Gynecologic Oncology Reports 33 (2020) 100592

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

CIC-rearranged round cell (Ewing-like) sarcoma of the uterus: Review of the literature

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ARTICLE INFO

Keywords:
CIC-rearranged round cell sarcoma
Ewing sarcoma
Uterine sarcoma
Uterine cancer
Ewing-like sarcoma

ABSTRACT

CIC-rearranged round cell sarcoma (CRS) is a rare entity that presents in various anatomical locations and involves deep soft-tissue structures and skin. Although commonly confused with and clinically similar to Ewing sarcoma (ES), investigators have recently shown that this unique condition maintains morphologic and pathologic features that are distinct from ES. In this report, we present and discuss a case of CRS of the uterus, the first of its kind to be reported in the English-language literature. We urge the scientific community to continue its investigations in elucidating the features of this entity, as young women who suffer from this condition have dismal prognoses and currently do not have access to therapeutic options for cure.

1. Introduction

Ewing sarcoma (ES) is a family of malignancies within the primitive neuroectodermal tumor (PNET) spectrum (Jawad et al., 2009; Loverro et al., 2015) which share common defining histologic and cytologic characteristics of neuroectodermal origin. Up to 85% of the time, these tumors display a translocation involving EWSR1 and ETS family transcription factors (Mashriqi et al., 2015; Pappo and Dirksen, 2018). ES of the female genital tract is a rare subset that most commonly involves the ovaries and may present in the vulva, vagina, cervix, and uterus (Loverro et al., 2015). To date, approximately 50 such cases have been reported in the literature, with most (75%) presenting in premenopausal women (Ren et al., 2011).

Round cell sarcoma, which is morphologically similar to ES and had once been considered to be the same entity, has recently been characterized as a distinct pathology based on its unique immunohistochemical and cytogenetic profile (Yoshimoto et al., 2017). Although these round cell tumors may also display overexpression of ETS transcription factors like those found in ES, this entity exclusively harbors a CIC-DUX4 translocation (Pappo and Dirksen, 2018; Specht et al., 2014). Both ES and CIC-rearranged round cell sarcomas (CRS) stain positively for CD99 on immunohistochemistry. However, CRS often shows diffuse staining of CD99 compared to its stronger-staining ES counterpart. Furthermore, CRS often expresses ETV4 and occasionally WT-1, ERG and FLI, while ES expresses NKX2-2.6 (Brcic et al., 2019; Sbaraglia et al., 2019).

Notably, CRS has been previously reported to affect the skin and soft tissues of the trunk, pelvis, and extremities (Carter and Patel, 2019). Here, we present a case of CRS of the uterus, significant for its uncommon immunohistochemical and cytogenetic profile and unique presentation in a location that is unreported in the English language literature. Further, we discuss the current methodology for clinical management and highlight the need for investigations to more effectively combat this pathologic entity.

2. Case presentation

A 28-year-old female with no significant medical history presented to the emergency department in an outside hospital complaining of abdominal pain. Ultrasound imaging showed a pelvic mass, interpreted to be a uterine leiomyoma. The patient was taken for laparoscopic uterine myomectomy, but the procedure was aborted, as the mass was firmly adherent to the uterine wall. No biopsies were taken at the time. The patient was subsequently placed on oral contraceptive pills, which

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https://doi.org/10.1016/j.gore.2020.100592
Received 28 February 2020; Received in revised form 15 May 2020; Accepted 27 May 2020
Available online 30 May 2020

