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# CIC-DUX4 Sarcoma Involving the Skull Base: A Rare Presentation and Review of the Literature

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## Abstract

**Background** CIC-DUX4 sarcoma is a rare, aggressive tumor that is difficult to diagnose. Although it is closely related to Ewing's sarcoma, each is a distinct pathologic entity and both have been previously reported in the skin, lymph nodes, and viscera. We report the first description of CIC-DUX4 involving the posterior cranial fossa and review the distinctive symptomatology, morphology, immunoprofile, and genetic signature that differentiate this rare tumor.

**Case Report** A 32-year-old man presented with an enlarging right lateral neck mass, progressive hoarseness, and orofacial pain. Biopsy revealed a high-grade undifferentiated malignant neoplasm. Imaging demonstrated an 8-cm mass in the right neck extending to the skull base and abutting the carotid sheath, in addition to pulmonary nodules and pelvic lymphadenopathy. Despite initial response to chemotherapy, he experienced disease progression and underwent surgical resection, radical neck dissection, and brachytherapy. Definitive pathologic diagnosis was achieved with next-generation sequencing. Within weeks of treatment, he developed symptoms reflecting progression of disease involving the neck, posterior cranial fossa, and lung. Adjuvant chemotherapy was planned, but the patient succumbed to his disease prior to initiation of further therapy.

**Conclusion** CIC-DUX4 sarcomas are uncommon and can progress rapidly. Diagnosis requires either fluorescence in situ hybridization or next-generation sequencing. Due to its rarity, there is no standard-of-care treatment for this tumor and further investigations are needed to understand disease behavior and develop targeted therapeutic modalities.

**Keywords**
- CIC DUX4 sarcoma
- Ewing-like sarcoma
- round cell sarcoma

## Introduction

The finding of a progressively enlarging neck mass is concerning for malignancy in any adult patient, with over 75% of neck masses ultimately found to be cancerous.[1] This is especially true if the patient is found to have symptoms that suggest invasion of vitally important structures. Current

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practice guidelines indicate a persistent neck mass in an adult should be considered malignant until proven otherwise.[2] Cancers presenting as neck masses are most commonly squamous cell carcinomas, followed by lymphomas, thyroid cancer, and salivary gland malignancies.[2] It is wise to maintain a broad differential diagnosis, especially in a young patient or in the case where initial biopsy is not definitive, as less common malignancies may also arise in the neck.

CIC-DUX4 sarcomas are one such rare pathology. First reported in 1996, these sarcomas are closely related to Ewing's sarcoma.[3] However, CIC-DUX4 and other CIC-rearranged sarcomas do not display the EWSR1 gene translocation characteristic of Ewing's sarcoma and are classified as their own distinct pathologic entity.[4–10] The CIC-DUX4 rearrangement results in a transcriptional overactivation of the CIC gene and upregulation of downstream targets in the *PEA3* gene family.[6] Prior studies have demonstrated PEA3 gene family upregulation in other solid malignancies and have associated these genes with more aggressive phenotypes.[11–15] The CIC-DUX4 rearrangement has emerged as the most common genetic abnormality in Ewing-like sarcomas that lack the EWSR1 rearrangement.[16–18]

This uncommon and aggressive neoplasm is an undifferentiated small round cell sarcoma with a slight male predominance. These tumors typically affect younger adults, are mostly found in the soft tissues, and rarely arise in bone.[5,19] CIC-DUX4 tumors have also been reported in the skin, lymph nodes, neural tissue, and within the viscera.[5,20–24] These tumors frequently metastasize, often to the lung and brain, and offer substantially poorer prognosis than that of Ewing's sarcoma.[19] Given the rare and recently described nature of CIC-DUX4 sarcomas, there is no consensus regarding standard-of-care treatment. Here, we describe the presentation, treatment, and clinical course of a patient with a CIC-DUX4 sarcoma arising in the neck and ultimately involving the posterior cranial fossa.

