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A Rare Case of Round Cell Sarcoma with CIC-DUX4 Mutation Mimicking a Phlegmon: Review of Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest:

None declared

Patient: Male, 33-year-old
Final Diagnosis: CIC-DUX4 mutation sarcoma
Symptoms: Mass in abdomen
Medication: —
Clinical Procedure: —
Specialty: Oncology • Pathology

Objective: Rare disease

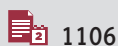
Background: Undifferentiated small blue round cell sarcomas with CIC-DUX4 translocation differ morphologically and in clinical outcomes from other types of sarcoma. Although classified by the World Health Organization as undifferentiated sarcomas, it is unclear whether these tumors are variants of Ewing's sarcoma or a distinct entity. This report describes a round cell sarcoma with CIC-DUX4 translocation that presented clinically as a phlegmon.

Case Report: A 31-year-old African American man presented with a mass in the right upper abdominal quadrant. Examination at a local hospital suggested an intra-abdominal abscess, and incision and drainage were performed. One week later, he returned with increased pain and bloody drainage from the incision site. Computed tomography showed a complex solid-cystic area measuring 7.8 cm suggesting a large phlegmon/abscess or neoplasm. Histologically, the sarcomatous malignancy was cellular, multinodular, and necrotic, with cells having round-ovoid to spindle nuclei and variable amounts of pale cytoplasm. Immunohistochemically, the mass was focally positive for CD99, but much less positive than an Ewing sarcoma. The mass also showed diffuse nuclear positivity for WT-1 and ETV4, but was negative for desmin. Fluorescence *in-situ* hybridization showed positivity for CIC-DUX4 gene fusion, resulting in a final diagnosis of round cell sarcoma with CIC-DUX4 translocation. The patient has completed 14 cycles of chemotherapy with no evidence of metastasis or local recurrence.

Conclusions: A round cell sarcoma with CIC-DUX4 translocation can present clinically as a phlegmon with pleomorphic morphology. Early tumor identification by molecular analysis and early initiation of treatment can improve patient prognosis.

MeSH Keywords: Mutation • Neoplasms, Connective and Soft Tissue • Sarcoma, Ewing • *In Situ* Hybridization, Fluorescence

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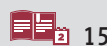
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Background

Capicua transcriptional repressor (CIC)-double homeobox 4 (DUX4) sarcomas (CDS) negative for the EWSR1/FUS gene, are undifferentiated small blue round cell sarcomas that clinically and morphologically resemble Ewing sarcoma (ES) [1]. CDS was recently determined to be a distinct neoplasm, differing histologically and immunohistochemically from Ewing-like sarcomas. Moreover, survival outcomes differ distinctly in patients with CDS and Ewing-like sarcomas. CDSs are aggressive soft tissue tumors occurring mainly in young to middle-aged adults but also occurring in children and adolescents. Most of these tumors are present in the trunk and extremities, followed by visceral structures, with tumors rarely occurring in bone [2].

The World Health Organization (WHO) currently classifies CIC-DUX4 sarcomas as undifferentiated sarcomas, although it is unclear whether these tumors are ES variants or a separate entity [2]. ES has been associated with the ETS transcription factor group, specifically with the EWSR1 gene on chromosome 22, whereas round cell sarcomas have different molecular profiles, influencing treatment and prognosis [3]. CIC-DUX fusion, common in CDS, has been found to result from t(4;19)(q35;q13) or t(10;19)(q26;q13) translocation [4–6]. This report describes an unusual presentation of this rare entity as a phlegmon, which affected its clinico-morphologic characteristics and patient survival [7].