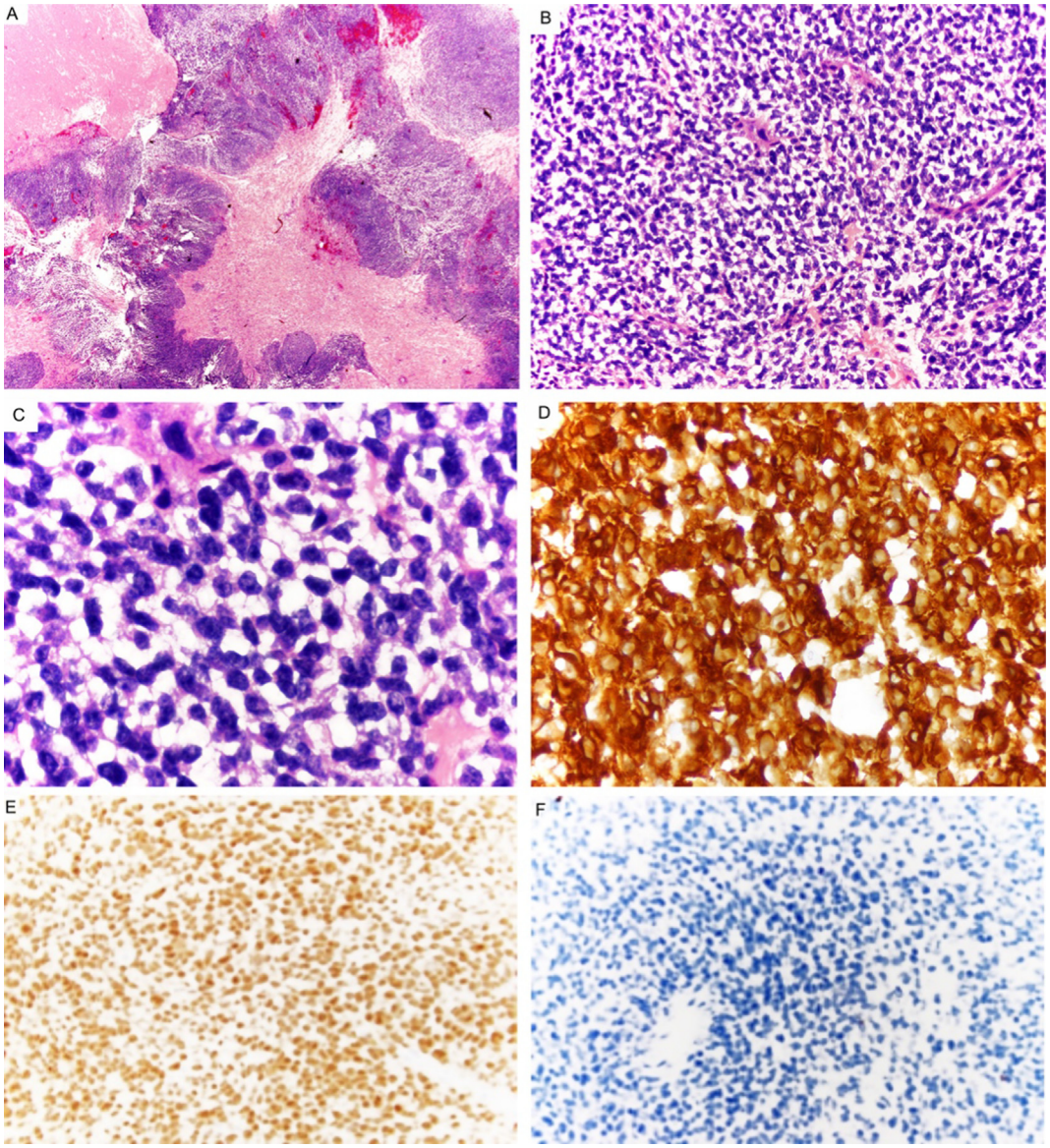

Fig. 1. A round cell sarcoma with solid and often nodular growth pattern and extensive areas of necrosis was noted (A, HE 2×). The neoplasm was composed by small to medium size round to ovoid cells with light eosinophilic to clear cytoplasm and eccentric nuclei (B and C, HE 4× and 10×). Immunohistochemistry showed positivity for CD99 (D), ETV4 (E), and negativity for pan-cytokeratin (F).

did not alleviate her symptoms.

Six months after her initial presentation, her pain progressed, to the point of limiting ambulation. Transvaginal ultrasound at the time showed significant growth of the suspected leiomyoma; attempted excision was planned. After significant delay due to insurance difficulties, the patient was taken for an exploratory laparotomy, total abdominal hysterectomy and right salpingo-oophorectomy. Intraoperative exploration showed gross extension of the tumor into the left pelvic sidewall in approximation to the sigmoid colon, without involvement of the ovarian or fallopian tubes. An R2 resection was performed with residual macroscopic residual tumor. Pathology demonstrated a cytologically malignant neoplasm, consisting of sheets of cells with variable palely amphophilic cytoplasm and rounded, tapering vesicular nuclei with small nucleoli, numerous mitotic figures, and areas of necrosis. Immunohistochemical (IHC) staining showed pan-keratin negativity, multifocal CD99 positivity CD99, diffuse positivity for ETV4, and mildly positivity for CD10 (Fig. 1). The specimen was negative for NKX2.2, pan-keratin, desmin, and WT-1 (staining not shown). FISH amplification studies demonstrated presence of CIC gene rearrangement (most likely CIC-DUX4 gene fusion). Targeted new generation sequencing revealed that the tumor had a low mutational burden and stable microsatellite status. (Additional immunohistochemistry was positive for TOP2A and negative for MGMT and TUBB3). Taken together, these findings classified this entity as a round cell sarcoma of the uterus.