## Case Description

A 32-year-old morbidly obese (BMI = 63) man with past medical history of deep vein thrombosis presented with an enlarging right lateral neck mass, progressive hoarseness, dysphagia, and orofacial pain. Computed tomography (CT) imaging of the head and neck demonstrated an 8-cm mass in the right neck abutting the carotid sheath (►**Fig. 1**), while CT imaging of the abdomen and pelvis demonstrated innumerable pulmonary nodules and pelvic lymphadenopathy. Prior to our evaluation, needle biopsy of the patient's neck mass revealed a high-grade undifferentiated epithelioid and round cell malignant neoplasm suggestive of Ewing's sarcoma. However, diagnosis remained uncertain and the patient's pathology was sent for external review. The tumor stained negative for a wide array of immunologic markers, demonstrated no reactivity with several antibodies indicating hematopoietic origin, and showed an absence of clonal T-cell or B-cell populations on flow cytometry. Thus, definitive diagnosis remained elusive. Obtaining additional tissue for pathologic characterization was recommended and may have been performed, although records of this biopsy were not available for review.

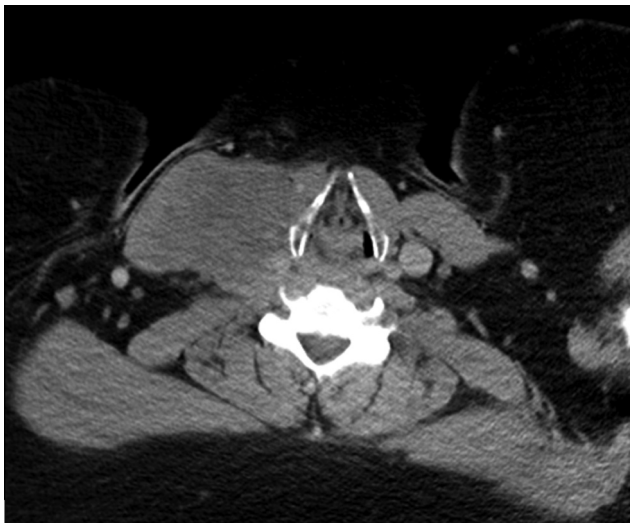

**Fig. 1** Computed tomography (CT) of the head and neck with contrast (axial view) demonstrating 8-cm mass in the right neck.

The patient was initiated on a chemotherapy regimen appropriate for a presumptive diagnosis of Ewing's sarcoma. Despite initial response to chemotherapy, he experienced disease progression, prompting presentation to our institution. Initial physical examination revealed a bulky right neck mass, approximately 13 cm in greatest diameter. While the patient had demonstrated some response when treated according to an Ewing's sarcoma paradigm, his clinical picture was atypical for this disease given the lack of bone lesions and presence of cervical lymphadenopathy. Given his progressive head and neck disease and the desire to obtain additional tissue to establish definitive diagnosis, it was recommended he undergo locally ablative therapy. His absolute body weight precluded the use of gantry-based external beam radiation; thus, surgical resection, radical neck dissection, and brachytherapy were performed upon referral to our center (►**Fig. 2**).

Intraoperatively, the tumor was grossly inseparable from the superior laryngeal nerve, vagus nerve, and occipital artery. The occipital artery could not be preserved due to its complete encasement in the tumor. Preservation of the vagus was attempted; however, the lesion was completely adherent to the nerve at the carotid bifurcation. The superior portion of the vagus was transected, producing notable bradycardia. Despite concern for residual disease along the superior portion of the vagus nerve, there was reluctance to chase tumor along the skull base given his lung metastasis and cardiac response to nerve sacrifice and subsequent proximal nerve margin manipulation.