Case Report

A 31-year-old African American man presented to a local hospital with a mass in his right upper abdominal quadrant. Incision and drainage were performed, which revealed blood clots, and his abdomen was stapled. One week later, he returned to the

local hospital with increased abdominal pain, nausea, and bloody drainage from his abdominal wound. He was unable to eat much because of increased pain when he was full. He denied fever, chills, and vomiting. Examination showed that the wound area was infected with a bloody purulent discharge. A computed tomography (CT) scan showed a complex solid-cystic area measuring 7.8×7.0×6.5 cm (Figure 1). Differential diagnosis included a large phlegmon/abscess, a pyogenic granuloma or a potential neoplastic process. Another incision and drainage were performed, and the wound was thoroughly cleansed. He was referred to our institution, where the specimen was resected after biopsy confirmation (Figure 2).

Histologic examination showed a poorly circumscribed mass extending into the reticular dermis and subcutaneous tissue. The specimen was an exceedingly cellular, multinodular neoplasm consisting of malignant cells with round-ovoid to spindle-shaped nuclei, small nucleoli distributed throughout the open chromatin, and variable amounts of pale cytoplasm (Figures 3, 4). More than 30 mitotic figures per 10 high-powered fields (HPF) were present. Differential diagnosis included round cell sarcoma similar to ES, desmoplastic round cell tumor, epithelioid sarcoma, poorly differentiated synovial sarcoma and undifferentiated round cell sarcoma. Immunohistochemically, the specimen was focally positive for CD99, but CD99 expression was much lower than in ES (Figure 5). The mass showed diffuse nuclear positivity for both WT-1 (Figure 6) and ETV4, but was negative for desmin, CK8/18, S100, CD34 and SMA and CD45 expression, suggesting a diagnosis of high-grade carcinoma. Fluorescence *in-situ* hybridization (FISH) showed that the mass was positive for CIC-DUX4 gene fusion t(4: 19). The patient completed 14 cycles of chemotherapy with etoposide and ifosfamide and has been followed up since July 2018.

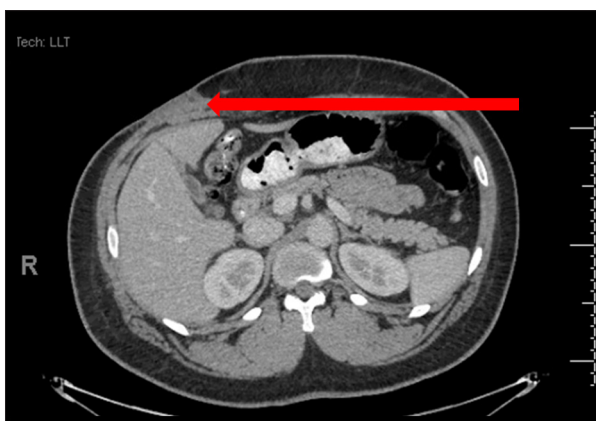


Figure 1. CT scan of the right upper abdominal quadrant, showing a subcutaneous based solid-cystic attenuating mass measuring 7.8 cm with complex abscess formation (red arrow).

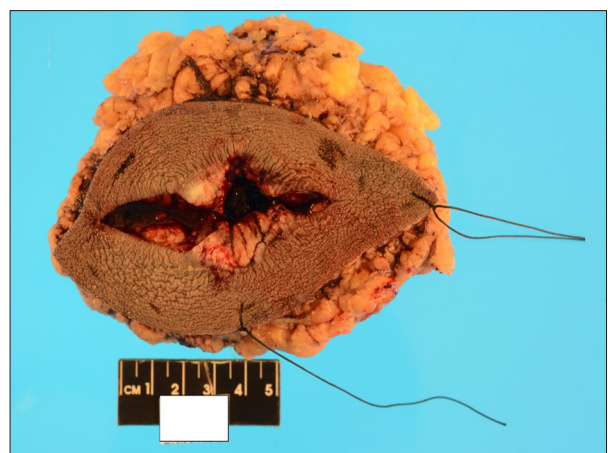


Figure 2. Gross specimen showing ellipse of the skin with an underlying tumor measuring 12.2×9.4×5.5 cm and a longitudinal surgical defect in the center.