One month after surgical resection and diagnosis, an outside hospital Computed Tomography (CT) scan was performed, and it reported tumor recurrence with an 11 cm pelvic mass. Positron emission tomography/computed tomography (PET/CT) performed at the time reported metastatic lesions to the liver. She was urgently treated with combination chemotherapy consisting of doxorubicin (90 mg/m^2 bolus with dexrazoxane cardioprotection) with ifosfamide (10 gm/m^2 divided over 5 days) (AI) plus alternating vincristine, doxorubicin, and cyclophosphamide (VAC) chemotherapy (dosage given unavailable). One and a half months after beginning chemotherapy, she developed abdominal pain likely secondary to tumor response and follow-up CT scans were reported as showing partial response to therapy. She remained on VAC, alternating with AI. However, 2.5 months into her chemotherapy regimen, her abdominal pain worsened, and repeat CT

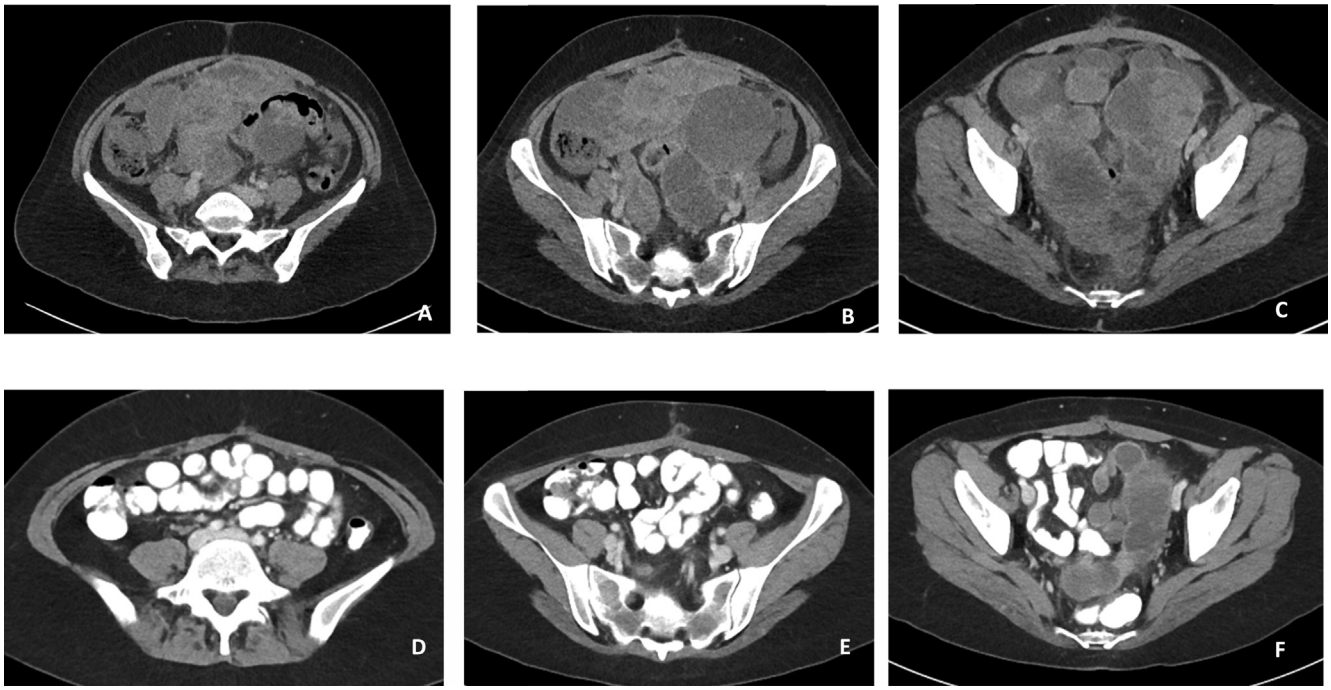

Fig. 2. Representative Computer Tomography Scan images of abnormal findings in abdomen and pelvis. 2 (A–C): Show tumor progression with large multilobulated abdominopelvic masses refractory to gemcitabine/paclitaxel (treated at outside institution) and before starting chemotherapy with high dose ifosfamide (when care was transferred to our institution). 2 (D–F): Show tumor response to therapy at 5 months interval after 4 of cycles with high dose ifosfamide.