Surgical pathology report described a 10.1-cm high grade CIC-rearranged sarcoma with focal lymphovascular invasion. No metastatic tumor was seen in resected cervical lymph nodes. Histological analysis revealed a small round blue cell tumor, while immunohistochemical analysis demonstrated

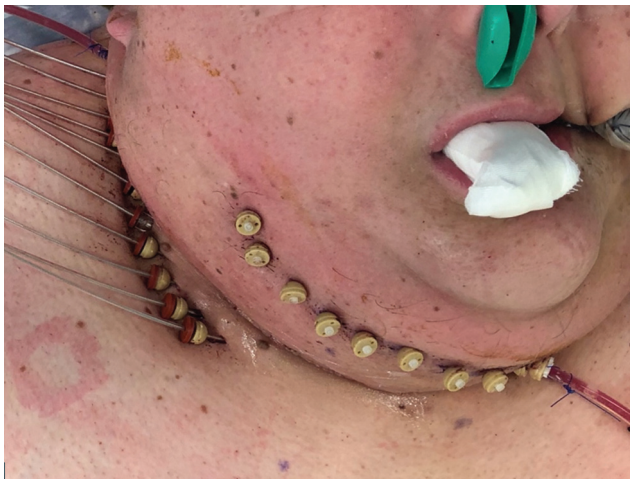

**Fig. 2** Brachytherapy catheters in place.

diffuse WT1 and CD99 positivity (►**Fig. 3**). In addition, the patient's tumor stained negative for immunologic markers including AE1/3, S100, SOX10, desmin, SMA, MYOD1, myogenin, CD45, CD20, Pax5, CD3, BCL1, CD34, STAT6, SATB2, NSE, synaptophysin, chromogranin, p63, CK5/6, PAS, and PAS-D. Fluorescence in situ hybridization (FISH) analysis for the Ewing sarcoma breakpoint region 1 (EWSR1) gene was negative. Definitive pathologic diagnosis via identification of the CIC-DUX4 gene translocation was achieved with next-generation sequencing.

Within 8 weeks of treatment, he developed diplopia, dysphagia, and dyspnea reflecting progression of disease involving the neck, posterior cranial fossa, and lung. CT head venogram showed soft-tissue lesions in the right neck with encasement of the hypoglossal nerve and carotid space, thrombus in the upper internal jugular vein, and dural sinus thrombosis extending into the sigmoid sinus (►**Fig. 4**). Additional cranial neuropathies including right anisocoria, right-sided hearing loss, and central facial nerve palsy raised concern for leptomeningeal disease. Adjuvant chemotherapy was planned, but the patient succumbed to his disease prior to initiation of further therapy.

## Discussion

CIC-DUX4 sarcoma is a recently described subgroup of Ewing-like sarcomas that mostly affect young adults and have a propensity for both local progression and distant metastasis. This report details the first case described in the literature of a CIC-DUX4 sarcoma involving posterior cranial fossa structures. While this aggressive tumor can cause significant morbidity and mortality no matter where it arises in the body, our case demonstrates the unique challenges posed by a CIC-DUX4 sarcoma arising in an anatomic location such as the skull base where multiple vitally important structures in close proximity may be affected. Despite multiple attempts made to characterize his tumor, this patient experienced a delay in definitive pathologic diagnosis. While this patient underwent chemotherapy, radiation, and