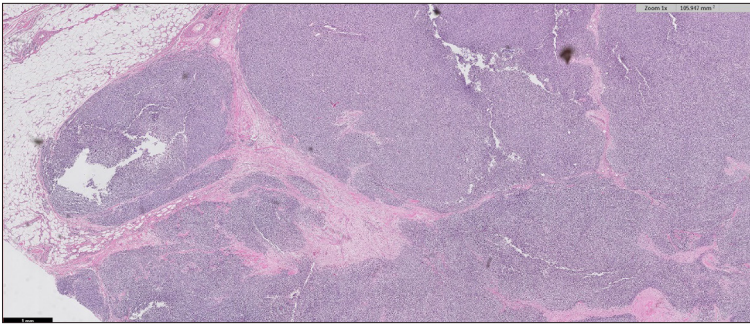


Figure 3. Histology of the tumor, showing a nodular growth pattern with infiltration into the surrounding adipose tissue (H&E staining, 4×).

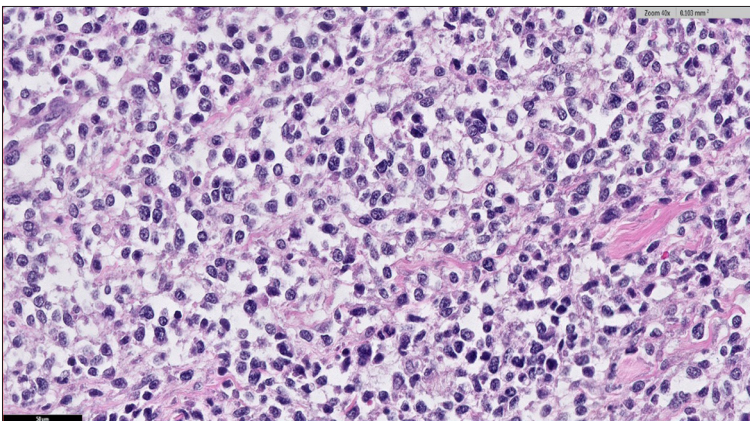


Figure 4. Histology of the tumor, showing round-ovoid to spindle cells with prominent nucleoli, and ill-defined, eosinophilic cytoplasm (H&E staining, 40×).

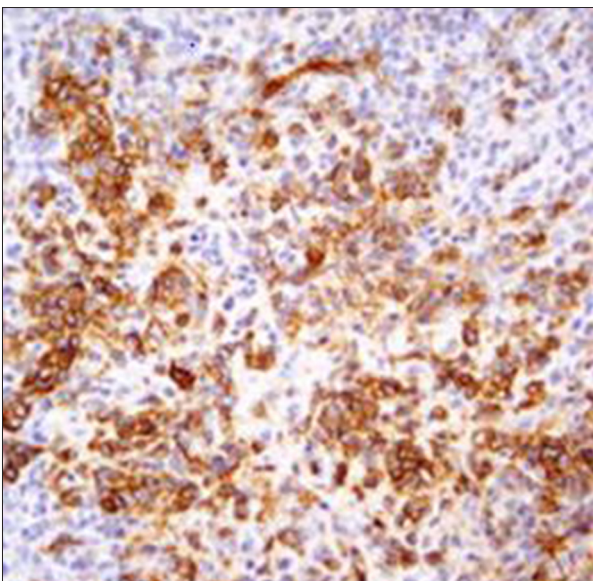


Figure 5. Immunohistochemical staining of the tumor with anti-CD99 antibody, showing patchy membranous positivity of tumor cells with focal staining.