scans reported new progression of disease, including accompanying peritoneal sarcomatosis. She was immediately started on gemcitabine/paclitaxel. The patient received two doses of this therapy without clinical or radiographic response (Fig. 2, A–C). At this point (6 months after her surgical diagnosis), the patient's care was transferred to our institution and was started on a cycle of high dose ifosfamide 14 gm/m^2 (2 gm/m^2 infused over 2 h every 12 h for 7 doses) for 6 cycles; she tolerated therapy well. After cycle 4 (8 months from surgical diagnosis), CT scan demonstrated interval decrease in peritoneal disease (Fig. 2, D–F). Over the course of her therapy with ifosfamide, the patient visited the emergency department multiple times, suffering from neutropenic fever and partial obstruction, secondary to external mass compression of the sigmoid colon.

Upon completion of chemotherapy the patient's disease quickly progressed while on a 2-month drug holiday (11 months from surgical diagnosis) (Fig. 3A). She was unable to tolerate PO intake due to sigmoid obstruction. A palliative resection of the residual sarcoma including proctectomy, sigmoidectomy with a descending colostomy (Hartman pouch) was performed. Fig. 4 shows gross pathology of the surgical specimen. IHC of the specimen confirmed previous diagnosis of CIC-rearranged round cell sarcoma.

Due to the rapidly progressive nature of her disease, tumor recurrence and subsequent colonic obstruction recurred just one month later. The patient decided to withdraw all treatment and continue only with palliative ifosfamide chemotherapy; she subsequently opted for hospice care and succumbed to her disease, 15 months after her surgical diagnosis.

3. Discussion

This is the first reported case of a CIC-rearranged round cell sarcoma (CRS) of the uterus. While several cases of CRS have been referenced in larger case series in the pelvis, perineum, and retroperitoneum (Antonescu et al., 2017; Yoshida et al., 2016) detailed descriptions, including clinical course and treatment, have not been provided.

Until recently, CRS was considered a part of the Ewing sarcoma (ES) family of tumors and treated according to ES protocols. However, over the last several years there has been an increasing amount of evidence that CRS is genetically (Brcic et al., 2019), clinically (Antonescu et al., 2017; Yoshida et al., 2016), and pathologically (Specht et al., 2014) distinct from ES.

Although both ES and CRS express CD99 on immunohistochemical analysis, investigators have shown that CRS often displays a focal or patchy staining pattern (Specht et al., 2014) which is consistent with our current report. NKX2.2, pan-keratin, and desmin all stained negatively, confirming previous reports of CRS and indicates that the pathology is not likely classical ES. However, unlike what Specht et al. reports, our current pathology does not stain positively for WT-1. Definitive diagnosis of CRS depends on the cytologic profiling of the tumor. This pathology most commonly contains cytogenetic abnormalities including t(4;19) or t(10;19) with *CIC-DUX4* fusion while Ewing sarcomas have the pathognomonic *EWSR1-ETS* translocation (Specht et al., 2014). Our patient's pathology was positive for CIC gene rearrangement.

Clinically, CRS most commonly presents in the deep soft tissues of the extremities, trunk, or head and neck rather than in bones (as seen with ES). This pathology occurs in patients in adulthood with the highest prevalence in the fourth decade compared to in the second decade in ES and may have a more aggressive clinical course than ES (Antonescu et al., 2017). 5-year overall survival in the largest cohorts (Antonescu et al., 2017; Yoshida et al., 2016) has been observed at around 40% or lower, which is about half the overall survival observed in matched controls with EWSR1-rearranged ES. Even when considering only patients presenting with localized disease, 5-year survival still was only about 50% (Antonescu et al., 2017).

