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

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Background: CIC-DUX4 sarcoma is a rare, aggressive tumor that is difficult to diagnose. Though 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 morbidly obese 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.

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

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Abstract:

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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:

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 (Figure 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, though records of this biopsy were not available for review.

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 exam 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 (Figure 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 diffuse WT1 and CD99 positivity (Figure 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. FISH analysis for the Ewing sarcoma breakpoint region1 (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 (Figure 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.

References


Figure 1: CT Head and Neck with Contrast (axial view) demonstrating 8cm mass in right neck

Figure 2: Brachytherapy catheters in place

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

Figure 4: CT Venogram demonstrating cavernous sinus thrombosis in axial (L) and coronal (R) view