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CASE REPORT

CIC-DUX4 Sarcoma: A Case Report and Review of the Literature

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CIC-DUX4 sarcoma is highly aggressive and rapidly develops lethal metastatic disease and chemoresistance. Its histology is similar to that of Ewing sarcoma and other small round cell sarcomas. Correlation with clinical data, radiological findings, pathological results (including immunohistochemistry and fluorescence *in situ* hybridization), and/or molecular techniques is necessary. We present the case of a 44-year-old woman who was initially diagnosed as having high-grade undifferentiated round cell sarcoma confirmed to be a CIC-DUX sarcoma by next-generation sequencing.

Key words: CIC-DUX sarcoma, small round cell sarcoma, Ewing-like sarcoma

INTRODUCTION

Soft-tissue sarcoma is rare, with an annual incidence rate of <1% of all malignant tumors.[1] Small round cell sarcomas (SRCSs) are typically characterized by sheets of small, round, blue cells with a prominent nucleus and scant cytoplasm. Most SRCSs can be categorized according to their morphological, immunohistochemical, and molecular features. Ewing sarcomas are one of the SRCSs with specific gene fusions between Ewing sarcoma breakpoint region 1 (EWSR1) and E-twenty-six (ETS) transcription factor family members in almost all cases.[1] However, a few SRCSs with an aggressive behavior and a morphology similar to that of Ewing sarcoma but with either non-EWSR1-ETS fusions or no known genetic abnormalities are referred to as "Ewing-like sarcomas." Owing to the advantage of the advances in molecular technologies, novel fusion genes such as Capicua transcriptional repressor (CIC)-double homeobox 4 (DUX4)[2] or BCL-6 corepressor-cyclin B3[3] are identified in these SRCSs. Either (4;19)(q35;q13) or (10;19)(q26;q13) translocation results in CIC-DUX4 fusion.[2,4] CIC-DUX4 sarcomas (CDSs) arise in the soft tissue of children or young adults and elderly patients.[5,6]

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We present the case of a 44-year-old woman who was initially diagnosed as having high-grade undifferentiated round cell sarcoma confirmed to be a CDS by next-generation sequencing (NGS).

CASE REPORT

A 44-year-old woman presented to our orthopedic outpatient department owing to a palpable, tender, rubber-like soft-tissue mass over her left popliteal fossa region, which she first noticed 1 month before. Magnetic resonance imaging revealed a lobulated mass approximately 6.9 cm × 6.5 cm × 12.7 cm in size, with central necrosis, focal extracapsular extension, and adjacent soft-tissue invasion [Figure 1a-c]. Chest radiography revealed multiple nodules, and lung metastasis was suspected. The excision biopsy of the tumor in the popliteal fossa showed a solid growth pattern and infiltrating borders [Figure 2a]. The discohesive tumor cells had small-to-medium-sized irregular vesicular nuclei, scattered small nucleoli, amphophilic cytoplasm, and frequent mitotic figures [Figure 2b]. The tumor cells were focally immunoreactive to CD99, WT-1, and ETV4 [Figure 3a-c] but negative for cytokeratin, CD45, desmin, or NKX2.2. High-grade undifferentiated round cell

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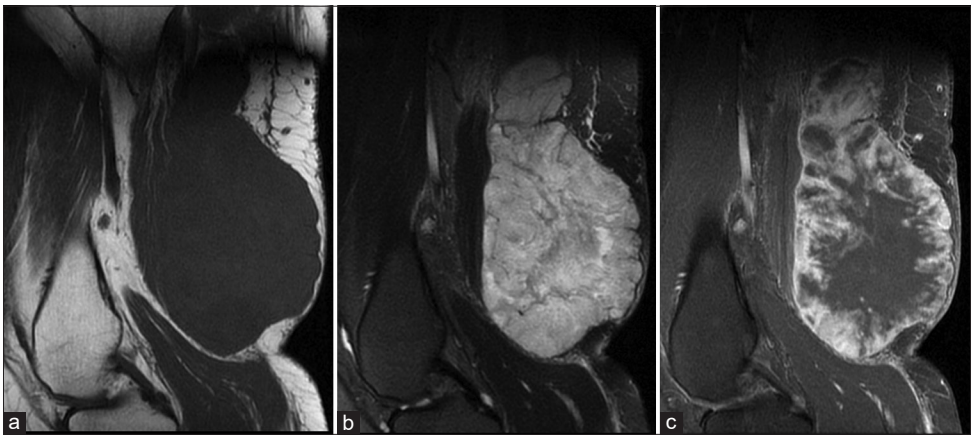

Figure 1: A magnetic resonance image of the tumor over the left popliteal fossa. (a) T1-weighted, (b) T2-weighted, and (c) contrast-enhanced T1-weighted images showing a lobulated mass approximately 6.9 cm × 6.5 cm × 12.7 cm in size, with central necrosis, focal extracapsular extension, and adjacent soft-tissue invasion