ES classically demonstrates response to systemic chemotherapy. Due to clinicians' unfamiliarity with CRS, this entity has mostly been treated with ES protocols (Antonescu et al., 2017), which typically include vincristine, doxorubicin, and cyclophophamide along with ifosfamide and etoposide (VDC/IE; Grier et al., 2003). However, they have shown minimal and short-lived response to chemotherapy, and, in those with responses, drug resistance has rapidly developed with subsequent

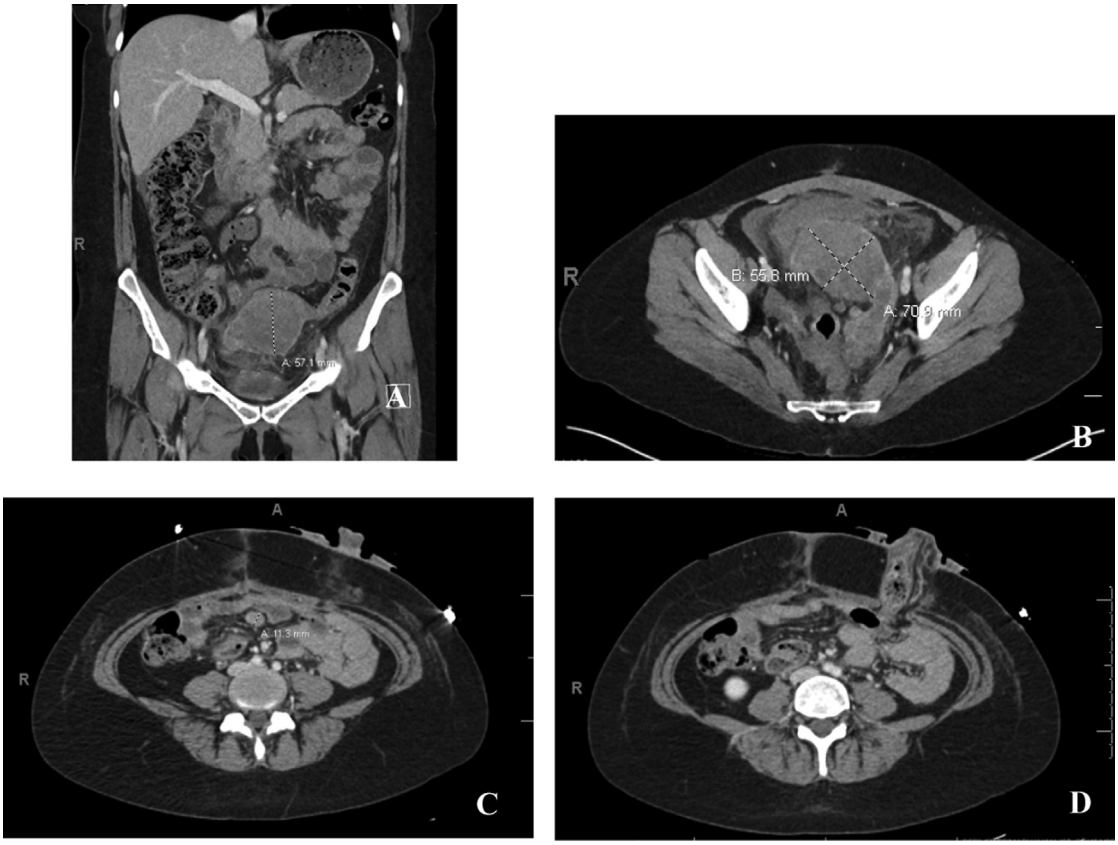

Fig. 3. Contrast CT studies of abdomen and pelvis demonstrating recurrence of CIC-Sarcoma of the uterus before (A, B) and after (C, D) subtotal radical resection and simultaneous proctectomy, sigmoidectomy, and descending colostomy.