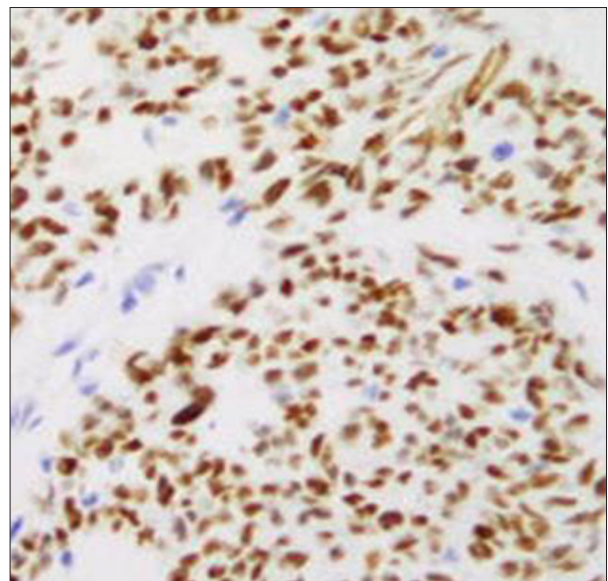


Figure 6. Immunohistochemical staining of the tumor with anti-WT1 antibody, showing nuclear staining of most tumor cells.

Discussion

CDSs are a very aggressive subgroup of round cell sarcomas affecting young children and adults. A study of 111 patients with CDS found that their mean age was 32 years, indicating that these tumors occur in younger adults, with peak incidence

during the third decade of life [2]. Similarly, ES is predominant in young individuals, with a mean age at diagnosis of about 15 years [8]. Most (86%) CDSs are located in somatic soft tissues, most commonly in the trunk and extremities, but rarely in bones. As in our patient, these tumors can also occur

intra-abdominally, including within visceral organs, including the stomach, intestines, kidneys, prostate and tonsils [2].

Cytologically, CDSs have a heterogeneous presentation, being composed of mixtures of round-ovoid to epithelioid cells, as well as spindle cells, of small to medium-size. These cells lack a specific type of differentiation and can vary from being packed in sheets to having more spindled arrangements [2,9]. The tumor in our patient consisted of a combination of solid and cystic areas with areas of hemorrhage and was composed predominantly of epithelioid to spindle cells having pale cytoplasm. Similar findings were reported in the study of 111 patients with CDS, with 50% of these lesions having pleomorphic cells with nucleomegaly, open chromatin, prominent nucleoli present focally, and abundant light eosinophilic cytoplasm [2]. Although CDSs contain myxoid stroma, ESs do not [10,11].

Immunophenotypically, the lesion in our patient was focally positive for CD99, as well as showing strong diffuse positivity for WT1 and ETV4. Variable weak and focal expression of CD99 has been reported in other CDSs, whereas strong and diffuse expression of CD99 has been reported in ES. Furthermore, strong diffuse WT1 overexpression/immunoreactivity has been reported in CDS due to transcriptional upregulation [10–14]. A study of nine patients with CIC-DUX sarcomas found that five were positive for CD56, three were positive for ERG, and eight each were positive for CD99 and WT1 [12]. Another study reported that seven of seven CDSs were focal positive for CD99 and five of five were strongly positive for WT1 [14].

CDS is a highly aggressive sarcoma with a 53% metastasis rate, most frequently to the lungs, and 2 year and 5-year overall

survival rates of 53% and 43%, respectively [2]. CDS have been reported to be less sensitive to a chemotherapy regimen used to treat ES. However, our patients did not report any metastasis. Moreover, he has responded well to chemotherapy since his initial diagnosis in early 2018.

The dysregulation of DUX4 expression by CIC-DUX4 fusion remains poorly understood [2]. The CIC-DUX4 fusion sequence shows strong transcriptional activity in NIH3 3T3 fibroblasts, upregulating the expression of genes in the PEA3 family while playing an important role in tumorigenesis. CIC enhances transcriptional activity, resulting in the dysregulation of expression of downstream targets [6]. A monoclonal antibody against the C-terminus of DUX4 protein showed 100% sensitivity, staining CIC-DUX4 fusion-positive round cells diffusely including strong nuclear staining. This antibody, however, did not stain other round cell tumors, making the antibody highly specific for CIC-DUX4 tumors. This anti-DUX4 antibody can be used to differentiate CDS from its histological mimics [15]. Further molecular testing is needed to confirm the diagnosis of CDS.