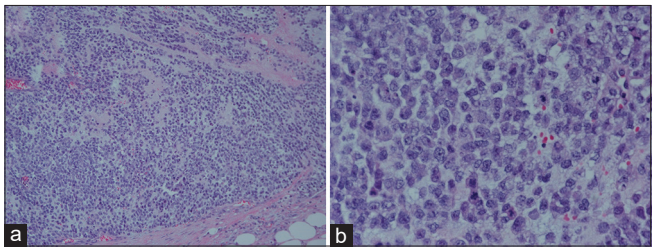

Figure 2: Histopathology of the tumor. (a) The tumor cells show a solid growth pattern with extension into the surrounding soft tissue (H and E staining, original magnification ×100). (b) The tumor cells are discohesive and have a high nuclear–cytoplasmic ratio. Small-to-medium-sized vesicular nuclei, scattered small nucleoli, amphophilic cytoplasm, and frequent mitotic figures can be observed (H and E staining, original magnification ×400)

sarcoma was impressed, and CDS was suspected. However, the fluorescent *in situ* hybridization (FISH) probes for CIC rearrangement revealed negative results. The patient underwent a wide excision of the left popliteal fossa tumor and a subsequent pulmonary metastasectomy after the diagnosis. Systemic chemotherapy with adriamycin + ifosfamide was administered in three cycles, but poor tolerance was observed owing to Grade 2 nausea with vomiting and Grade 2 anorexia. Local recurrence was found 1 month after the diagnosis, and she underwent a left above-the-knee amputation. Moreover, she developed multiple pulmonary recurrences, and the treatment was shifted to pazopanib. Despite the treatment, poor response was still observed. NGS (FoundationOne Heme) was performed, and CDS was diagnosed. However, no therapies or clinical trials were available for the sarcoma. Her condition deteriorated rapidly, and she died 7 months after the diagnosis.

DISCUSSION

CDS is a rare sarcoma but has an aggressive behavior with rapid progression. Ewing sarcoma is the most important differential diagnosis among SRCSs. In the largest CDS cohort reported by Antonescu *et al*., most patients were young adults in their fourth decade of life, and the tumors were found in deep soft tissues, either in the extremity or the trunk.[6] By contrast, most Ewing sarcomas occur in children with a peak incidence at 15 years of age and most commonly involve the pelvis and proximal long bones.[2] Antonescu *et al*. analyzed differences in 2- and 5-year survival rates between 57 patients with CIC-rearranged sarcomas and 57 age- and stage-matched patients with Ewing sarcoma. The patients with Ewing sarcoma had significantly better 2- and 5-year survival rates (87% vs. 53% and 77% vs. 43%, respectively).[6]

Immunohistochemistry (IHC) staining is an important tool for differential diagnosis of SRCSs. IHC staining for CDS frequently shows focal and heterogeneous membranous reactivity to CD99, and NKX2.2 is negative in most cases. By contrast, Ewing sarcomas have a diffuse, strong membranous expression of CD99 and often show overexpression of NKX2.2.[5] Both ETV4 and WT1 have high sensitivity for CIC-rearranged sarcomas. The combination of diffuse ETV4 and at least focal nuclear WT1 expression is helpful for the distinction of CIC-rearranged sarcomas from other histologic mimics.[6,7] CIC-DUX4 fusion results from either a t(4;19)(q35;q13) or a t(10;19)(q26;q13) translocation.[2,4] In the reported studies, t(4;19)(q35;q13) translocation is the most prevalent gene mutation.[6,8] Our patient had focal positivity for CD99 and focal nuclear positivity for WT-1 and ETV4 but negativity for NKX2.2. These IHC staining findings may support the evidence of CDS. However, the FISH probes for CIC rearrangement revealed negative results. CIC-break-apart FISH analysis was reported to have a 14% false-negative rate for CIC-rearranged sarcomas.[9] The patient was confirmed as having CDS after the NGS analysis. A NGS analysis could be used to identify potential targeted therapy

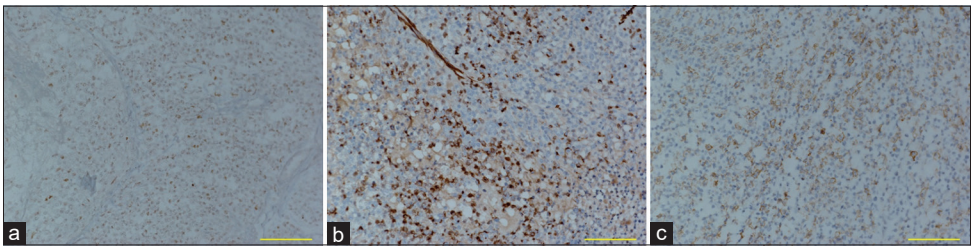

Figure 3: Immunohistochemistry staining of the tumor (original magnification ×200). (a) ETV4: Focal, weak nuclear staining pattern of the tumor cells. (b) WT1: Focal, weak nuclear staining pattern of tumor cells. (c) CD99: Focal, weak membranous staining pattern of tumor cells

options, detect alterations in prognostic genes, and subclassify sarcoma diagnoses. Brčić *et al*. reported that by using a NGS-based approach, they detected CIC-DUX4 fusion with t(4;19)(q35;q13) translocation in all the cases in their study.[8]

Treatment of metastatic CDS remains a challenge. Italiano *et al*. recommended treating patients with CDS with aggressive anthracycline-based chemotherapy regimens used in the management of Ewing sarcoma.[4] However, poor response to chemotherapy is common. In our case, the tumors did not respond to the standard dose of adriamycin + ifosfamide and tyrosine kinase inhibitor with pazopanib. Okimoto *et al*. demonstrated that ETV4, the downstream target protein of CIC-DUX4, mediates metastasis, and the CCNE-CDK2 complex is a molecular target of the CIC-DUX4 oncoprotein that controls tumor growth and survival. [10] These findings provide the therapeutic targets to improve the outcomes of CDS.

CONCLUSION

CDS is highly aggressive and rapidly develops a lethal metastatic disease and chemoresistance. Owing to its histological similarity with Ewing sarcoma and other SRCSs, correlation with clinical data, radiological findings, pathological results (including IHC and FISH), and/or molecular techniques is necessary.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institute (IRB NO B202105100). Informed written consent was obtained from all patients prior to their enrollment in this study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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