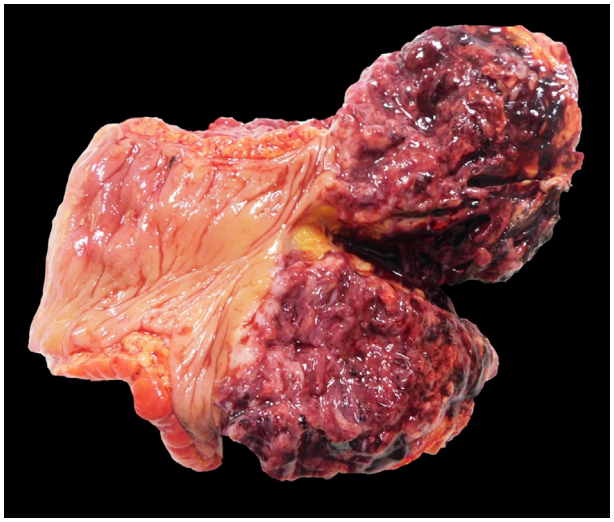

Fig. 4. Gross surgical specimen: A 10 × 8 × 7.5 cm necrotic well circumscribed mass was identified involving the periocolic fatty tissue of a segment of colon. The mass extended up to the external muscle layer of the colon, up to 0.2 cm of the surface of the pericolonic fatty tissue, 6.0 and 3.5 cm from the colonic surgical margins and 3.4 cm from the mesenteric surgical margin. The colonic mucosa was red-tan and normally folded.

disease progression (Haidar et al., 2015). Even for the small minority of patients with a robust pathologic response to chemotherapy, no correlation has been shown with survival (Antonescu et al., 2017). For patients with localized disease, those treated with surgery and adjuvant chemotherapy have displayed a trend toward improved overall survival compared to those treated with neoadjuvant chemotherapy followed by surgery (Antonescu et al., 2017), suggesting a role for adjuvant chemotherapy.

Currently, optimal treatment for CRS is poorly defined but based on the available evidence the authors have several recommendations for staging and treatment. Since CRS frequently metastasizes to the lungs and there have also been reported cases of metastasis to the brain, liver, lymph nodes, and bone (Haidar et al., 2015; Yoshida et al., 2016), PET/CT should be obtained to assess for distant metastasis and inform the subsequent decision regarding surgery. Given the rapid and aggressive clinical course and poor outcomes seen in the above retrospective data along with the poor sensitivity to chemotherapy, localized disease may best be treated with surgery to achieve local control as quickly as possible followed by adjuvant chemotherapy.

There are no established targeted therapies for CRS. However, research is ongoing regarding potential molecular targets for therapy (Yoshimoto et al., 2017). Treatments used for other sarcomas are being investigated as potential treatments for CRS, with some promising early *in vivo* results in mice with the chemotherapeutic agent, trabectedin (Yoshimoto et al., 2017). Further research is needed to better elucidate and establish promising potential therapies for CRS and to advance their use to clinical trials and/or expanded use.

In conclusion, we report a case of CIC-rearranged sarcoma of the uterus with aggressive clinical course that transiently responded to chemotherapy and progressed rapidly after surgical resection. Early detection, oncologic R0 excision while the disease is localized, and consideration of an appropriate adjuvant chemotherapy regimen is essential to optimize outcomes.

Informed consent

Informed consent has been established and the patient in this case has agreed to sharing her medical information for publication.

CRediT authorship contribution statement

Shaina Sedighim: Conceptualization, Investigation, Resources, Writing - original draft, Writing - review & editing, Supervision. **Jonathan Burke:** Conceptualization, Investigation, Resources, Writing - original draft, Writing - review & editing, Supervision. **Douglas Schneider:** Conceptualization, Investigation, Resources, Writing - original draft. **Talia Kamdjou:** Conceptualization, Investigation, Resources, Writing - original draft. **Julio A. Diaz-Perez:** Investigation, Resources. **Jonathan Trent:** Investigation, Resources, Writing - review & editing, Supervision. **Mecker Möller:** Investigation, Resources, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgements

We would like to acknowledge the contribution of Dr. Andrew E. Rosenberg, Director of Bone and Soft Tissue Pathology at the University of Miami Miller School of Medicine, for providing analysis of the pathological specimens used in this case report. We would further like to acknowledge the contribution of Dr. Christopher D.M. Fletcher, Professor and Vice Chair of Anatomic Pathology in the Department of Pathology at Brigham and Women's Hospital who provided us with the pathology slides and FISH analysis for the primary diagnosis of the described patient's condition.

References

Antonescu, C.R., Owosho, A.A., Zhang, L., Chen, S., Deniz, K., Huryn, J.M., Fletcher, C.D., 2017. Sarcomas with CIC-rearrangements are a distinct pathologic entity with aggressive outcome: a clinicopathologic and molecular study of 115 cases. Am. J. Surg. Pathol. 41 (7), 941–949. https://doi.org/10.1097/PAS.0000000000000846.