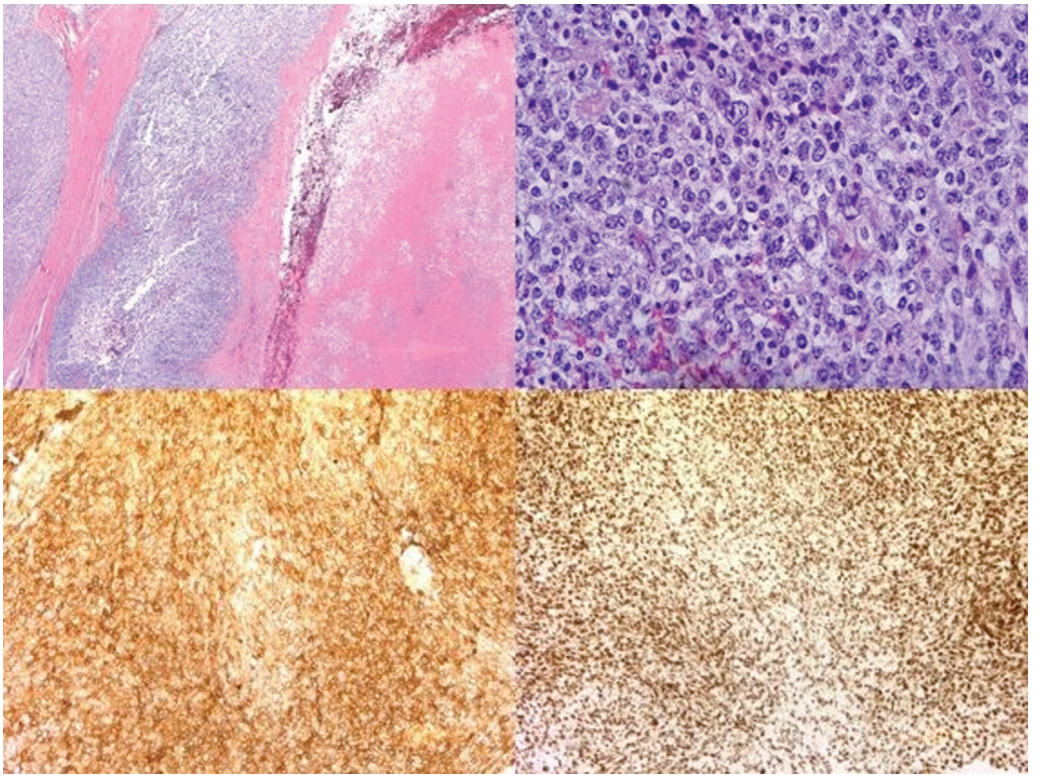

**Fig. 3** Hematoxylin and eosin (H&E; top panel) demonstrating small round blue cell tumor with extensive necrosis (25 ×; left) and cytologic features of this tumor including vesicular chromatin, irregular nuclear membranes, and numerous mitotic figures (400 ×; right). Immunohistochemistry (bottom panel) staining diffusely positive for CD99 (L) and WT-1 C-terminal (R).

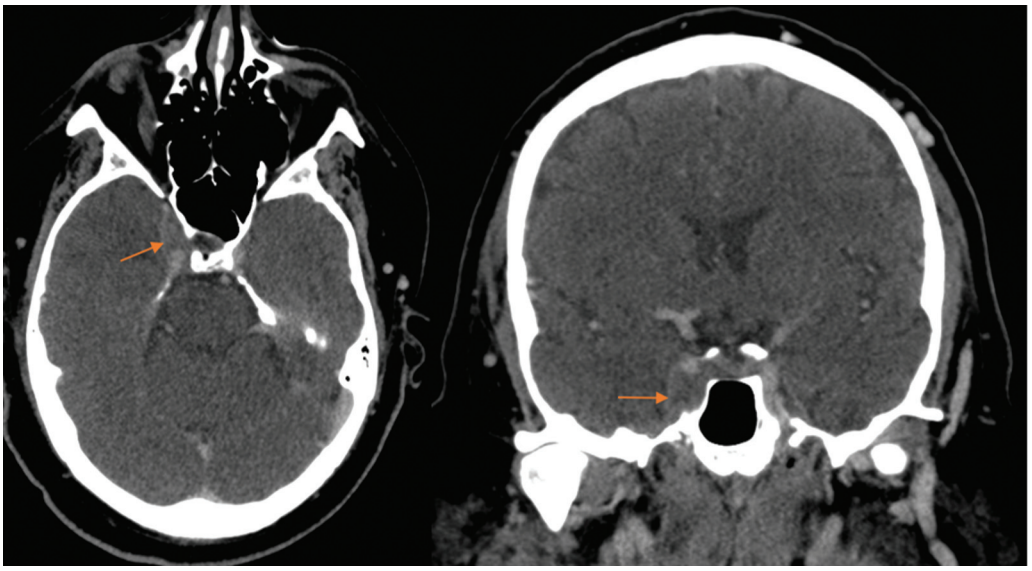

**Fig. 4** Computed tomography (CT) venogram demonstrating cavernous sinus thrombosis in axial (left) and coronal (right) views.

