumors must be separated from ES, as well as from other URCSs and small blue round cell sarcomas. Correct classification has an immense impact on the appropriate management and establishment of new treatment protocols for these patients.

In conclusion, we report a case of CIC-rearranged sarcoma of the uterine cervix with an aggressive clinical course that showed a near-complete pathologic response to radiation and systemic chemotherapy followed by complete surgical resection. Our patient is currently on adjuvant chemotherapy with no evidence of disease. The best chemotherapy regimen for CIC-rearranged sarcoma is yet to be defined and complete surgical resection is key. Other chemotherapy agents such as trabectedin and novel therapies possibly targeting highly upregulated downstream proteins such as the PEA3 family of transcription factors are worthy of exploration.

Contributions

All authors contributed significantly to the manuscript. All authors provided critique and feedback on the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate/consent for publication

The ethics committee of the Hospital Sírio-Libanês approved this case report. The patient provided consent and agreed to share her medical information for publication.

Declaration of Competing Interest

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

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