Brcic, I., Brodowicz, T., Cerroni, L., Kashofer, K., Serbanescu, G.L., Kasseroler, M.T., Liegl-Atzwanger, B., 2019. Undifferentiated round cell sarcomas with CIC-DUX4 gene fusion: expanding the clinical spectrum. Pathology. https://doi.org/10.1016/j.pathol.2019.09.015.

Carter, C.S., Patel, R.M., 2019. Important recently characterized non-Ewing small round cell tumors. Surg. Pathol. Clin. 12 (1), 191–215. https://doi.org/10.1016/j.path.2018.10.008.

Grier, H.E., Krailo, M.D., Tarbell, N.J., et al., 2003. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N. Engl. J. Med. 348 (8), 694–701. https://doi.org/10.1056/NEJMoa020890.

Haidar, A., Arekapudi, S., DeMattia, F., Abu-Isa, E., Kraut, M., 2015. High-grade undifferentiated small round cell sarcoma with t(4;19)(q35;q13.1) CIC-DUX4 fusion: emerging entities of soft tissue tumors with unique histopathologic features–a case report and literature review. Am. J. Case Rep. 16, 87–94. https://doi.org/10.12659/AJCR.892551.

Jawad, M.U., Cheung, M.C., Min, E.S., Schneiderbauer, M.M., Koniaris, L.G., Scully, S.P., 2009. Ewing sarcoma demonstrates racial disparities in incidence-related and sex-related differences in outcome: an analysis of 1631 cases from the SEER database, 1973–2005. Cancer 115 (15), 3526–3536. https://doi.org/10.1002/cncr.24388.

Loverro, G., Resta, L., Di Naro, E., Caringella, A.M., Mastrolia, S.A., Vicino, M., Schonauer, L.M., 2015. Conservative treatment of Ewing's sarcoma of the uterus in young women. Case Rep. Obstet. Gynecol. 2015, 871821. https://doi.org/10.1155/2015/871821.

Mashriqi, N., Gujjarlapudi, J.K., Sidhu, J., Zur, M., Yalamanchili, M., 2015. Ewing's sarcoma of the cervix, a diagnostic dilemma: a case report and review of the literature. J. Med. Case Rep. 9, 255. https://doi.org/10.1186/s13256-015-0733-2.

Pappo, A.S., Dirksen, U., 2018. Rhabdomyosarcoma, Ewing sarcoma, and other round cell sarcomas. J. Clin. Oncol. 36 (2), 168–179. https://doi.org/10.1200/JCO.2017.74.7402.

Ren, Y.L., Tang, X.Y., Li, T., 2011. Ewing sarcoma-primitive neuroectodermal tumor of the uterus: a clinicopathologic, immunohistochemical and ultrastructural study of one case. Arch. Gynecol. Obstet. 283 (5), 1139–1143. https://doi.org/10.1007/s00404-010-1557-3.

Sbaraglia, M., Righi, A., Gambarotti, M., Dei Tos, A.P., 2019. Ewing sarcoma and Ewing-like tumors. Virchows Arch. https://doi.org/10.1007/s00428-019-02720-8.

Specht, K., Sung, Y.S., Zhang, L., Richter, G.H., Fletcher, C.D., Antonescu, C.R., 2014. Distinct transcriptional signature and immunoprofile of CIC-DUX4 fusion-positive round cell tumors compared to EWSR1-rearranged Ewing sarcomas: further evidence toward distinct pathologic entities. Genes Chromosomes Cancer 53 (7), 622–633. https://doi.org/10.1002/gcc.22172.

Yoshida, A., Goto, K., Kodaira, M., Kobayashi, E., Kawamoto, H., Mori, T., Kawai, A., 2016. CIC-rearranged sarcomas: a study of 20 cases and comparisons with Ewing sarcomas. Am. J. Surg. Pathol. 40 (3), 313–323. https://doi.org/10.1097/PAS.0000000000000570.

Yoshimoto, T., Tanaka, M., Homme, M., Yamazaki, Y., Takazawa, Y., Antonescu, C.R., Nakamura, T., 2017. CIC-DUX4 induces small round cell sarcomas distinct from Ewing sarcoma. Cancer Res. 77 (11), 2927–2937. https://doi.org/10.1158/0008-5472.CAN-16-3351.