Conclusions

CDSs have a unique clinical manifestation, morphology, immunohistochemistry, and genetics. Most of these tumors behave aggressively, with poor survival outcomes, differentiating these tumors from ESs and other small round blue cell tumors and resulting in their classification as a separate entity by the WHO. This will have a significant impact on management and treatment of patients with CIC-DUX4 sarcomas.

References:

1. Tang S, Dodd LG: CIC-DUX4 sarcoma diagnosed by fine-needle aspiration cytology: A case report. *Diagn Cytopathol*, 2018; 46: 958–63
2. Antonescu CR, Owosho AA, Zhang L et al: Sarcomas with CIC-rearrangements are a distinct pathologic entity with aggressive outcome: A clinicopathologic and molecular study of 115 cases. *Am J Surg Pathol*, 2017; 41: 941–49
3. Delattre O, Zucman J, Plougastel B et al: Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumours. *Nature*, 1992; 359: 162–65
4. Choi EY, Thomas DG, McHugh JB et al: Undifferentiated small round cell sarcoma with t(4;19)(q35;q13.1) CIC-DUX4 fusion: A novel highly aggressive soft tissue tumor with distinctive histopathology. *Am J Surg Pathol*, 2013; 37: 1379–86
5. Italiano A, Sung YS, Zhang L et al: High prevalence of CIC fusion with double-homeobox (DUX4) transcription factors in EWSR1-negative undifferentiated small blue round cell sarcomas. *Genes Chromosomes Cancer*, 2012; 51: 207–18
6. Kawamura-Saito M, Yamazaki Y, Kaneko K et al: Fusion between CIC and DUX4 up-regulates PEA3 family genes in Ewing-like sarcomas with t(4;19)(q35;q13) translocation. *Hum Mol Genet*, 2006; 15: 2125–37
7. Abstracts and Case Studies From the College of American Pathologists 2019 Annual Meeting (CAP19). *Arch Pathol Lab Med*, 2019; 143: e2–226
8. Sankar S, Lessnick SL: Promiscuous partnerships in Ewing's sarcoma. *Cancer Genet*, 2011; 204: 351–65
9. Yoshimoto T, Tanaka M, Homme M et al: CIC-DUX4 induces small round cell sarcomas distinct from Ewing sarcoma. *Cancer Res*, 2017; 77: 2927–37
10. Yoshida A, Goto K, Kodaira M et al: CIC-rearranged sarcomas: A study of 20 cases and comparisons with Ewing sarcomas. *Am J Surg Pathol*, 2016; 40: 313–23
11. Gambarotti M, Benini S, Gamberi G et al: CIC-DUX4 fusion-positive round-cell sarcomas of soft tissue and bone: A single-institution morphological and molecular analysis of seven cases. *Histopathology*, 2016; 69: 624–34
12. Yamada Y, Kuda M, Kohashi K et al: Histological and immunohistochemical characteristics of undifferentiated small round cell sarcomas associated with CIC-DUX4 and BCOR-CCNB3 fusion genes. *Virchows Arch*, 2017; 470: 373–80
13. Specht K, Sung YS, Zhang L et al: 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*, 2014; 53: 622–33
14. Brčić I, Brodowicz T, Cerroni L et al: Undifferentiated round cell sarcomas with CIC-DUX4 gene fusion: Expanding the clinical spectrum. *Pathology*, 2020; 52: 236–42
15. Siegele B, Roberts J, Black JO et al: DUX4 immunohistochemistry is a highly sensitive and specific marker for CIC-DUX4 fusion-positive round cell tumor. *Am J Surg Pathol*, 2017; 41: 423–29