surgical resection, he ultimately succumbed to his disease less than 4 months after presentation at our institution. Unfortunately, this outcome is not uncommon, as CIC-DUX4 sarcoma has a 2-year overall survival rate of 53%—significantly worse than that of Ewing sarcoma patients.[5]

This poor prognosis may be partially explained by the reality that diagnosis, as in this case, can be challenging given both the rarity of the neoplasm and the need for genetic analysis to determine diagnosis. Depending on location, these tumors can be mistaken for abscesses, phlegmons, or other tumors with similar histologic backgrounds.[25] As in our case, many patients are initially misdiagnosed and time is spent treating an incorrect diagnosis before CIC-DUX4 sarcoma is ultimately discovered. In one study, over 90% of patients were treated for CIC-DUX4 sarcoma only after completing a chemotherapy regimen meant to treat Ewing's sarcoma.[5] In this case, we saw the patient only after he had been treated as above and it is quite likely that his body habitus also contributed to his diagnosis in a more advanced stage.

Immunohistochemical analysis can be heterogeneous, although the majority of tumors show some degree of CD99 positivity and WT1 nuclear expression.[5,26] Histologic findings also vary, but typically demonstrate small round and short spindle cells with abundant stroma, often with myxoid stromal change.[4,5,26] Most tumors display a solid growth pattern, although up to a third are also characterized by some degree of nodular growth.[5,26] A monoclonal antibody to DUX4 has been developed that displays high sensitivity and specificity for CIC-DUX4 sarcomas versus tumors with similar histologic features, and may be used to point toward this diagnosis.[27] However, definitive diagnosis requires either molecular analysis and FISH or next-generation sequencing to confirm presence of the CIC-DUX4 gene fusion product. These tumors harbor either a t(4;19)(q35;q13.1) or t(10;19)(q26.3;q13) translocation, with t(4;19) being the more common of the two.[19]

Given the rarity of this disease, there is no consensus regarding standard-of-care treatment. Resection and radiation therapy are the mainstays of sarcoma treatment and have been employed with some success in this subset of tumors, especially those without evidence of distant metastasis. However, this pathology exhibits a metastasis rate of 53%, meaning that many patients require some form of systemic therapy.[5] Chemotherapy regimens involving various combinations of doxorubicin, ifosfamide, vincristine, cyclophosphamide, cisplatin, and Adriamycin in the neoadjuvant and adjuvant setting have been attempted with mixed results, even though CIC-DUX4 sarcomas appear to be much less responsive to chemotherapy than Ewing's sarcoma.[19,25,26] One study found that those patients treated with neoadjuvant chemotherapy demonstrated inferior survival compared to patients who underwent surgery first, although those patients who underwent neoadjuvant chemotherapy also demonstrated larger tumor size at initial staging than those patients initially treated with surgery.[5] Unfortunately, the CIC-DUX4 gene fusion product has proven difficult to target with specific drugs, although investigations of possible molecular targets downstream and adjacent to the CIC-DUX4 gene product are ongoing.[28,29] Currently, there are no available therapies that specifically target this mutation. While combinations of radiation, chemotherapy, and surgical resection have proven successful in some cases, CIC-DUX4 sarcoma patients' median survival remains below 2 years.[16,19,26] Further study is needed to characterize this tumor and determine optimal therapeutic modalities to improve morbidity and mortality.

### Conflict of Interest

None declared.

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